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Abstract

The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis

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Objectives: To examine the effectiveness and cost-effectiveness of symptomatic versus aggressive treatment in patients with established, stable rheumatoid arthritis (RA).
Design: A randomised observer-blinded controlled trial and economic evaluation with an initial assessment at randomisation and follow-ups at 12, 24 and 36 months.
Setting: Five rheumatology centres in England. The 'symptomatic care' patients were managed predominantly in primary care with regular visits by a rheumatology specialist nurse. The 'aggressive care' patients were managed predominantly in the hospital setting.
Participants: Patients with RA for more than 5 years were screened in rheumatology clinics.
Interventions: The symptomatic care patients were seen at home every 4 months by a rheumatology specialist nurse and annually by the rheumatologist. The aim of treatment was symptom control. The aggressive care patients were seen at least every 4 months in hospital. Their treatment was altered (following predefined algorithms) with the aim of suppressing both clinical and laboratory evidence of joint inflammation.
Main outcome measures: The main outcome measure was the Health Assessment Questionnaire (HAQ). Others included the patient and physician global assessment, pain, tender and swollen joint counts, the erythrocyte sedimentation rate and the OSRA (Overall Status in Rheumatoid Arthritis) score. X-rays of the hands and feet were performed at the beginning and end of the study. The EQ-5D was used in the health economic evaluation. Comprehensive costs were also estimated and were combined with measures of outcome to examine between-group differences.
Results: A total of 466 patients were recruited; 399 patients completed the 3 years of follow-up. There was a significant deterioration in physical function (HAQ) in both arms. There was no significant difference between the groups for any of the clinical outcome measures except the physician global assessment [adjusted mean difference 3.76 (95% CI 0.03 to 7.52)] and the OSRA disease activity component [adjusted mean difference 0.41 (95% CI 0.01 to 0.71)], both in favour of the aggressive arm. During the trial, second-line drug treatment was changed in 77.1% of the aggressive arm and 59.0% of the symptomatic arm. There were instances when the rheumatologist should have changed treatment but did not do so, usually because of mild disease activity. The symptomatic arm was associated with higher costs and higher quality-adjusted life-years (QALYs). There was a net cost of £1517 per QALY gained for the symptomatic arm. Overall, the primary economic analysis and sensitivity analyses of the cost and QALY data indicate that symptomatic treatment is likely to be more cost-effective than aggressive treatment in 58–90% of cases.
Conclusions: This trial showed no benefit of aggressive treatment in patients with stable established RA. However, it was difficult to persuade the rheumatologist and/or the patient to change treatment if the evidence of disease activity was minimal. Patients in the symptomatic arm were able to initiate changes of

therapy when their symptoms deteriorated, without frequent hospital assessment. Approximately one-third of current clinic attenders with stable RA could be managed in a shared care setting with annual review by a rheumatologist and regular contact with a rheumatologist nurse. Further research is needed into disease progression and the use of biological agents, minimum disease activity level below which disease progression does not occur,
cost-effectiveness through shared care modelling, the development of a robust and fail-safe system of primary-care based disease-modifying anti-rheumatic drug (DMARD) monitoring, and predicting response to DMARDs.

Contents

List of abbreviations

ACR	American College of Rheumatology
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ARC	Arthritis Research Campaign
AUR	auranofin
AZA	azathioprine
BROSG	British Rheumatoid Outcome Study Group
CI	confidence interval
COX	cyclooxygenase
CRP	C-reactive protein
CYP	ciclosporin
DMARD	disease-modifying anti-rheumatic drug
D-PEN	D-penicillamine
ESR	erythrocyte sedimentation rate
HAQ	Health Assessment Questionnaire
HCQ	hydroxychloroquine
HRQoL	health-related quality of life
ICC	intra-class correlation coefficient
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
ITT	intention-to-treat
LEF	leflunomide
MCP	metacarpophalangeal
MTP	metatarsophalangeal
MTX	methotrexate
MYO	intramuscular gold
NICE	National Institute for Health and Clinical Excellence
NSAID	non-steroidal anti-inflammatory drug
OMERACT	Outcome Measures in RA Clinical Trials
OSRA	Overall Status in Rheumatoid Arthritis
PIP	proximal interphalangeal
QALY	quality-adjusted life-year
RA	rheumatoid arthritis
RCT	randomised controlled trial
RR	relative risk
SASP	sulfasalazine
SD	standard deviation
SF-36	Short Form with 36 Items
VAS	visual analogue scale

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

Executive summary

Objectives

To examine the effectiveness and cost-effectiveness of symptomatic versus aggressive treatment in patients with established, stable rheumatoid arthritis (RA).

Design

A randomised observer-blinded controlled trial and economic evaluation with an initial assessment at randomisation and follow-ups at 12, 24 and 36 months.

Setting

Five rheumatology centres in England. The 'symptomatic care' patients were managed predominantly in primary care with regular visits by a rheumatology specialist nurse. The 'aggressive care' patients were managed predominantly in the hospital setting.

Patients

Patients with RA for more than 5 years' duration were screened in rheumatology clinics. They were asked to participate if they had been on stable therapy for at least 6 months and had no evidence of systemic rheumatoid disease or other serious co-morbidity.

Interventions

The symptomatic care patients were seen at home every 4 months by a rheumatology specialist nurse and annually by the rheumatologist. The aim of treatment was symptom control. The aggressive care patients were seen at least every 4 months in hospital. Their treatment was altered (following predefined algorithms) with the aim of suppressing both clinical and laboratory evidence of joint inflammation.

Outcome measures

The main outcome measure was the Health Assessment Questionnaire (HAQ). Others included the patient and physician global assessment, pain, tender and swollen joint counts, the erythrocyte sedimentation rate and the OSRA (Overall Status in Rheumatoid Arthritis) score. X-rays of the hands and feet were performed at the beginning and end of the study. The EQ-5D was used in the health economic evaluation. Comprehensive costs were also estimated and were combined with measures of outcome to examine between-group differences.

Results

A total of 466 patients were recruited; 399 patients completed the 3 years of follow-up. There was a significant deterioration in physical function (HAQ) in both arms. There was no significant difference between the groups for any of the clinical outcome measures except the physician global assessment [adjusted mean difference 3.76 (95% CI 0.03 to 7.52)] and the OSRA disease activity component [adjusted mean difference 0.41 (95% CI 0.01 to 0.71)], both in favour of the aggressive arm. During the trial, second-line drug treatment was changed in 77.1% of the aggressive arm and 59.0% of the symptomatic arm. There were instances when the rheumatologist should have changed treatment but did not do so, usually because of mild disease activity. The symptomatic arm was associated with higher costs and higher quality-adjusted life-years (QALYs). There was a net cost of £1517 per QALY gained for the symptomatic arm. Overall, the primary economic analysis and sensitivity analyses of the cost and QALY data indicate that symptomatic treatment is likely to be more cost-effective than aggressive treatment in 58–90% of cases.

Conclusions

This trial showed no benefit of aggressive treatment in patients with stable established RA.

However, it was difficult to persuade the rheumatologist and/or the patient to change treatment if the evidence of disease activity was minimal. Patients in the symptomatic arm were able to initiate changes of therapy when their symptoms deteriorated, without frequent hospital assessment. Approximately one-third of current clinic attenders with stable RA could be managed in a shared care setting with annual review by a rheumatologist and regular contact with a rheumatology nurse.

Recommendations for further research

The following areas are suggested for further research.

- A trial to establish whether disease progression can be retarded in patients with mild, stable established RA using biological agents. There is evidence from the TEMPO Trial that the combination of methotrexate and etanercept can halt radiological progression in patients with active established RA. Would the same effect be seen in patients with relatively inactive disease?
- Refinement of the model of shared care that was found to be cost-effective in this trial. For example, is contact with a nurse every 4 months (based in either hospital or primary care) essential? Could the contact be replaced by a telephone call or a postal questionnaire?
- Development of a robust and fail-safe system of disease-modifying anti-rheumatic drug (DMARD) monitoring that is primary care based. If patients are going to be managed in shared care with annual review by a rheumatologist, then the DMARD monitoring should also be able to detect non-attendance for blood tests, should be able to prevent prescriptions from being issued if monitoring is not taking pace, should be able to detect abnormal results and bring them to the prescriber's attention and should protect the nurse or doctor from having to check large numbers of normal results. Such a system should be computerised and link into both GP and hospital systems. The rheumatologist should be available to provide advice in the case of abnormal results.
- Further studies to predict response to DMARDs.
- Further research to establish whether there is a minimum disease activity level below which disease progression does not occur.

Chapter 1
Introduction

The prevalence of rheumatoid arthritis in the UK

Rheumatoid arthritis (RA) is a chronic inflammatory condition which predominantly involves the synovial joints. It affects around 0.81% of the adult population in the UK (i.e. about 386,600 people).[1] The prevalence is 1.16% for women and 0.44% for men with a female:male ratio of 2.7:1. The peak age of onset is 65–74 years for women and ≥ 75 years for men.[2] The median age at onset of symptoms is 55 years.

The natural history of rheumatoid arthritis

The condition usually starts in the small joints of the hands and feet and is characterised by pain and soft tissue swelling. The arthritis later spreads to involve the larger joints. The inflamed synovium erodes the cartilage of the joint, leading to progressive deformities. These erosions, once they have extended to the cortex of the bone, are visible on X-ray. The combination of pain, swelling and deformity leads to physical disability and handicap. RA is also associated with generalised symptoms such as fatigue, malaise and early morning stiffness. Some patients have involvement of other organs such as the skin, lungs, peripheral nerves and heart. RA is also associated with a reduced life expectancy.[3]

Management of rheumatoid arthritis: general principles

There is no cure for RA. The goals of treatment are summarised in *Table 1*. These goals are achieved by a combination of non-pharmacological, pharmacological and surgical interventions.

TABLE 1 *Goals of treatment in RA*

- Decrease and control pain and stiffness
- Reduce or prevent cumulative joint damage
- Maximise physical function
- Improve quality of life

Non-pharmacological treatment begins early in the disease with educating the patient about their disease, the risk of joint damage and the risks and benefits of different treatment modalities.[4] The physiotherapist, occupational therapist, chiropodist and social worker all have an ongoing role in helping the patient to protect their joints from damage and maximise physical function and independence.

Responsibility for prescribing and monitoring drug therapy is usually shared between primary and secondary care. The chief categories of drugs used are as follows.

Analgesics

Most patients with RA require simple analgesics during flares of their disease or if they have mechanical pain resulting from damaged joints.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to relieve the joint pain and stiffness of RA and so to improve function. They do not, however, alter the course of RA. One of the key ways in which NSAIDs work is by inhibiting cyclooxygenase (COX), which is an enzyme involved in the synthesis of pro-inflammatory prostaglandins. COX has two isoforms, COX-1 and COX-2. The COX-2 isoform is the main form involved in the inflammatory process. COX-1 is present on many cells including platelets and cells of the gastric and intestinal mucosa. Most of the older NSAIDs inhibit both COX-1 and COX-2. Inhibition of COX-1 is probably responsible for the high rate of peptic ulcer complications in RA patients on NSAIDs. The newer COX-2-selective NSAIDs have a better gastrointestinal safety profile and are recommended for patients at high risk of these complications.[5] Alternatively, patients on the older NSAIDs may be co-prescribed a proton pump inhibitor or misoprostol. COX-2-selective NSAIDs are substantially more expensive than older NSAIDs. National Institute for Health and Clinical Excellence (NICE) guidelines[5] came into force during the British Rheumatoid Outcome Study Group (BROSG) trial and will have had an impact on the management of these patients.

TABLE 2 *Licensed DMARDs used in the treatment of RA (data from references 4 and 6)*

Drug (abbreviation)	Time to benefit	Usual maintenance dose	Toxicities requiring monitoring
Auranofin (AUR)	4–6 months	3 mg twice daily	Myelosuppression, proteinuria
Azathioprine (AZA)	2–3 months	2.5 mg/kg/day	Myelosuppression, liver toxicity
Ciclosporin (CYP)	6 weeks–3 months	2.5–4 mg/kg/day	Anaemia, renal impairment, hypertension
D-Penicillamine (D-PEN)	3–6 months	250–750 mg daily	Myelosuppression, proteinuria, auto-immune disease
Hydroxychloroquine (HCQ)	3–5 months	200 mg on 5 days per week to 200 mg twice daily	Retinal toxicity
Intramuscular gold (i.m. gold)	3–6 months	20–50 mg every 2–4 weeks	Myelosuppression, proteinuria
Leflunomide[a] (LEF)	1–6 months	20 mg daily	Myelosuppression, liver toxicity, hypertension
Methotrexate (MTX)	6 weeks–3 months	7.5–25 mg weekly p.o., s.c. or i.m.	Myelosuppression, liver toxicity, allergic reactions
Sulfasalazine (SASP)	3 months	1 g two or three times daily	Myelosuppression, liver toxicity

[a] Introduced during the time of the BROSG trial.

Disease-modifying anti-rheumatic drugs

Disease-modifying anti-rheumatic drugs (DMARDs) have been used in the treatment of RA for well over 50 years. They control rather than cure the disease. Most were discovered by 'serendipity' and their mode of action is poorly understood. The DMARDs licensed for use in RA are listed in *Table 2*. The DMARDs have in common a long lag time before any benefit is seen. Many require monitoring with regular blood and/or urine tests, which adds to their cost.

In the past, DMARDs were used as part of the so-called 'pyramid' approach – that is, they were only introduced after it was clear that symptomatic therapy had failed.[6] Now it is recognised that the best approach is to introduce DMARDs early (see the section 'The treatment of early rheumatoid arthritis', p. 3) and to use them continuously and serially – the so-called 'saw-tooth' approach.[7] Many factors influence the choice of DMARD in the individual patient, including co-morbidity, patient preference, likelihood of compliance and previous drug history. Hence the management of RA has become an interactive approach with patients being assessed periodically for evidence of disease activity or progression. Patients with sustained high disease activity for more than 3 months on the maximum dose of their DMARD should have that DMARD changed or move on to combination therapy.[4] A number of combinations of DMARDs have been shown to be beneficial (*Table 3*) and to carry no more toxicity than single DMARD therapy. The role of combination therapy continues to evolve, in particular as to whether combination therapy should be initiated and then some drugs withdrawn once response is established (step-down approach) or whether a second or third DMARD should be added if response to the first DMARD is partial (step-up approach).[8]

Corticosteroids

Low-dose corticosteroids are usually defined as ≤7.5 mg of prednisolone per day in the UK and ≤10 mg of prednisolone per day in the USA. Patients with active RA may experience rapid improvement in their symptoms within a few days of starting low-dose corticosteroids. They are, therefore, very useful when a speedy response is needed and can be used as 'bridging therapy'

TABLE 3 *Combinations of DMARDs shown to be effective in RA*

Initial:	MTX + SASP
	MTX + HCQ
	MTX + SASP + HCQ
	MTX + LEF
Step-up:	CYP + HCQ
	CYP + MTX
	MTX + SASP
	MTX + HCQ
	MTX + HCQ + SASP

when starting a new DMARD. However, the side-effects of long-term steroid use (osteoporosis, hypertension, diabetes, weight gain, cataracts, skin fragility) and the difficulty of getting patients off steroids make most rheumatologists reluctant to prescribe them. There is some evidence that low-dose steroids slow the rate of radiographic progression in early RA[9] but not in established RA. A patient who has active disease in only one or two joints can be helped by injecting the affected joints with intra-articular steroid[4] without a need to change DMARD therapy. An intramuscular bolus injection of a depot steroid preparation may also be used to tide a patient over a flare of RA or while a new DMARD starts to work.[10]

Biological agents

The development of genetically engineered biological agents that selectively block cytokines in the short term represents a major advance in the treatment of RA. However, these agents were only licensed and approved for use in specific circumstances[11] after the BROSG Trial was completed. They had no impact on the conduct of the trial but they do influence the way in which the trial should be interpreted.

The treatment of early rheumatoid arthritis

There is increasing evidence that early and aggressive treatment of RA can radically alter the rate of progression of the disease.[12]

In 1995, Egsmose and colleagues[13] published the 5-year follow-up data from a trial in which 137 patients with early (<2 years) RA were randomised to receive auranofin either immediately or after a delay of 8 months (during which they received oral placebo). The benefit of early treatment was still apparent 5 years later, with respect to both clinical and radiographic outcome.[13] A similar benefit was seen with early HCQ treatment. A total of 119 patients participated in a 9-month placebo controlled trial of HCQ. At 3 years, the early treatment group still had a better outcome.[14]

A third study in which second-line therapy was delayed for up to 1 year found a benefit for early treatment in terms of disability, pain and joint scores, but not X-rays.[15]

A study in The Netherlands showed that patients with recent onset (<1 year) RA managed aggressively (early start of treatment with the aim of reducing C-reactive protein (CRP) by at least 50%) had a better radiological outcome than those managed in a conventional stepwise fashion.[16]

Observational studies give the same message. The data from four European inception cohorts of patients with early RA showed that early and continuous treatment with effective DMARDs results in a more rapid reduction in disease activity and less radiographic damage after 5 years than delayed treatment.[17] Patients who are first seen (and treated) within 5 years of symptom onset have a lower mortality than those who present late.[18] Another observational study from Glasgow stratified 440 patients on intramuscular gold according to their disease duration at the time the gold was started. Only patients with a disease duration of <2 years when the gold was started had long-lasting improvement in their disability scores.[19] The most recent evidence suggests that early aggressive therapy in RA may permanently lower the 'trajectory' of the rate of X-ray progression.[20]

From the point of view of the current trial, the question is: if this 'window of opportunity' to alter the course of RA has been missed, is there still the opportunity to change the course of the disease later by aggressive therapy, albeit less dramatically?

The treatment of established rheumatoid arthritis

There is no firm definition of either 'early' RA or 'established' RA. Early RA is usually taken as being within 2 years or even 1 year of symptom onset. By 5 years from symptom onset, the disease may be regarded as established.[21]

There are few, if any, clinical trials which have recruited patients exclusively with established RA. Anderson and colleagues[22] analysed the primary trial data from 14 randomised controlled trials (RCTs) involving 1435 patients with RA. They found that disease duration had a strong effect on the likelihood of patient response. With any active treatment, the response rate was 53% for patients with <1 year of disease, 43% for 1–2 years, 44% for 2–5 years, 38% for 5–10 years and 35% for >10 years. Nevertheless, it is generally accepted that continued treatment with DMARD is desirable. Analysis of 2888 RA patients followed for an average of 9 years on the ARAMIS database in the USA found up to a 30% reduction in disability with consistent DMARD use.[23] However, many patients have to stop DMARD therapy

because of side-effects or inefficacy. After 5 years, only 20% of patients will still be taking SASP, intramuscular gold or D-PEN.[24] MTX has a somewhat better record of 'survival' with more than 50% of RA patients prescribed MTX still taking it beyond 3 years.[25] There is also evidence that patients with a longer disease duration are more likely to discontinue therapy than patients with early RA.[19]

Setting for the delivery of rheumatology care

Patients enrolled in the BROSG trial had stable RA. Usually such patients are seen at regular intervals in rheumatology outpatient clinics. An RCT from Leeds showed that patients who were seen every 2 months by a rheumatology nurse practitioner had lower levels of pain, greater levels of knowledge about their disease and were more satisfied with their care than patients seen by a consultant rheumatologist.[26] A trial conducted in Bristol randomised 209 RA patients to shared care (no routine hospital review but rapid access on request) or traditional hospital care (routine review every 3–4 months) for 2 years.[27] At the end of the trial, the shared care group reported significantly less pain and reported greater satisfaction with their care. The overall cost for managing the shared care group was £208 per patient per year compared with £313 per patient per year for the traditional care group. In both of these trials, the treatment philosophy was the same in the two arms and neither looked at physical function as an outcome measure.

Costs of rheumatoid arthritis

RA imposes a substantial economic burden on both the patient and society.[28] The only UK cost-of-illness study (using a top-down approach) estimated that the total direct costs of RA in the UK in 1992 were £604 million.[29] The largest single cost was for hospital inpatient stays (£171 million) followed by drugs (including monitoring and toxicity) (£95 million). It is clear that the functional status of the patient is the most consistent and strongest determinant of the costs of RA.[28] It might, therefore, be expected that treatments which slow or halt the functional decline of RA patients would have an effect on the long-term costs of RA.

Relatively few trials in RA have included a cost component (*Table 4*). The closest in design is the study by Hewlett and colleagues[27] which found equivalent outcome in patients in shared care but at reduced cost. The costs were assessed from the perspective of the NHS only.

Rationale for the study

As shown in the section 'The treatment of early rheumatoid arthritis' (p. 3), there is increasing evidence that, to gain maximum benefit, DMARD treatment must be started early in the course of RA. This should ideally be within 3 months of symptom onset. Once the inflammatory process has become chronic and joint erosion has started, the potential for disease modification is less, since some progression is inevitable as a result of mechanical factors. It is agreed that, in early RA, treatment should be aggressive and should aim to keep laboratory tests and clinical signs normal. It is not clear, however, for how long this aggressive treatment philosophy should be continued or whether the goal of suppressing all laboratory and clinical signs of inflammation is achievable in established RA.

Although DMARDs are very effective at controlling the symptoms of RA, most DMARD therapy (with the exception of MTX) has to be discontinued within 24 months of starting owing to either toxicity or inefficacy. The same is true of MTX, but after 5 years rather than 2 years. Since there are a limited number of DMARDs, this means that the patient is beginning to run out of therapeutic options during the second decade of disease. The next layer of drugs (cytotoxics and steroids) is considerably more toxic, especially in the longer term.

There is, therefore, a genuine dilemma regarding how best to treat the patient with established RA. Should the aggressive policy of the first few years be maintained on the premise that the long-term outcome of RA is determined by the cumulative inflammatory burden? Pursuing this policy is likely to necessitate the use of combination therapy and the newer drugs such as CYP and LEF. Or should the approach be more parsimonious as the years go by, saving the remaining DMARDs for as long as possible, on the premise that it becomes increasingly difficult to suppress the inflammatory process and that cumulative damage is largely driven by mechanical factors?

Patients with established RA will have had a variety of previous treatments. This trial, therefore, compared two treatment policies

TABLE 4 *Clinical trials in RA which have included a cost component*

	Country	Study	Total *n*	Active RA patients included	Cost assessment	Description of costs	Economic evaluation	Conclusion
Thompson *et al.*, 1988[30]	USA	Cost-effectiveness of AUR vs placebo	311	Adult onset Unremitting RA >6 months Maintained on basic conservative programmes (rest/physical therapy/ salicylates/ NSAIDs) >3 months	Cost of treatment Additional medical costs Costs averted Cost of transport for outpatient visits Non-medical expenses, e.g. paid/unpaid help Changes in income	E.g. outpatient visits, other medication, aids/devices, surgery, X-rays Extra laboratory utilisation Based on cost of AUR and hospitalisation Cost per mile, cost assigned to time of accompanying people	Bivariate analysis between treatment groups	Point gain of 0.020 HAQ in patients treated with AUR Additional costs of AUR treatment $1160 vs $778 placebo. Non-significant. 2 patients accounted for a greater amount than the difference between groups Difference in total cost (including cost to society) of $855 for AUR. No statistical precision to test for this in most components of this cost
Helewa *et al.*, 1989[31]	Canada	Inpatient vs intensive outpatient treatment	71	Active RA by ACR criteria 2 New York criteria for RA 8 actively inflamed joints Steinbrocker functional class II or III Female aged 18–65 years	Total cost to society Cost to Ministry of Health Cost to hospitals Costs for physician services Costs for patients	25 unit costs variables calculated for each patient based on consumption	Sensitivity analysis to account for differences in arbitrary cost assumptions	Inpatient treatment resulted in a 3-fold increase in health status and 2.5-fold increase in cost

continued

TABLE 4 *Clinical trials in RA which have included a cost component (cont'd)*

	Country	Study	Total *n*	Active RA patients included	Cost assessment	Description of costs	Economic evaluation	Conclusion
Lambert *et al*., 1998[32]	UK	Day care vs inpatient	118	↓ Functional status Active synovitis Need: review of DMARD regimen Need: physiological or psychological treatment	Unit cost/day Total hospital costs Community costs Transport costs	Medical/service/ overheads/opportunity costs Hospital days[a] unit cost Attendance/social support/ Domestic help/non-prescription drug costs Total distance by ambulance or car	Cost minimisation technique Cost effectiveness analysis Equivalence design Total direct costs	Day care equivalent to Inpatient care Day care may be marginally cheaper – 95% CIs overlap Total cost per day care patient £1789 (95% CI £1539 to 2027) compared with £2021 (95% CI £1834 to 2230) per inpatient
Verhoeven *et al*., 1998[33]	The Netherlands	COBRA Trial. Prednisolone, MTX and SASP vs SASP alone	154	Early, active disease ACR criteria Age 18–70 years	Cost of protocol treatment Cost of non-protocol treatment Direct non-medical costs	Drugs and monitoring; treatment and monitoring of adverse effects. Price[a] vol. first 56 weeks NSAIDs, gastro protective drugs, DMARDs and miscellaneous. All other therapeutic visits/treatment Travel; non-NHS medication; extra energy/clothing/help costs; lost time	Direct costs related to QALYs[b] – cost–utility ratios Difference in mean cost – *t*-test	Combined treatment more effective (mean improvement 1.1 vs 0.7, $p < 0.0001$) at equal or lower costs

continued

TABLE 4 *Clinical trials in RA which have included a cost component (cont'd)*

	Country	Study	Total *n*	Active RA patients included	Cost assessment	Description of costs	Economic evaluation	Conclusion
Hewlett *et al.*, 2000[27]	UK	Shared care vs rheumatologist-initiated review	182	Established RA by ACR criteria	Healthcare costs	Visit to health professionals recorded by diary – costs calculated using local NHS Trust figures	Cost per patient per year (total group cost/*n*) Sensitivity analysis, account for inaccurate costing	Equivalent care or small benefit in shared care group at a significant cost reduction ($p < 0.001$) of 33.5%
					Unit cost data	GP visits, District Nursing and hospital transport		
Maetzel *et al.*, 2002[34]	North America	Cost comparison of LEF, MTX and placebo in RA patients	482	Active RA by ACR criteria >6 months ≥18 years old	Utilities	100-point health scale rating and standard gamble measurement	Utility per person year of observation compared using Tukey's studentised range test for pairwise comparisons	Utility measures for MTX and LEF (rating scale only) were significantly different from placebo ($p > 0.05$), but not each other
					Treatment cost	Health resources used not specified by clinical protocol, expenses incurred by patient, loss in patient or caregiver productivity	Bootstrap samples to calculate 95% CI for means	No significant difference between MTX and LEF on annualised total cost of these two groups and placebo on direct costs
					Health-resource utilisation	Number, duration and type of ICU or nursing home stays, emergency treatment, visits to health professionals, diagnostic and laboratory tests and outpatient procedures	Non-parametric bootstrap to compare arithmetic mean costs	LEF significantly more costly than MTX and placebo MTX more economical than LEF owing to acquisition cost of LEF

ACR, American College of Rheumatology; CI, confidence interval; ICU, intensive care unit.
[a] National Pharmacotherapeutical Catalogue, 1996.
[b] Utility calculated using Maastricht Utility Measurement Questionnaire.

(symptomatic versus aggressive therapy) and did not compare one drug with another drug. Treatment algorithms (see Appendix 1) were developed to try to standardise the choice of therapy in a particular circumstance. A new second-line agent, LEF, was launched during the trial. It was possible to incorporate this into the treatment algorithms.

This trial was conceived before the advent of the biologic agents (e.g. anti-tumour necrosis factor α drugs and interleukin-1 receptor antagonists). It was completed before NICE published its report on the use of these agents in RA.[11] Nevertheless, the results of this trial remain relevant in this new era of RA treatment. If the trial shows that the complete suppression of disease activity in established RA is feasible and of benefit using conventional therapy, then this may be a valid alternative to biologic therapy in those patients.

The study recruited patients with stable disease. If both arms of the study have a similar outcome, then this too will have implications for the delivery of care to patients with RA. It will indicate that, in such patients, there is no need for regular aggressive treatment follow-up beyond an annual review, as the patient or a nurse can initiate urgent interim review when symptoms deteriorate.

Aims and hypotheses of the study

The aim of the project was to inform policy and treatment decision-makers about the relative clinical effectiveness, cost-effectiveness and utility of symptomatic and aggressive treatment for established RA.

Specific objectives were to:

1. Assess the clinical outcome over a 3-year period in RA patients managed either using a regime focusing on symptom (i.e. pain and stiffness) control or a more aggressive regime focusing on both symptom control and control of laboratory and clinical indices of joint inflammation.
   (a) The primary outcome measure was physical disability measured using the Health Assessment Questionnaire (HAQ)[35] modified for British use.[36]
   (b) Secondary outcome measures included the OMERACT (Outcome Measures in RA Clinical Trials) core set of outcome measures for use in RA clinical trials (*Table 5*).
2. Assess the costs and outcomes associated with the two treatment arms by examining the following:
   (a) The total direct costs per patient of both types of treatment.
   (b) The impact of both types of treatment on direct costs from the perspectives of the NHS, by sector (e.g. primary or secondary care), social support services and patients.
   (c) The health status and associated utility of both types of treatment.
   (d) The incremental cost-effectiveness ratio (ICER) of aggressive treatment compared with symptomatic treatment.
   (e) The impact on the indirect costs due to changes in the nature of, or time away from, productive activity.

TABLE 5 *OMERACT core set of end-point measures for RA clinical trials*[37]

• Patient's global assessment • Physician's global assessment • Tender joint count • Swollen joint count • Pain score • Acute phase reactants (e.g. ESR/CRP) • Physical disability • X-rays (for trials lasting > 1 year)
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

The null hypotheses of the study were that there would be no difference in:

- the clinical outcomes between the two treatment arms
- the total costs incurred by patients in each of the treatment arms.

Chapter 2
Methods

Study design

The study was designed to compare two treatment policies (symptomatic versus aggressive therapy). The primary outcome was physical function. We initially considered delivering both treatment arms within the hospital setting. However, since it would be impossible to blind the patient or the rheumatologist to the treatment allocation, we felt that it would be impossible to carry out this design without bias. We therefore opted to deliver the symptomatic arm in the primary care setting using a research nurse. This gave the added advantage of further evaluating a model of shared care that is already being advocated in many parts of the country.[27]

The trial was a multicentred, randomised, controlled, observer-blinded study of effectiveness and cost-effectiveness.

Setting

The BROSG is a group of rheumatologists from five centres in England who have a major interest in documenting and influencing the outcome of RA. The five centres are geographically dispersed and include teaching hospitals and large and small district general hospitals and serve urban and rural populations. They are:

The Haywood Hospital	Stoke-on-Trent (large specialist rheumatology hospital serving a predominantly urban population)
King's College Hospital	London (teaching hospital serving a predominantly urban population)
Royal Cornwall Hospital	Truro (large district general hospital serving a predominantly rural population)
Macclesfield District General Hospital	Macclesfield (small district general hospital serving a mixed urban and rural population)
Cannock Chase Hospital	Cannock (small specialist rheumatology unit serving a mixed urban and rural population)

Ethical permission for the trial was obtained from the Research Ethics Committees of each of the five centres.

Sample size

The primary outcome measure was the HAQ score.[37] The HAQ is a validated self-administered questionnaire on physical function. It is widely used in routine practice and research for RA patients. The score ranges from 0 (no disability) to 3 (maximum disability). Published data suggested that the standard deviation (SD) for a cohort of RA patients with 5–20 years' duration of disease would be around 0.76.[38] In order to detect a difference of 0.25 between the groups with a power of 90% and significance of 5%, we would need 199 patients in each treatment group (total 398). We aimed to recruit 480 patients, allowing for 20% loss to follow-up. The HAQ increases in units of 0.125. The minimum clinically important difference in HAQ scores is reported to be 0.22.[39] We chose a difference of 0.25 because it is the nearest increment of HAQ to 0.22.

Training of blinded assessors for joint examinations

Each centre was asked to identify one or more 'blinded assessors'. These were either rheumatologists or rheumatology specialist nurses who were familiar with the technique of standardised joint examination in RA patients. The blinded assessors were not involved in the day-to-day care of the trial participants whom they assessed and were blind to treatment allocation. Their task was to perform an annual examination of the joints for inflammation (tenderness and/or swelling – 28 joints)[40] and damage (deformity, reduced range of movement or surgery – 43 joints).[41] They recorded their findings on a joint examination manikin (Appendix 2). As far as possible, each individual patient was examined by the same blinded assessor throughout the trial.

Before recruitment to the trial began, all the blinded assessors and research nurses were invited to a meeting at King's College Hospital in which

the design and assessment processes of the trial were explained. During this meeting, the joint examination procedure was demonstrated on a patient with RA and the meeting participants were given the opportunity to conduct the assessment themselves and ask questions.

Comparative assessments of joint examinations

The blinded assessors came together to compare their joint examination findings on two occasions. One was held at the Haywood Hospital, Stoke, on 5 December 1997 and the other at Cannock Chase Hospital on 25 March 1999. On each occasion, the host department asked six RA patients with a range of disease duration, disease activity and severity to participate in the exercise. Each patient was on a couch in a separate room. The blinded assessors examined each patient in a predefined order for tender, swollen, deformed and operated joints, recording their findings on the trial manikins (Appendix 2). *Table 6* illustrates how the examinations were set up on both occasions.

At the end of the session, any disagreements recorded were discussed and the 'rules' were further defined. The results were then formally assessed statistically using analysis of variance (ANOVA) (with the examiner, the patient and the order being separate reasons for variation) and intra-class correlation coefficients (ICCs). Separate analyses were conducted for tender, swollen, both tender and swollen, and damaged joint counts.

Results of evaluation of inter-rater reliability for joint examinations

The results in *Table 7* indicate that examiners differed systematically from one another in 1997 for three types of joint count (tender, tender and swollen and deformed/operated) but not for the swollen joint count. In 1999, the examiners differed only for the deformed/operated joint count and by a smaller extent than in 1997, showing the lasting benefit of the training sessions. The ICC was used to assess reliability and the proportion of the overall variance which can be attributed to the examiners. If most of the

TABLE 6 *Study design for inter-rater variability*

	Time					
Rater	**1**	**2**	**3**	**4**	**5**	**6**
1	Patient A	Patient F	Patient E	Patient D	Patient C	Patient B
2	Patient B	Patient A	Patient F	Patient E	Patient D	Patient C
3	Patient C	Patient B	Patient A	Patient F	Patient E	Patient D
4	Patient D	Patient C	Patient B	Patient A	Patient F	Patient E
5	Patient E	Patient D	Patient C	Patient B	Patient A	Patient F
6	Patient F	Patient E	Patient D	Patient C	Patient B	Patient A

TABLE 7 *Results of the test for systematic difference between blinded observers for joint counts in 1997 and 1999*

Year	Parameter	Swollen joint counts	Tender joint counts	Swollen and tender joint counts	Deformed + operated joint counts
1997	ICC	0.12	0.94	0.57	0.49
	Lower 95% CI	0.03	0.83	0.29	0.21
	Proportion of variance due to examiners,	0.18	0.03	0.12	0.21
	F = RMS/EMS	2.5205	5.0253	3.1760	4.9648
	p-Value	0.056	0.003	0.024	0.003
1999	ICC	0.78	0.93	0.89	0.63
	Lower 95% CI	0.56	0.84	0.74	0.35
	Proportion of variance due to examiners,	0.04	0.00	0.01	0.13
	F = RMS/EMS	2.1743	1.0662	1.6058	4.0572
	p-Value	0.089	0.402	0.195	0.008

EMS, error mean square; RMS, rater mean squares.

variance can be attributed to between-patient differences then small, but significant, differences between examiners may be of no consequence. The reliability of the joint counts improved following the first training session and the proportion of variance attributable to examiners was small for tender, swollen and tender and swollen joint counts in 1999.

Study population: inclusion and exclusion criteria

Patients were recruited after giving informed consent. The entry and exclusion criteria (*Table 8*) were applied at the end of the outpatient visit immediately preceding randomisation.

Generalisability

In order to establish the proportion of RA patients attending rheumatology clinics to which the results of the trial would apply, a Clinic Review Week took place in each of the five centres for 1 week in 1997 (17–21 November), 1998 (16–20 November) and 1999 (22–26 November). The aim of the review weeks was to determine the proportion of RA patients who attended clinics that week who would be eligible to enter the BROSG Trial (and therefore to whom the final results could be generalised). A BROSG Clinic Review Week (Patient Form 1) was placed on the front of the notes of each patient attending each clinic during the week, and a BROSG Clinic Review Week (Clinic Form 2) was completed for each clinic for that week. This form covered criteria 3–6 (see *Table 8*) for enrolment in the trial. Specialist RA clinics, general rheumatology and other specialist clinics were all included. Patients who were already recruited to the BROSG Trial who attended during the study week were included in the review. Patients who attended during the clinic review week for more than 1 year were included in the analysis for each year in which they attended.

Baseline assessment

The local research nurse explained the trial to the patient. At baseline, all patients underwent a history and examination in order to determine their eligibility for the trial (see *Table 8*). Eligible patients were asked to give their informed consent. A history of their previous DMARD use, response and side-effects was noted. Information was collected on the OMERACT core set of outcome measures (*Table 5*). The joints were examined for tenderness, swelling and deformity by the blinded assessor and the results recorded on the study manikin (Appendix 2). Evidence of extra-articular disease was noted. Patients had baseline laboratory assessment of disease activity [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)] and a full blood count and biochemical profile. X-rays of the hands and feet were requested. The patient was asked to complete an HAQ, Short Form with 36 Items (SF-36)[43] and EQ-5D[44] and other details for the economic evaluation (see the section 'Statistical analysis', p. 15).

TABLE 8 *Inclusion and exclusion criteria*

Inclusion criteria:
1 Age ≥ 18 years
2 RA (1987 ACR criteria – list method)[42]
3 Current outpatient attender for ≥ 12 months
4 Disease duration ≥ 5 years and < 20 years[a]
5 If on DMARD therapy or steroids, no change in drug or dosage for ≥ 6 months
6 On no more than 7.5 mg of prednisolone or equivalent daily
7 Informed consent
Exclusion criteria:
1 Baseline HAQ score ≥ 2.5
2 Pregnancy at the time of enrolment
3 Systemic complications of rheumatoid disease
4 Current participation in another clinical trial
5 Major co-morbidity – life expectancy of < 5 years owing to other illness such as cancer or severe ischaemic heart disease
[a] The disease duration criterion was later amended so that all patients with a disease duration of ≥ 5 years were eligible.

Randomisation procedure

Randomisation was carried out at the Arthritis Research Campaign (ARC) Epidemiology Unit using a minimisation computer program that was written 'in-house'. The program was written to ensure minimisation on the following variables: age (in three bands: <35, 35–54, ≥55 years), gender, centre and disease duration (in three bands: <10 years, 10–14 years, ≥15 years). Owing to an error in the program, two centres, Macclesfield and Stoke, were pooled.

Following the randomisation visit, the patient's GP was sent a letter explaining the study and their possible role in it. The GP and the patient were only informed of the allocated group once the GP's consent had been obtained.

Interventions: the treatment algorithms

Patients were randomly allocated to one of two treatment groups.

Group 1 (symptomatic treatment: shared care arm)

Group 1 was managed predominantly in the primary care setting. The goal was to control joint pain, stiffness and related symptoms. The following treatment modalities were allowed: analgesics, NSAIDs, intra-articular steroid injections (up to a maximum of one per month), DMARDs (antimalarials, SASP, intramuscular gold, penicillamine, AZA, MTX, LEF) and low-dose steroids (≤7.5 mg daily). Non-drug modalities, such as physiotherapy referral, were also used as the GP felt appropriate. DMARD therapy was monitored using the standard guidelines in current use in the five centres. These guidelines specify the frequency of blood and urine tests and the indications for stopping or reducing the dose of the drug. Routine safety monitoring does not include measuring the ESR or CRP. The patient was encouraged to visit the GP if she/he developed any new or deteriorating symptoms. The GP was provided with an algorithm (abbreviated form, Appendix 1) to guide treatment decisions. The GP was asked to contact the rheumatologist if she/he felt that a change in DMARD was indicated or that there was a need to start steroids. The GP was also free to contact the local rheumatology department for advice or to refer the patient back for a specialist assessment at any time.

In addition, the patient had a contact telephone number for the research nurse. This nurse visited the patient at home once every 4 months. During this visit, she conducted a semi-structured interview to establish whether the patient's symptoms were under adequate control. Any problems identified were dealt with either by herself, or referred on to the GP or the hospital at her discretion. The aim of this treatment arm was to mirror as closely as possible the model for 'shared care' being explored in a number of rheumatology units and to incorporate all the features of current good practice.

Patients in this group were not discharged from hospital. It is accepted that a valuable part of the rheumatologist's role is to screen for the complications of RA[4] and so patients in both groups attended an Annual Review Clinic (see the section 'Definitions of treatment compliance', p. 14).

Group 2 (aggressive therapy: hospital arm)

Group 2 were managed predominantly in the hospital clinic setting. The goal was to control joint pain, stiffness and related symptoms and to suppress clinical **and** laboratory evidence of inflammation. The following treatment modalities were allowed: any of the Group 1 drugs plus, if necessary, CYP, parenteral steroids, medium-dose oral steroids (up to 10 mg daily) and cyclophosphamide (see abbreviated algorithm in Appendix 1). Non-drug modalities such as physiotherapy could also be used, as could hospital admissions. If the GP was monitoring the DMARD before the patient entered the trial, this arrangement remained in place. The patient attended the hospital clinic once every 4 months or more often if clinically indicated. Before or during each clinic visit, the ESR and CRP were measured and the number of inflamed joints was assessed. The clinician aimed to minimise the number of inflamed joints and to keep the CRP below twice the upper limit of normal. Patients also had the contact number of the research nurse who saw them at each clinic visit. She did not, however, visit these patients at home. The aim of this treatment arm was to mirror as closely as possible the model of routine rheumatological practice that would be necessary if tight control of the rheumatological disease process were shown to be desirable. All consultants had a laminated version of the treatment algorithms (Appendix 1). These algorithms were agreed by consensus at the beginning of the trial.

Outcome measures

OMERACT core set

The study used the internationally agreed OMERACT set of core outcome measures for use in all RA clinical trials[37] (*Table 5*). The set includes a patient global assessment, a physician global assessment, a pain score, a tender and a swollen joint count, an index of self-reported physical function (the HAQ), laboratory measures of the acute phase response (ESR and CRP) and (for studies lasting >1 year) X-rays at the beginning and end of the study. The OMERACT core set was collected at the beginning of the study and annually thereafter. The pain score and global assessments were performed using a 10-cm visual analogue scale (VAS). For the physician global assessment, the score ranged from 0 to 100, with 0 indicating that the patient was 'very well' and 100 indicating that the patient was 'very unwell'. The patient's global assessment scale ranged from 0 to 100, with 100 representing 'best imaginable state of health' and 0 representing 'worst imaginable state of health'. A 28-joint tender and swollen joint count[40] was performed by the blinded assessor. All patients were asked to have X-rays of their hands and feet performed at the beginning and end of the study.

Health status and health utility measures

Patients completed the HAQ, SF-36 and EQ-5D 4-monthly under the supervision of the research metrologist. Group 1 patients completed these assessments at home and Group 2 in the clinic. The SF-36 is a generic self-administered assessment of health status [health-related quality of life (HRQoL)][43] which measures physical function, social function, role limitations due to physical problems, role limitations due to emotional problems, mental health, vitality, pain and general health perception. Raw data from the 36-item questionnaire were transformed to a scale ranging from zero (poor health) to 100 (good health) for each domain using the method described in the UK SF-36 analysis and interpretation manual.[45] The EQ-5D is a generic health utility index[44] which covers five aspects of health: mobility, self-care, usual activities, pain, discomfort and anxiety/depression. In addition, patients completed a patient satisfaction questionnaire (Appendix 3). This questionnaire was developed specifically for this study and was not validated separately.

Other outcome measures

The blinded assessor measured the OSRA at the beginning of the study and annually thereafter. The OSRA is an observer-administered instrument which assesses RA disease activity and damage, each on a 0–10 scale. It was developed and validated by three of the applicants.[46] Information was also collected about orthopaedic procedures in the two groups.

Follow-up assessments

All patients were followed 4-monthly either in their homes by the research nurse or in the hospital clinic by the rheumatologist. The measures performed are shown in *Table 9*.

Annual review

Patients in both groups attended the hospital rheumatology clinic once a year to be screened for the complications of RA. The components of this review are shown in *Table 10*. At this review, blood was also taken for full blood count, creatinine and liver function tests unless there were results available within the last 3 months. The ESR and CRP were also checked, but for patients in the

TABLE 9 *Summary of follow-up assessments*

Follow-up	Group 1: shared care (symptomatic) arm	Group 2: hospital (aggressive) arm
4-monthly	HAQ SF-36 EQ-5D Economic data	HAQ SF-36 EQ-5D Economic data ESR, CRP Tender and swollen joint count
Annual	OMERACT core set Assessment of extra-articular features	OMERACT core set Assessment of extra-articular features
Beginning and end of study	X-rays of hands and feet	X-rays of hands and feet

TABLE 10 *Components of annual review of all patients*

Examination	Looking for	Possible action
Joints	Inflammation	Change in treatment
	Deformities/instability	Orthopaedic referral/orthotics
Skin	Ulcers/vasculitis	Change in treatment
Chest	Pleural effusion Basal crepitations Pericardial rub/effusion	Further investigation
Abdomen	Hepatosplenomegaly	Further investigation
Urinalysis	Proteinuria	Further Investigation

shared care arm the results were not made available to the rheumatologist until after the clinic visit. The results of this review were recorded on a standard proforma.

Definitions of treatment compliance

Treatment success was defined as follows:

Symptomatic arm:
1. The patient's symptoms were controlled. Treatment success was judged at each scheduled visit by the research nurse (i.e. 4-monthly throughout the trial). If this goal was not reached, then the patient was advised to consult their GP or given an extra hospital appointment as judged appropriate by the research nurse.

Aggressive treatment arm:
1. The patient's symptoms were controlled.
2. The patient had no actively inflamed (i.e. tender and swollen) joints.
3. The patient's CRP was less than twice the upper limit of the normal range for the patient's hospital.

Treatment success was judged at each scheduled hospital visit (i.e. 4-monthly throughout the trial). If this goal was not achieved, then the hospital consultant should either have changed the patient's medication (according to the treatment algorithm – see Appendix 1) or injected the inflamed joints with steroid. A failure to change the treatment if treatment success was not achieved on two consecutive occasions was defined as 'non-compliance'. This could be non-compliance by the rheumatologist (who did not think the next step on the treatment algorithm could be justified clinically) or non-compliance by the patient (who refused to take the additional medication recommended). The reasons for non-compliance were recorded at the time of the hospital visit.

X-ray reading

A single observer, Dr J Saklatvala, Consultant Musculoskeletal Radiologist at the Staffordshire Rheumatology Centre, read all X-rays. She was blind to treatment allocation.

Each patient's X-rays were read as a set, with the order of the X-rays known as would happen in routine practice. The Larsen Method of RA X-ray scoring was used.[47] The Larsen method gives a global grading for each joint from 0 to 5. The grading is judged by comparison with a standard atlas of radiographs. Zero is normal. Eroded joints score ≥2. The joints read were the wrist joints, metacarpophalangeal (MCP) joints 1–5 and proximal interphalangeal (PIP) joints 1–5 in each hand and metatarsophalangeal (MTP) joints 2–5 in each foot. The wrist joint score is multiplied by five to allow for the fact that this is a larger and more complex joint. The potential range of total Larsen scores is from 0 to 190.

To assess intra-observer variability, Dr Saklatvala read 19 sets of X-rays on two separate occasions some months apart. As described for the assessment of inter-observer variability for the joint examinations (in the section 'Results of evaluation of inter-rater reliability for joint examinations', p. 10), an ANOVA table was produced which included the *F*-statistic. The *F*-statistic for the total Larsen score was 61.12 and for the eroded joint count 20.57. This was statistically significant in both cases, showing that the two sets of X-ray readings did differ from one another. However, the ICC for the Larsen score

was 0.92 and for the eroded joint count 0.97. The proportion of variability due to the examiner was 0.09 and 0.02 (i.e. very low), respectively.

Comparisons were made between the number of eroded joints per patient at baseline and 3-year follow-up and the median Larsen score at baseline and 3-year follow-up for each treatment arm using analysis of covariance (ANCOVA) to adjust for baseline differences between those who completed or did not complete the trial.

Statistical analysis

Basic data analysis

The research nurses in the individual centres entered data from the patient assessments on to an Access database. The data were then combined in a number of tables and analysed using Stata Release 7.[48]

Basic analysis of primary and secondary outcomes was based on the 36-month follow-up assessment. ANCOVA was used to examine the difference in means between the shared care and hospital arms at the end of follow-up with baseline values of the variable, age at randomisation, gender, disease duration and treatment centre as the covariates. 95% CIs are listed for the main outcome measures.

Baseline patient global assessment was found to be predictive of outcome, and so was included in the regression models along with the other baseline covariates. For some outcomes there was evidence of skewness. There was also a floor and ceiling effect for VASs with a restricted range and for joint counts. In such instances, the bootstrap[49] was used to check the robustness of the conclusions to departures from normality.

Missing data and intention-to-treat (ITT)

In a randomised trial involving outpatients, it is inevitable that there will be some missing follow-up data owing to patient withdrawal, loss to follow-up or incomplete data recording. Such non-response may bias the estimate of the treatment effect unless the missing data can be said to be **missing completely at random**. If non-response is predictable from baseline variables, inclusion of predictors of non-response as covariates will reduce bias in estimates where the missing data can be said to be **missing at random**. Whether data are **missing at random** as compared with **informatively missing** is an untestable assumption without additional information. Hence in this analysis data were assumed to be **missing at random**. It was therefore important to maximise data accrual. To this end, great effort was made to achieve as complete a response as possible. For a small group of subjects the primary outcome measure (HAQ) was obtained by telephone at the end of the follow-up period. At the analysis stage a logistic regression model was used to identify predictors of non-response. These were then included as covariates in the models of outcome.

The relationship between response patterns and outcome was also investigated graphically by comparing the profiles for the two treatment groups according to last recorded outcome as suggested by Everitt and Pickles.[50] Subject to the availability of follow-up data, patients were analysed according to the ITT principle.

Longitudinal analysis of primary outcome (HAQ)

Patients completed the HAQ questionnaire at baseline, and approximately 4, 8, 12, 16, 20, 24, 28, 32 and 36 months post-randomisation. Higher HAQ scores represent worse physical function, hence a decline in physical function for a subject is represented by a positive gradient over the follow-up period.

A general linear mixed model applied to longitudinal data[51] was used to compare the two interventions. This may be thought of as fitting lines to each patient, with differences in the intercept and gradient of these lines corresponding to variation between subjects. Variance terms were included in the model to account for between-subject variation in the intercept and the gradient and also fixed covariate effects to account for systematic difference due to intervention, assessment point or patient characteristics.

Post-randomisation values of HAQ were modelled using covariates for **intervention group** (shared care or hospital), **baseline HAQ** (time-point 0), and **assessment** (4, 8, 12, 16, 20, 24, 28, 32, 36 months). Other covariates included age, gender, disease duration and treatment centre (as for the basic analysis). As the **patient's global score** at baseline was again found to be predictive of outcome in a logistic regression analysis of non-response, this was added to the set of baseline covariates.

A difference between the two treatments could be manifest either as different mean levels across all time-points or the mean line for each group could

have a different gradient over time with a positive gradient corresponding to decline in physical function. To test for differences in mean level and gradient between intervention groups, models with and without these terms were compared using a likelihood ratio test.

All models included a random intercept term to model variation between subjects in the average level across all time-points. Some models included a random gradient term to model variation between subjects in the gradient over time.

Normal probability plots were used to check distributional assumptions of the model for residuals of within and between subject variance terms.

Economic evaluation

Patients were issued with a record sheet (diary). They were asked to record the following information:

Direct costs:
- visits and admissions to hospital (not only to the rheumatology clinic)
- visits to the GP
- visits by the research nurse
- visits to other healthcare professionals (e.g. physiotherapy, occupational therapy, chiropody)
- blood tests and where performed
- joint injections
- visits to the pharmacist and the name of the drugs dispensed.

Indirect costs
- time off work
- time and cost of travelling to hospital, GP, etc.
- cost of footwear
- visits to alternative practitioners.

Perspective

The economic evaluation used the perspectives of the NHS, social support services and patients. It assumed that these would represent the main stakeholders and thus approximate a societal perspective. The evaluation was designed to inform policy and treatment decisions in the practice setting of a district general hospital and primary care in the UK. Secondary analysis assessed the extent to which the results were transferable to alternative settings.

The evaluation used self-reported data collected from the patient diaries to estimate the resource use and utilities associated with symptomatic (shared care) and aggressive (hospital) treatment. This was supplemented with unit cost data from published national databases. National average unit costs were used to approximate the relative opportunity costs of different types of resource use and service in routine primary and secondary care. In addition, protocol-driven resource use, such as additional study visits, were excluded from the primary analysis to increase the likely transferability of the results.

The framework of cost-effectiveness analysis was used to compare the costs and outcomes of the two groups and estimate an ICER. Net benefit statistics were calculated and cost-effectiveness acceptability analysis used to estimate the probability that shared care was cost-effective compared with hospital, and the level of uncertainty around that estimate.[52,53] The primary outcomes for the economic analysis were the ICER and associated net benefit statistic.

The evaluation estimated costs and utility for a 3-year period from the day of randomisation to the end of scheduled follow-up. The data were also used to generate measures of annual cost and utility.

Outcomes

Health outcomes

Health outcomes were measured by the health states reported by patients using the EQ-5D at 4-monthly intervals from baseline to 36 months. These health profiles were converted to utility values using the published population utility tariffs for the EQ-5D.[54] It was assumed that the utility values generated by the EQ-5D and population weights would be negatively associated with HAQ scores at each assessment point (i.e. lower utility scores indicating lower health states would be associated with higher HAQ scores indicating poorer health states) and the duration of disease at baseline, and positively associated with the status of the patient in terms of whether they were alive or dead at each assessment point (where dead = 0 and alive = 1). To test these assumptions and provide an indirect measure of the validity of the EQ-5D in this population group, Pearson correlation statistics were calculated to test whether these measures were associated.

Missing data for patients who completed scheduled follow-up but had missing observations were imputed by linear interpolation (value of previous period plus value of next period divided

by two) if observations either side of the missing item were available. If data for the baseline assessment were missing, but all subsequent assessments were completed, then the baseline value was imputed as the first observation carried backwards. If EQ-5D data for the month 36 assessments were missing, but all other data for that assessment and EQ-5D for previous assessments were completed, then the month 36 EQ-5D value was imputed as the last observation carried forward. This approach to missing observations was based on the assumption that time and utility values at each assessment were linearly related to the values in previous and future assessments. The quality-adjusted life-years (QALYs) for this group of patients were estimated as

$$\text{QALY} = \sum[(U_i + U_{i+1})/2]\ (t_{i+1} + t_i)$$

Patients with two or more missing observations at the end of follow-up were treated as representing censored cases. For patients with censored data due to withdrawal or loss to follow-up, missing utility values and time between assessments were imputed from the mean values of those who completed scheduled follow-up or died, for each treatment allocation (i.e. symptomatic or aggressive). Cox regression was used to estimate the survival function and probability of survival at each assessment point, using patient status (alive, dead or withdrawn) and treatment allocation. The QALYs for this group were estimated as

$$\text{QALY}_C = \sum[(U_i + U_{i+1})/2]\ [(S_i + S_{i+1})/2] \times (t_{i+1} + t_i)$$

where U is the utility value, S is the probability of survival and t is the number of days between assessments.

Direct costs

The direct costs were measured as resource use multiplied by the unit cost or price of the resource item. The mean cost (standard deviation) of events was estimated from the trial data and published national cost data. Patients who did not complete scheduled follow-up owing to reasons other than death were treated as censored cases. An average cost for each subsequent assessment period was imputed as the probability of survival (as estimated for the QALY data above) for that assessment period multiplied by the average cost for that assessment period of those patients who were alive in that assessment period. A separate average cost was estimated for the shared care and hospital groups.

The majority of the data on drug use were based on patient self-report. This meant that in many cases (>50%) data on the use of drug therapy were incomplete. In addition, there were inconsistencies in the data that require further investigation. Particular problems were that (1) the dose regimens for each drug were variously reported as total number of tablets per assessment period, number of tablets or dose per day but no information on number of days, dose with no information on number of days or dose per day and (2) patients did not report whether the drug was dispensed at a community or hospital pharmacy or administered directly by a healthcare professional. At this stage, the approach used to address these issues was to estimate the minimum cost of drug therapy for each patient.

The net ingredient cost per prescription for each individual preparation was estimated from prescription cost analysis data for England (http://www.doh.gov.uk/stats/pca2000.htm). If data on the duration of a course of drug therapy were available, they were used to estimate the number of prescriptions and total cost for each preparation for each patient. If no data on duration were available, it was assumed that only a minimum cost of one prescription or course was incurred. The costs of dispensing were not included. It was assumed that the costs of healthcare professionals to administer drug therapy were included in the costs of reported outpatient visits and primary care or other healthcare consultations. It was also assumed that none of the preparations reported by patients was dispensed by the hospital. This may overestimate the costs of drug therapy if drugs were routinely dispensed in the hospital rather than community setting. The potential impact of this latter assumption on relative costs was tested in the sensitivity analysis by excluding the costs of drug therapy from total costs.

The trial included protocol-driven visits, that is, visits required by the design of the study, rather than the provision of a service in routine care circumstances. The majority of patients did not report these visits and so the costs of these were not included in the primary analysis. However, the additional visits could be considered to be part of the interventions tested. For the shared care arm, this comprised an additional home visit by a hospital-based clinical nurse specialist every 4 months and for the hospital treatment arm this comprised an additional visit to the rheumatology outpatient clinic every 4 months. In the sensitivity analysis, the costs of these protocol defined visits

were added to the total costs of each patient if they did not report the specialist nurse home visit (shared care) or a visit to the rheumatology clinic (hospital treatment).

Overall, the approach taken to estimation of the direct costs is likely to give an underestimate of total costs.

Incremental cost-effectiveness ratio (ICER)

The ICER was the primary outcome and estimated as the net cost of shared care (cost of shared care minus the cost of hospital treatment) divided by the net QALY of shared care (QALY of shared care minus the QALY of hospital treatment). It was assumed that there was a statistical association between QALYs and costs for each person, in that poorer health status is associated with increased resource use and cost and lower QALYs. This means that it was appropriate to relate the net costs of the strategies to patient outcomes. In the past, economists have argued that, if there is evidence that there are no statistically significant differences in health outcomes, the economic evaluation can be reduced to a cost minimisation analysis. However, it is also clear that in many cases, even if there are no statistically significant differences in effectiveness or costs, analysis of the cost-effectiveness plane indicates that a proportion of cases are less effective and/or more costly. This means that it was more relevant to calculate ICERs and estimate the uncertainty around the ICER, even if there are no statistically significant differences in mean QALYs and costs between shared care and hospital treatment.

Cost-effectiveness acceptability analysis was used to estimate net benefit statistics and quantify uncertainty.[53,55,56] The cost-effectiveness acceptability analysis estimates the probability that both the incremental QALYs of an intervention (in this case shared care) are ≥ 0 and that the cost per QALY gained by the intervention is less than a maximum ceiling ratio of £50,000 compared with the comparator.[53] The cost-effectiveness acceptability analysis estimated the probability that shared care was cost-effective by revaluing the bootstrapped estimates of incremental cost per QALY using hypothetical values of willingness to pay to gain one QALY. For this analysis, the willingness to pay values that were used to revalue the costs per QALY were in the range from £0 to £50,000 per life-year gained, in increments of £1000. The net benefit statistic is the mean of these revalued cost/QALYs. The cost-effectiveness acceptability curve summarises the information at each willingness to pay value to gain a QALY.

Discounting

The expected costs, outcomes and net benefits were evaluated for 3 years following initiation of treatment in the trial context. This meant that discounting costs and benefits occurring in the future was necessary. Costs and QALYs were discounted at 3.5%, the current social time preference rate recommended by the UK Treasury.

Economic data analysis

Primary analysis

The primary analysis estimated the mean (SD) costs, utility values and QALYs associated with each intervention and the ICER. The primary measure of interest for the economic analysis was the ICER. Accordingly, any differences between allocation groups for utility, QALYs or costs were not tested for statistical significance.
Bootstrapping techniques were used to derive a cost-effectiveness plane of the ICER, net benefit statistic and cost acceptability curve to determine the probability that shared care was cost-effective compared with hospital treatment. The net benefit and cost acceptability analysis used a £0–50,000 range of cost/QALY threshold values, in increments of £1000, to estimate mean net benefit and the probability that shared care was cost-effective.

Sensitivity analyses

A number of assumptions were required to deal with differences in baseline utility values, missing observations and censored cases, for both QALYs and costs. The impact of these assumptions on the results was tested by adjusting the results for the difference in utility values at baseline and by using alternative approaches to imputation of missing data. Discount rates were varied between 0 and 6% in the sensitivity analysis. The impact of including and excluding the costs of drug therapy and protocol-driven visits was also tested in the sensitivity analysis.

Chapter 3
Trial results

Recruitment to the study

A total of 466 patients were recruited to the study over a period of 17 months. The original recruitment period was extended by 5 months, but nevertheless recruitment was 14 less than the target sample size. However, the original sample size calculations had allowed for 20% loss to follow-up and a trial of 466 patients would still have sufficient power providing follow-up did not fall below 18%.

Baseline characteristics and comparison between treatment arms and centres

A total of 233 patients were recruited to the symptomatic and 233 to the aggressive treatment arm. However, owing to a communication error one patient allocated to the symptomatic arm was recorded at the centre as being allocated to the aggressive arm and managed accordingly. For the ITT analysis, this patient was analysed as being in the symptomatic arm. (*Table 11*).

As noted in the section 'Randomisation procedure' (p. 12), an error in the minimisation program resulted in counts from Stoke and Macclesfield being pooled. Consequently, there were proportionately more patients in the aggressive treatment arm at Macclesfield (61%) and fewer in Stoke (47%). However, the groups were well balanced with respect to age, gender and disease duration and across other centres.

There were no significant differences between centres in the proportion of women recruited or in the disease duration (*Table 12*). There were small but significant differences in age, with patients from King's being somewhat older and those from Stoke being younger and having shorter disease duration.

Patient follow-up rates

Seventeen (3.6%) patients died during the 3-year follow-up period, seven from the symptomatic and 10 from the aggressive treatment arm (*Figure 1*).

An additional 50 patients (10.7%) were either lost to follow-up or withdrew from the study. Hence 399 patients (85.6%) completed the study. However, two patients did not complete an HAQ at their final assessment. On the other hand, seven patients who had withdrawn from the study completed a final HAQ by telephone. HAQ data at 3 years were, therefore, available on 404 patients.

In terms of complete follow-up, 440 patients (94.4%) attended for their first-year follow-up, 412 (88.4%) for their first- and second-year follow-up and 399 (85.6%) for their first-, second- and third-year follow-up (*Figure 2*).

Clinical outcome at 3 years

There were data on all the main OMERACT outcome measures for 451 out of 466 patients at baseline and 380 out of 399 patients at follow-up (*Table 13*). In a logistic regression, none of the baseline variables was predictive of membership of the 14% of patients who failed to complete the study.

Primary outcome measure: disability (HAQ)

The HAQ scores in the two treatment arms were similar at baseline (*Table 13*). The median HAQ score deteriorated significantly in both treatment arms during the course of the trial. In the symptomatic arm, the median HAQ rose from 1.30 to 1.50 ($p = 0.035$) and in the aggressive arm, the median HAQ rose from 1.25 to 1.50 ($p = 0.043$) (Mann–Whitney *U*-test).

The ANCOVA analysis of the mean difference between the two treatment arms was not significant (*Table 14*) (symptomatic adjusted mean 1.40; aggressive treatment adjusted mean 1.45; mean difference 0.01; 95% CI –0.07 to 0.09).

Longitudinal analysis of HAQ data

At least one follow-up assessment was obtained for 97% (226/233) of patients in the symptomatic group and 99% (231/233) of patients in the aggressive treatment group (*Table 15*). A logistic regression model was used to identify predictors of non-response. This identified **assessment number**

TABLE 11 *Baseline characteristics by treatment arm*

		Symptomatic arm		Aggressive treatment arm		Overall	
Centre	Cannock	48	(20.6%)	47	(20.2%)	95	(20.4%)
	King's	45	(19.3%)	45	(19.3%)	90	(19.3%)
	Macclesfield	23	(9.9%)	37	(15.9%)	60	(12.9%)
	Stoke	85	(36.5%)	75	(32.2%)	160	(34.3%)
	Truro	32	(13.7%)	29	(12.4%)	61	(13.1%)
	All centres	233	(100%)	233	(100%)	466	(100%)
Sex	Female	159	(68.2%)	158	(67.8%)	317	(68.0%)
Age at randomisation (years)	Mean (SD)	60.4	(11.1)	60.8	(11.3)	60.6	(11.2)
	Median (range)	61.8	(27.1–61.8)	62.5	(30.1–87.4)	62.1	(27.1–87.4)
16–44		23	(9.9%)	24	(10.3%)	47	(10.1%)
45–64		119	(51.1%)	127	(54.5%)	246	(52.8%)
65+		91	(39.1%)	82	(35.2%)	173	(37.1%)
Disease duration (years)	Mean (SD)	12.6	(6.7)	12.5	(6.8)	12.5	(6.7)
	Median (range)	11.0	(5.0–42.0)	11.0	(5.0–46.0)	11	(5.0–46.0)

TABLE 12 *Baseline demographic characteristics by centre*

		Cannock		King's		Macclesfield		Stoke		Truro		Overall		*p*-Value
No. of patients		95		90		60		160		61		466		
Sex	Female (%)	66	(69.5)	66	(73.3)	47	(78.3)	99	(61.9)	39	(63.9)	317	(68.0)	0.114
Age at randomisation (years)	Mean (SD)	59.7	(10.9)	64.6	(11.1)	60.8	(10.7)	58.5	(11.1)	61.4	(11.0)	60.6	(11.2)	
	Median (range)	60.3	(33.8–87.4)	66.1	(30.2–83.3)	62.3	(36.5–79.2)	59.8	(27.1–82.2)	61.0	(38.7–80.5)	62.1	(27.1–87.4)	0.0005
16–44, *N* (%)[a]		8	(8.4%)	5	(5.6)	7	(11.7)	20	(12.5)	7	(11.5)	47	(10.1)	
45–64, *N* (%)[a]		53	(55.8%)	35	(38.9)	30	(50.0)	99	(61.9)	29	(47.5)	246	(52.8)	
65+, *N* (%)[a]		34	(35.8%)	50	(55.6)	23	(38.3)	41	(25.6)	25	(41.0)	173	(37.1)	
Disease duration (years)	Mean (SD)	12.0	(7.0)	13.7	(8.9)	13.0	(6.1)	11.9	(5.5)	12.7	(5.9)	12.5	(6.7)	
	Median (range)	10.0	(5.0–35.0)	11.0	(5.0–46.0)	13.0	(5.0–33.0)	11.0	(5.0–28.0)	11.0	(6.0–31.0)	11	(5.0–46.0)	0.405 K–W

K–W, Krusskal–Wallis.
[a] Within centre.

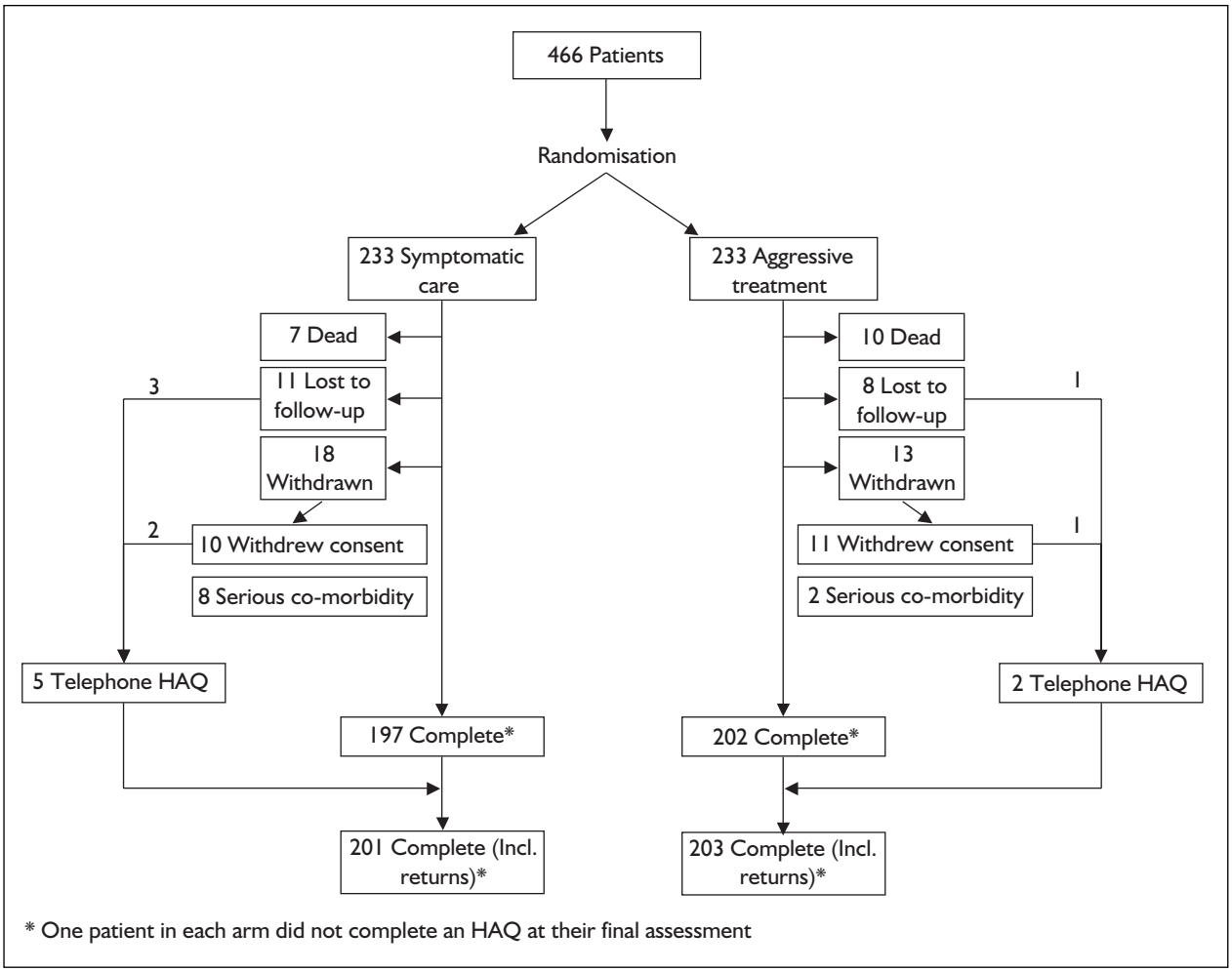

FIGURE 1 *Flowsheet indicating numbers of patients withdrawn, lost to follow-up or died in each arm of the trial*

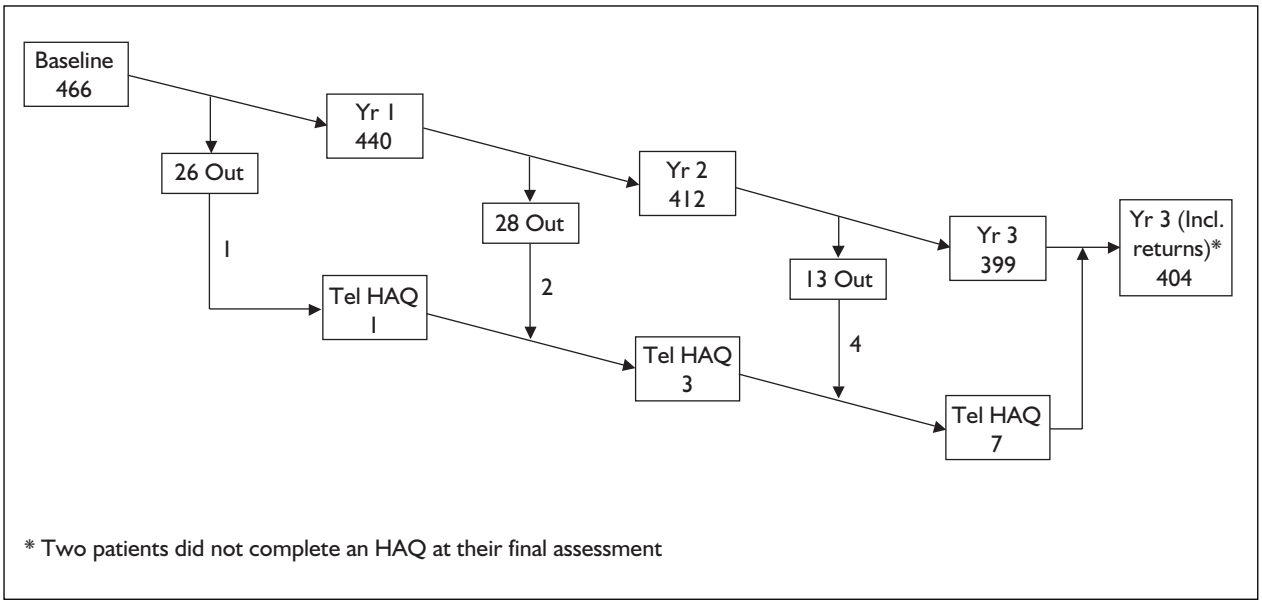

FIGURE 2 *Annual follow-up numbers*

TABLE 13 *Comparison of median values treatment arms for primary and secondary outcome variables of the OMERACT core set at baseline and 3-year follow-up*

		Symptomatic treatment		Aggressive treatment		Overall	
		N	**Median (IQR)**	***N***	**Median (IQR)**	***N***	**Median (IQR)**
HAQ	Baseline	233	1.38 (0.75, 1.75)	233	1.25 (0.88, 1.88)	466	1.38 (0.75, 1.88)
	End of study	202	1.5 (0.88, 2)	204	1.5 (1, 2)	406	1.5 (1, 2)
Patient global (mm)	Baseline	222	64 (50, 76)	229	67 (52, 77)	451	66 (51, 77)
	End of study	195	59 (46, 75)	194	61.5 (48, 75)	389	60 (47, 75)
Physician global (mm)	Baseline	229	20 (8, 34)	231	23 (11, 37)	460	21 (9, 36)
	End of study	188	24.5 (7.5, 41)	195	23 (5, 36)	383	24 (6, 40)
Tender joints	Baseline	229	3 (1, 9)	231	3 (1, 7)	460	3 (1, 7.5)
	End of study	197	2 (1, 8)	200	2 (0, 6)	397	2 (0, 7)
Swollen joints	Baseline	229	3 (1, 7)	232	3 (1, 5.5)	461	3 (1, 6)
	End of study	197	2 (0, 5)	199	2 (0, 4)	396	2 (0, 4.5)
Pain (mm)	Baseline	222	41 (22, 60)	229	46 (23, 60)	451	44 (22, 60)
	End of study	195	47 (31, 63)	194	47 (26, 62)	389	47 (27, 63)
ESR	Baseline	218	18 (9, 32)	221	21 (10, 32)	439	19 (10, 32)
	End of study	182	18 (10, 30)	188	18 (10, 33.5)	370	18 (10, 32)
CRP	Baseline	227	8 (3, 17)	228	8 (3, 19)	455	8 (3, 17)
	End of study	186	8 (5, 16)	194	7 (3, 18)	380	8 (4, 17)
Larsen score	Baseline	199	67 (44, 96)	210	67 (39, 97)	409	67 (42, 96)
	End of study	171	77 (51, 110)	176	75.5 (50.5, 104)	347	76 (51, 109)
Eroded joint count	Baseline	199	11 (6, 16)	210	11 (5, 19)	409	11 (6, 18)
	End of study	171	12 (7,19)	176	13.5 (6.5, 18.5)	347	13 (7, 19)

IQR, interquartile range.

TABLE 14 *ANCOVA analysis of difference between treatment arms for variables of the OMERACT core set and the OSRA*

		Symptomatic arm			Aggressive arm			ANCOVA adjusted mean difference[a]		
		Mean	**SD**	***N***	**Mean**	**SD**	***N***	**Value**	**95% CI**	***p*-Value**
HAQ	Baseline	1.25	0.68	233	1.31	0.72	233			
	36 months	1.40	0.73	202	1.45	0.76	204	0.01	–0.07 to 0.09	0.82
Patient global (mm)	Baseline	62.3	17.9	221	64.7	17.7	230			
	36 months	59.0	20.5	195	59.7	19.7	194	–0.14	–3.93 to 3.66	0.94
Physician global (mm)	Baseline	23.5	18.6	228	25.1	18.0	232			
	36 months	27.7	21.8	188	24.6	20.3	195	–3.76	–7.52 to 0.03	0.045
Tender joint count	Baseline	5.7	6.3	228	4.6	5.4	232			
	36 months	5.0	5.9	197	4.4	5.7	200	0.11	–0.82 to 1.04	0.82
Swollen joint count	Baseline	4.5	4.5	228	3.9	3.8	233			
	36 months	3.2	3.8	197	2.7	2.9	199	–0.36	–0.97 to 0.25	0.25
Pain (mm)	Baseline	41.7	23.1	221	42.6	23.2	230			
	36 months	46.1	23.1	195	44.3	23.6	194	–1.65	–5.82 to 2.83	0.50
ESR (mm/h)	Baseline	22.6	21.9	217	25.0	23.7	222			
	36 months	23.1	17.6	182	24.5	21.9	188	0.68	–2.87 to 4.23	0.71
Larsen score	Baseline	70.6	38.3	199	71.1	41.7	210			
	36 months	78.6	39.4	171	77.9	42.4	176	1.46	–0.68 to 3.60	0.18
Eroded joint count	Baseline	11.75	7.62	199	12.1	8.22	210			
	36 months	13.1	7.8	171	13.4	8.2	176	0.25	–0.36 to 0.85	0.42
OSRA disease activity score	Baseline	2.27	1.79	229	2.27	1.75	231			
	36 months	2.28	1.74	187	1.82	1.63	198	–0.41	–0.71 to –0.01	0.010
OSRA damage score	Baseline	2.23	1.57	229	2.24	1.55	231			
	36 months	2.54	1.70	187	2.43	1.69	198	–0.06	–0.33 to 0.20	0.634

[a] Adjusted for baseline value of variable, age, gender, treatment centre, disease duration and patient global assessment.

TABLE 15 *HAQ by assessment and intervention group*

		Assessment (months)									
		0	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**
Symptomatic	Mean	1.25	1.30	1.29	1.31	1.32	1.34	1.38	1.39	1.4	1.42
	SD	0.68	0.74	0.74	0.72	0.73	0.71	0.71	0.73	0.75	0.72
	N	233	225	220	217	212	210	206	195	190	201
	Response (%)	–	97	94	93	91	90	88	84	82	86
Aggressive treatment	Mean	1.31	1.36	1.41	1.43	1.41	1.46	1.51	1.44	1.47	1.48
	SD	0.72	0.77	0.77	0.77	0.76	0.76	0.75	0.77	1	1
	N	233	228	225	224	210	209	207	196	192	203
	Response (%)	–	98	97	96	90	90	89	84	82	87
Total	Mean	1.28	1.33	1.35	1.37	1.36	1.4	1.44	1.42	1.44	1.45
	SD	0.70	0.75	0.76	0.74	0.74	0.74	0.73	0.75	0.73	0.73
	N	466	453	445	441	422	419	413	391	382	404
	Response (%)	–	97	95	95	91	90	89	84	82	87

as a strong predictor of non-response ($p = 0.0005$), which is not unexpected as non-response will increase as the trial progresses owing to withdrawals, loss to follow-up and deaths. **Age at randomisation** ($p = 0.017$) and the **patient's global score** at randomisation ($p = 0.024$) were also predictors of non-response. The patient's global score was added to the model to reduce bias due to non-response.

There was significant between-subject variation in the gradient (i.e. patients varied in the rate of increase in HAQ score) when models with and without the random gradient term were compared (likelihood ratio $\chi^2_2 = 196.9$, $p < 0.001$). Subsequent analyses therefore included a random gradient term in addition to a random intercept term in the model.

There was no evidence of an interaction between time and treatment group (likelihood ratio $\chi^2_1 = 1.06$, $p = 0.303$). The coefficient of the interaction (*Table 16*) was –0.0012 (95% CI –0.0035 to 0.0011), representing a lower, but statistically insignificant, rate of increase of HAQ over time for the aggressive treatment compared with the symptomatic group after adjustment for baseline covariates.

There was slight evidence of a systematic difference in the mean level across all time-points between the two treatment arms even after adjustment for baseline covariates (likelihood ratio $\chi^2_1 = 3.48$, $p = 0.062$). The coefficient of the treatment covariate (*Table 16*) was 0.054 (95% CI –0.003 to 0.111). Examination of the unadjusted mean profile for the two groups suggests that the symptomatic group had a persistently lower mean score HAQ (*Figure 3*). Across all follow-up time points the unadjusted difference in mean HAQ score is ~0.1. An analysis without adjustment for baseline covariates gives a difference between interventions of 0.098. There was also a slight difference between intervention groups at baseline, but adjustment for baseline in the above analysis has only halved the difference between the two groups.

There was a systematic increase in HAQ score over the trial of 0.051 (95% CI 0.037 to 0.065, $p < 0.0001$) units per year. This gives some interpretation to the observed difference between the two interventions. Hence the difference between the two treatment arms at baseline and throughout the study is the equivalent of approximately 1 year of disease. This difference was only borderline statistically significant ($p = 0.062$).

Baseline HAQ ($p < 0.0001$) and patient global score ($p < 0.0001$) were also strong predictors of HAQ score in the follow-up period (*Table 16*). For each unit increase in HAQ at baseline the patient's HAQ score at follow-up increased by 0.088 (95% CI 0.083 to 0.092) on average.

For each 10 mm increase in patient global score the HAQ score reduced by 0.032 (95% CI 0.015 to 0.049). There was also a suggestion that HAQ score increased with disease duration ($p = 0.05$). For each decade increase in disease duration, the patient's HAQ score increased by 0.043 (95% CI 0.00 to 0.085)

Other core disease activity measures

During the course of the study, the median patient global assessment fell (i.e. deteriorated) slightly in both arms. The median physician global assessment was unchanged in the aggressive treatment arm but rose (i.e. deteriorated) in the symptomatic arm. (The anchor points for the physician and patient global assessments were different – see the section 'OMERACT core set', p. 13.) The median number of tender and of swollen joints fell in both arms. The median pain score rose slightly in both arms. The median ESR and CRP remained the same in the symptomatic arm and fell slightly in the aggressive treatment arm. The difference in outcome between the treatment arms was assessed statistically using ANCOVA. This analysis adjusted for baseline differences and for gender, centre, age, and disease duration. It therefore allows for any differences between the treatment groups which occurred despite the randomisation procedure. All the changes observed were small (*Table 13*, *Figure 4*).

Only one of the ANCOVA analyses was statistically significant (*Table 14*). This was for the physician global assessment (in favour of a better outcome for the aggressive treatment arm). The OSRA disease activity score was also significantly more improved in the hospital arm.

C-reactive protein

One of the goals of the aggressive arm was to keep the CRP level below twice the upper limit of normal. The CRP normal range was different in each centre. The proportion of patients with a raised CRP remained fairly stable in the aggressive treatment arm, but rose and then fell back in the symptomatic arm (*Figure 5*). At the end of the study an 'unsuccessful CRP outcome' was said to have occurred if the CRP was above twice the upper limit for that centre (*Table 17*). The adjusted

TABLE 16 *Coefficients for models examining HAQ with and without treatment–assessment point interaction*

	Model with interaction[a]				Model without interaction[a]			
		95% CI				95% CI		
	Coefficient	**Lower**	**Upper**	**Wald *p***	**Coefficient**	**Lower**	**Upper**	**Wald *p***
Constant	0.286	0.059	0.512	0.013	0.282	0.056	0.509	0.015
Female	–0.024	–0.086	0.038	0.456	–0.024	–0.086	0.038	0.456
Age (years)	0.0021	–0.0005	0.0047	0.115	0.0021	–0.0005	0.0047	0.115
Disease duration (years)	0.0043	0.0000	0.0085	0.050	0.0043	0.0000	0.0085	0.050
HAQ at randomisation	0.875	0.829	0.920	0.000	0.875	0.829	0.920	0.000
Patient global (mm)	–0.003246	–0.00499	–0.00151	0.000	–0.00324	–0.00498	–0.0015	0.000
Centre								
King's[b]	–0.023	–0.114	0.068	0.614	–0.023	–0.114	0.067	0.613
Macc[b]	–0.006	–0.107	0.095	0.908	–0.006	–0.107	0.095	0.910
Stoke[b]	0.081	0.001	0.160	0.046	0.080	0.001	0.159	0.046
Truro[b]	0.031	–0.069	0.132	0.542	0.031	–0.069	0.132	0.542
Assessment (years)	0.058	0.039	0.078	0.000	0.051	0.037	0.065	0.000
Aggressive treatment arm	0.048	–0.010	0.106	0.106	0.054	–0.003	0.111	0.062
Interaction	–0.0012	–0.0035	0.0011	0.303				
Between-subject variance	Estimate	SE			Estimate	SE		
Intercept	0.0899	–0.0066			0.0899	–0.0066		
Gradient	0.00008	–0.00001			0.00008	–0.00001		

SE, standard error.
[a] Both models include between-subject variation in intercept and gradient.
[b] Relative to Cannock.

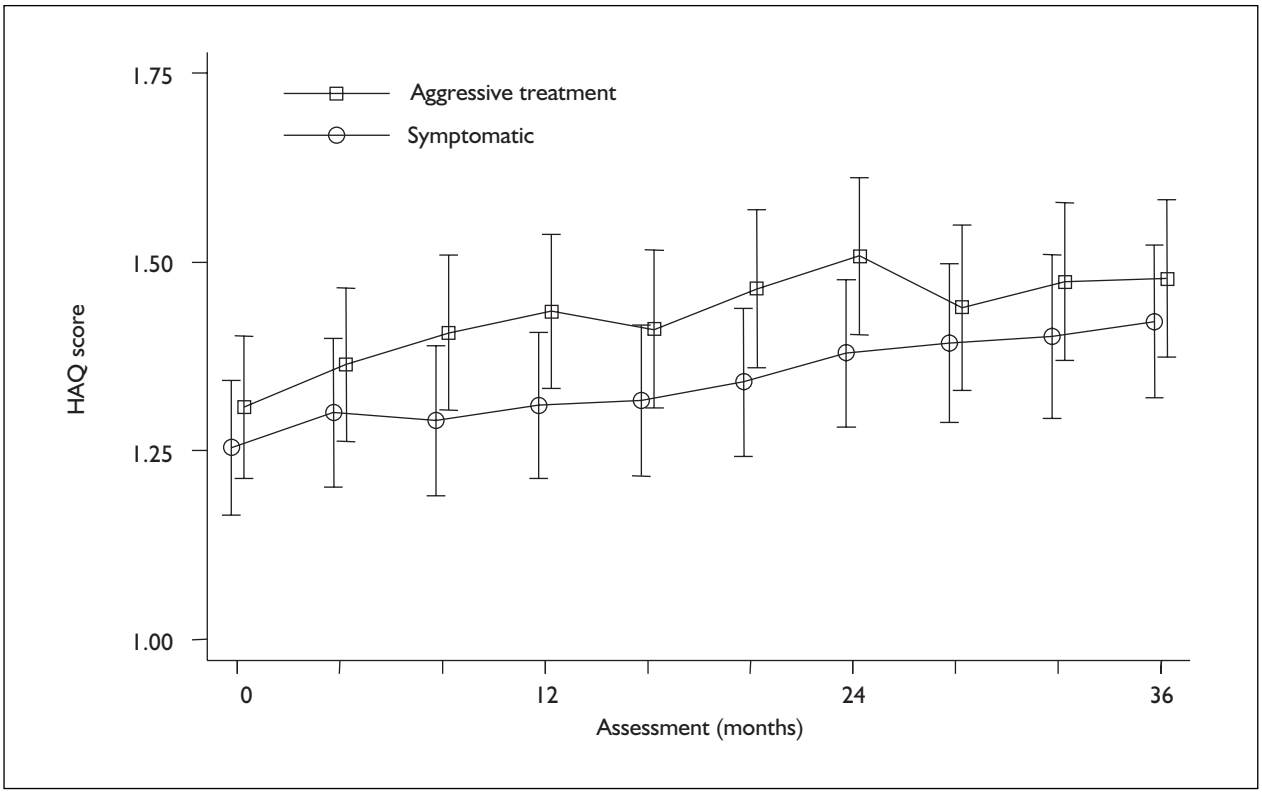

FIGURE 3 *HAQ score by assessment and intervention group*

relative risk (RR) showed that, despite the more aggressive management policy, patients in the hospital arm were as likely to have a raised CRP as those in the symptomatic arm (RR = 1.09, 95% CI 0.79 to 1.50).

Logistic regression showed that patients with a high baseline CRP and longer disease duration were most likely to have a raised CRP at 36 months (*Table 18*).

Radiologic outcome

Total Larsen score

The total Larsen score increased in both arms of the study (*Table 13*). The deterioration was significant in the symptomatic arm ($p = 0.035$) but not in the aggressive arm ($p = 0.093$). The difference was not statistically significant (*Table 14*).

Eroded joint count

The number of eroded joints also increased slightly in both treatment arms (*Table 13*) but the differences were not statistically significant (*Table 14*).

SF-36

During the course of the trial, the mean scores fell (i.e. deteriorated) in the majority of the eight domains in both arms (*Table 19*). The exceptions were the pain and mental health domains in the aggressive treatment arm, in which there was a minimal improvement.

There was no difference between the aggressive treatment and symptomatic care arm mean scores for the eight SF-36 domains at any of the assessment timepoints (*Figure 6*).

Orthopaedic surgery

During the course of the trial, 241 orthopaedic operations were performed in 86 patients in the aggressive treatment arm (36.9%) and 291 operations were performed in 92 patients (39.5%) in the symptomatic care arm. Forty-nine patients in each arm underwent a total joint replacement.

Patient satisfaction

All patients were asked to complete a patient satisfaction questionnaire at baseline and 12, 24 and 36 months (Appendix 3). The questionnaire comprised three questions covering the quality of service received, whether their needs had been met and their satisfaction with the service received. Each question had four responses coded from zero to three, with three being the most satisfied. The questionnaire scores, therefore, had a potential range from 0 to 9. There were no differences between the two arms (*Table 20*).

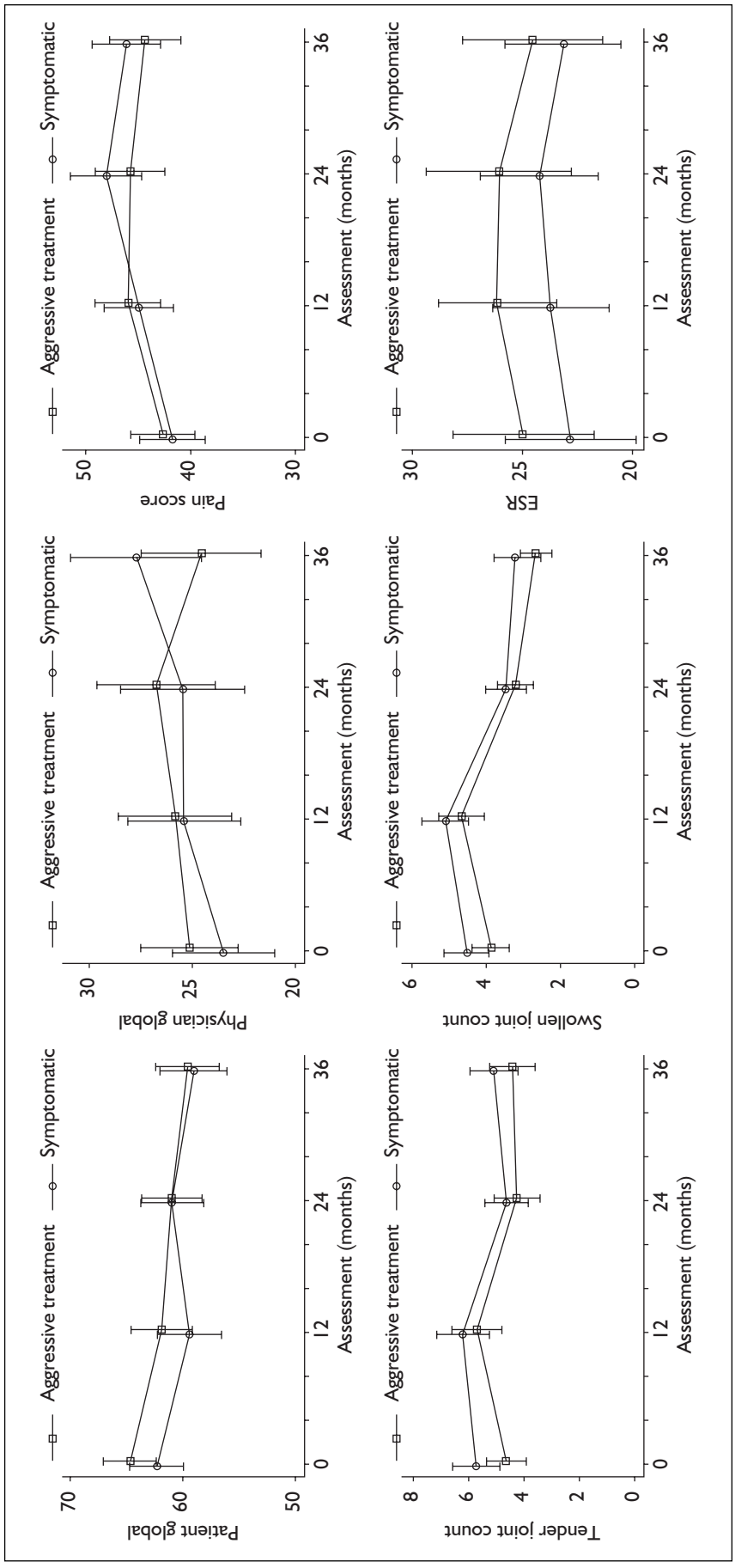

FIGURE 4 *A comparison of the aggressive treatment and symptomatic arms for the main OMERACT measures at 0, 12, 24 and 36 months*

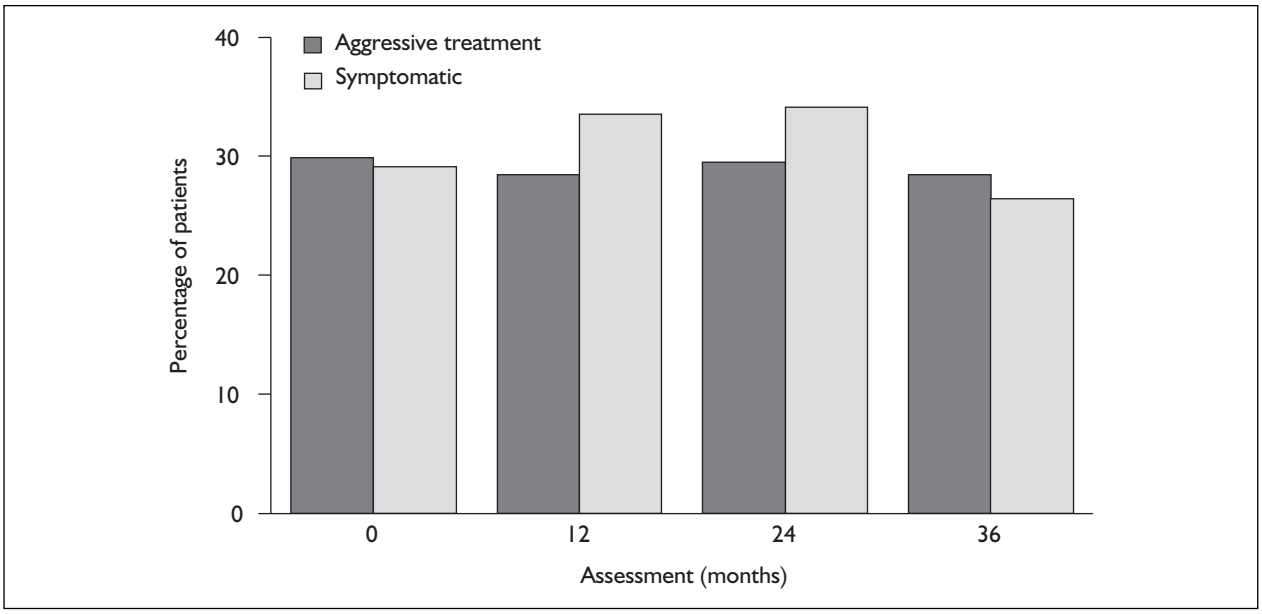

FIGURE 5 *Percentage of patients with CRP above twice the upper limit of normal*

TABLE 17 *Proportion of patients with CRP above twice the upper limit of normal at the end of the study*

Hospital	Twice upper limit of normal CRP (mg/l)	Symptomatic		Aggressive treatment		RR (95% CI)	
		N	%	*N*	%		
Cannock	18	12/42	29.6	14/40	35.0	1.23	(0.65 to 2.32)
Kings	10	9/22	40.9	8/30	26.7	0.65	(0.30 to 1.42)
Macclesfield	16	5/22	22.7	5/30	16.7	0.73	(0.24 to 2.23)
Stoke	18	12/74	16.2	16/71	22.5	1.39	(0.71 to 2.73)
Truro	10	11/26	42.3	12/23	52.2	1.23	(0.68 to 2.24)
Total	–	49/186	26.3	55/194	28.4	1.08	(0.77 to 1.49)
Adjusted[a]	–	–	–	–	–	1.09	(0.79 to 1.50)

[a] Mantel–Haenszel.

TABLE 18 *Predictors of a raised CRP (more than twice the upper limit of normal) at 12 and 36 months (all patients combined)*

	12 months odds ratio	95% CI	*p*-Value	36 months odds ratio	95% CI	*p*-Value
Sex (female)	0.90	0.52 to 1.56	0.719	1.09	0.63 to 1.85	0.765
Age (years)	1.03	1.00 to 1.05	0.027	0.99	0.97 to 1.01	0.418
Disease duration (years)	1.01	0.97 to 1.04	0.684	1.05	1.01 to 1.09	0.016
Baseline CRP > tuln	9.26	5.51 to 15.54	<0.0001	4.89	2.90 to 8.24	<0.0001
Patient global (min)	0.98	0.97 to 1.00	0.024	0.99	0.98 to 1.01	0.339
Centre						
Kings[a]	0.76	0.35 to 1.62	0.474	1.21	0.53 to 2.76	0.649
Macclesfield[a]	0.45	0.17 to 1.19	0.107	0.78	0.31 to 1.93	0.589
Stoke[a]	0.44	0.22 to 0.88	0.019	0.74	0.37 to 1.47	0.395
Truro[a]	1.21	0.54 to 2.68	0.641	2.38	1.06 to 5.34	0.035
Hospital arm	0.65	0.39 to 1.08	0.094	1.06	0.65 to 1.76	0.807

tuln, Twice upper limit of normal.
[a] relative to Cannock.

TABLE 19 *Results of SF-36 at baseline and 3 years*[a]

		Symptomatic						Aggressive treatment						Overall					
		N	Mean	SD	Lower quartile	Upper quartile	Median	*N*	Mean	SD	Lower quartile	Upper quartile	Median	*N*	Mean	SD	Lower quartile	Upper quartile	Median
Physical function	Baseline	228	40.6	25.5	37.2	43.9	40.0	223	43.3	25.0	40.0	46.6	35.0	451	41.9	25.2	39.5	44.2	40.0
	End of study	189	36.4	26.6	32.6	40.2	30.0	196	35.6	27.2	31.8	39.4	30.0	385	36.0	26.8	33.3	38.6	30.0
Role physical	Baseline	225	35.1	40.1	29.8	40.3	25.0	230	33.5	40.5	28.2	38.7	25.0	455	34.2	40.2	30.5	37.9	25.0
	End of study	192	29.3	39.9	23.6	34.9	0.0	200	31.8	40.6	26.1	37.4	0.0	392	30.5	40.2	26.5	34.5	0.0
Role emotional	Baseline	226	67.0	42.3	61.4	72.4	100.0	230	57.7	44.5	51.9	63.4	66.7	456	62.2	43.5	58.2	66.2	100.0
	End of study	195	54.2	46.0	47.7	60.6	66.6	199	51.8	46.1	45.3	58.2	33.3	394	52.9	46.0	48.4	57.5	66.6
Social functioning	Baseline	228	72.3	24.6	69.0	75.4	77.7	230	68.1	27.7	64.5	71.7	66.7	458	70.1	26.2	67.7	72.5	77.7
	End of study	196	65.5	27.7	61.6	69.3	66.6	199	64.8	26.6	61.1	68.5	66.7	395	65.1	27.1	62.4	67.7	66.6
Mental health	Baseline	227	72.2	18.4	69.8	74.5	76.0	228	69.1	17.8	66.7	71.4	70.0	455	70.6	18.1	68.9	72.2	72.0
	End of study	194	70.0	19.5	67.2	72.7	72.0	199	69.6	18.7	67.0	72.2	72.0	393	69.8	19.0	67.9	71.7	72.0
Energy/vitality	Baseline	228	47.3	20.3	44.6	49.9	47.5	229	44.9	20.9	42.2	47.6	45.0	457	46.0	20.6	44.1	47.9	45.0
	End of study	193	42.6	21.6	39.5	45.6	45.0	200	43.9	20.3	41.1	46.7	45.0	393	43.2	20.9	41.1	45.3	45.0
Pain	Baseline	227	49.8	21.1	47.0	52.5	44.4	230	47.1	22.2	44.3	50.0	44.4	457	48.4	21.6	46.5	50.4	44.4
	End of study	196	45.3	20.9	42.3	48.2	44.4	199	48.5	22.9	45.3	51.6	44.4	395	46.8	21.9	44.7	49.0	44.4
General health perception	Baseline	224	51.6	20.3	48.9	54.2	51.0	228	48.6	21.6	45.8	51.4	48.5	452	50.0	20.9	48.1	51.9	50.0
	End of study	191	48.1	21.2	45.0	51.0	47.0	200	46.6	20.9	43.7	49.4	45.0	391	47.2	21.0	45.2	49.3	45.0

[a] Shown with no imputed data.

TABLE 20 *Patient satisfaction scores*

	Symptomatic arm		Aggressive treatment arm		*p*-Value
	Median	IQR	Median	IQR	
Baseline	9	7, 9	8	7, 9	0.25
12 months	9	8, 9	8	7, 9	0.17
24 months	9	7, 9	8	7, 9	0.79
36 months	9	7, 9	8	7, 9	0.24

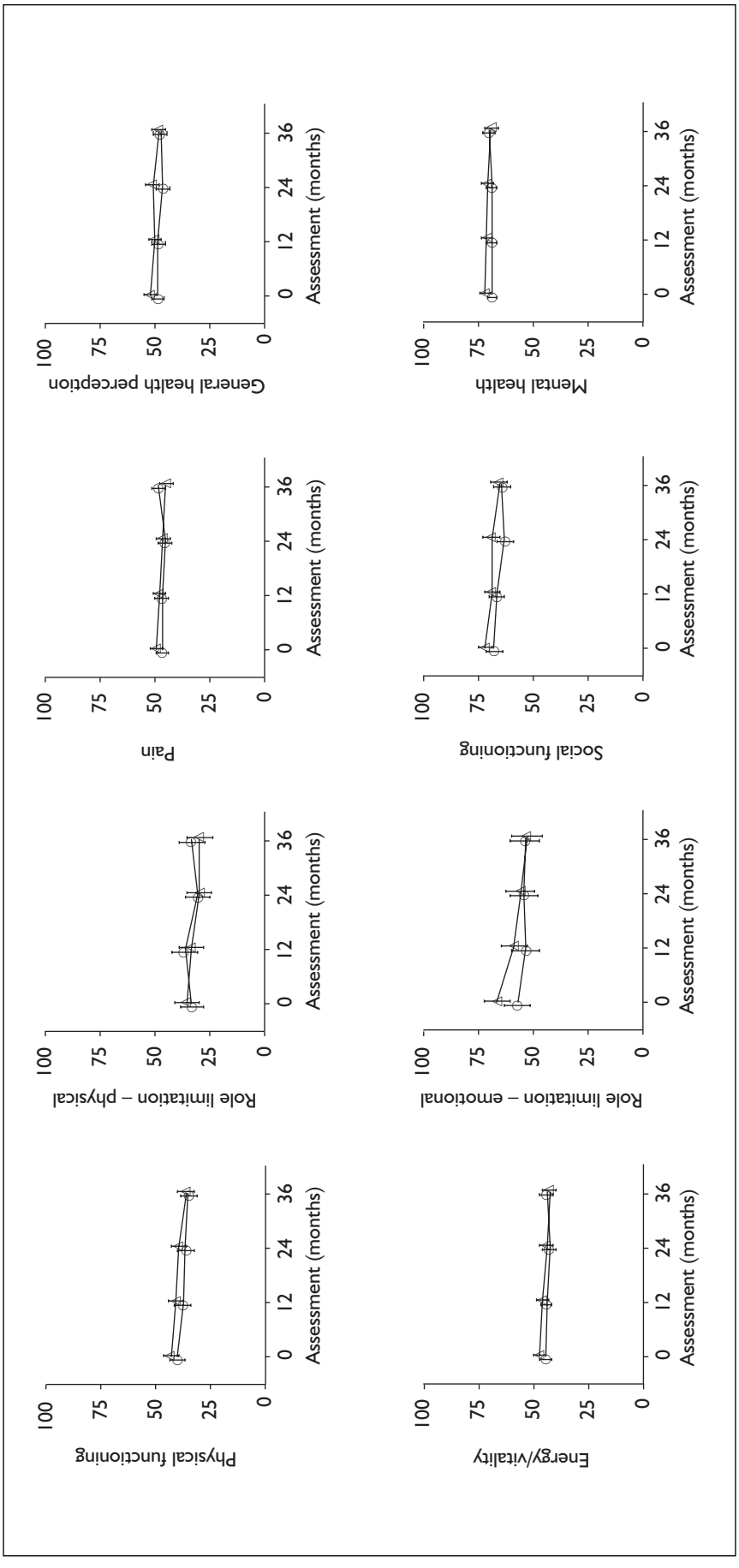

FIGURE 6 *Comparison of aggressive treatment and symptomatic arms of mean SF-36 domains scores. Allocated treatment: (△) symptomatic arm; (○) aggressive treatment arm. Error bars show 95% CI of mean.*

Efficacy analysis

The results described so far show that the two treatment arms had similar outcomes at 3 years with respect to physical disability, radiological damage and disease activity measures. There are a number of possible explanations for this. According to the protocol, patients in the aggressive treatment arm should have had their treatment changed whenever there was evidence of ongoing disease activity and the trial hypothesis was that this would result in improved outcome. There are five possible explanations for the observed results:

1. Patients in the aggressive treatment arm did not have evidence of ongoing activity and so treatment changes were not indicated.
2. Patients in the aggressive treatment arm did have evidence of disease activity but this was not acted on by the physician (or the patient refused to take any additional treatment that was recommended). We have called this 'non-compliance with the protocol'.
3. Patients in the aggressive treatment arm did have evidence of disease activity and their treatment was changed, but this did not result in improved disease activity.
4. Patients in the aggressive treatment arm had evidence of disease activity, their treatment was changed and their condition improved – but this still had no effect on outcome. This would either mean that treatment is ineffective in this group or the goal should have been set higher (e.g. normalising the CRP).
5. Patients in the symptomatic arm had their treatment changed as often as the patients in the hospital arm.

In this section, we explore these possible explanations.

Each time a patient was seen in the aggressive treatment arm the consultant completed a questionnaire which included the four questions in *Table 21*.

If the answer to the first question was 'no' and/or the answer to the second question was 'yes', then the treatment should have been changed. If there were one or two actively inflamed joints but the blood tests were normal, then the physician could inject the inflamed joint(s). If the physician failed to change the treatment (when indicated) on two consecutive occasions, the trial coordinator contacted the physician by telephone or letter to remind them of the protocol. As noted in the section 'Baseline characteristics and comparison between treatment arms and centres' (p. 19), one patient was allocated to the symptomatic arm but was inadvertently managed as being in the aggressive treatment arm. For this analysis, the patient was analysed in the aggressive treatment arm.

During the course of the study, 179/232 (77.1%) of the aggressive treatment arm and 131/234 (55.9%) of the symptomatic arm had some change in their disease suppressive treatment. This includes patients who had the dose of their suppressive treatment changed but does not include those who only had joint injection(s). Patients in the symptomatic arm were no more likely than patients in the aggressive treatment arm to have their treatment changed at the annual review.

There were 96 occasions in 24% patients in whom there was an indication to change DMARD/steroid therapy on two (or more) consecutive occasions and in whom no change was made (not even a joint injection). The reasons given are shown in *Table 22*. Fourteen patients refused to increase their treatment although it was recommended. On 37 occasions in 24 patients, the rheumatologist declined to increase the medication. On most occasions, this was either because the CRP was more than twice the upper limit of normal but there were no actively inflamed joints (24.3%) or

TABLE 21 *Consultant-completed questionnaire at hospital follow-up*

	YES	NO
Is the CRP below twice the upper limit of normal?	☐	☐
Are there any actively inflamed (i.e., tender and swollen) joints?	☐	☐
Have you changed the patient's suppressive treatment?	☐	☐

If not – why not? _____

TABLE 22 *Reasons why DMARD/steroid treatment was not changed when indicated in aggressive treatment patients*

	Occasions	Patients[a]
Patient refused	26	14
Doctor refused[b]	37	24
Treatment had recently been increased	10	7
Other reason for raised CRP	15	13
Other/no reason	4	4
End of study	4	4

[a] The total number of patients exceeds 56 because some patients should have had their treatment changed on more than one occasion.
[b] Usually due to a discrepancy between CRP and joint activity.

TABLE 23 *Treatment success at the final visit (in patients who had been seen on at least seven occasions during the trial)*

	Symptomatic arm	Aggressive treatment arm
Symptom control	123/192 = 64.1%	134/190 = 70.5%
CRP less than twice upper limit of normal	–	127/190 = 77.8%
No actively inflamed joints	–	134/190 = 70.5%
All three of the above	–	93/190 = 48.9%

because the CRP was normal and there were only one or two inflamed joints (54.1% – usually small joints of the hand). There were only two patients who had active disease (both high CRP and inflamed joints) on two (or more) consecutive occasions and in whom further changes were not thought to be justified. There were three patients in whom intercurrent illness precluded an increase in DMARD therapy.

There were only 21 patients (10.4%) who completed the final assessment in the aggressive treatment arm who did not have an indication for a change in treatment at any point in the follow-up period. Hence we see that there was evidence of disease activity in the aggressive treatment arm patients. This was acted on by the physician only half of the time. The main reason for not changing the treatment was a discrepancy between the examination findings and the blood test results.

We defined 'treatment successes' in the symptomatic arm as being those patients who achieved symptom control at their final visit (and who had been seen by the nurse on at least seven occasions during the trial). In the aggressive treatment arm, we defined 'treatment successes' as being those patients who had symptom control and no evidence of clinical disease activity at their final visit (and who had attended for follow-up on at least seven occasions during the trial).

Approximately half the patients in the aggressive treatment arm were treatment successes at the end of the trial (*Table 23*). This was approximately the same proportion that could be defined as treatment successes at each individual visit. Hence, the changes in treatment were not producing lasting benefit to the patient.

Treatment was changed in the symptomatic arm patients more often (in 55.9% of patients) than might have been expected at the beginning of the trial. The patients in this arm of the trial were obviously able to access specialist rheumatology care (either via the nurse or at their annual assessment) and to have their treatment changed when symptom control deteriorated.

Hence it seems that there are three reasons why the outcome was the same in the two arms of the trial: in the aggressive treatment arm treatment was not always changed when it should have been (mainly because disease activity was only mild); when the treatment was changed in the aggressive treatment arm it was not of lasting benefit; and treatment was changed in the symptomatic arm more often than might have been expected.

TABLE 24 *Number of RA patients seen in clinic review week who were eligible for inclusion in BROSG trial*

	1997			1998			1999		
Centre	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**
Cannock	4	1	3	4	1	3	25	3	22
King's	9	1	8	4	0	4	2	0	2
Macclesfield	3	1	2	2	0	2	4	2	2
Stoke	45	16	29	59	22	37	50	18	32
Truro	14	5	9	20	8	11	22	10	12
Total	75	24	51	89	31	57	103	33	70
Eligible (%)		32	68		35	64		32	68

External validity

Comparison between those recruited to the trial and other clinic attenders with RA

A total of 1899 patients attended rheumatology clinics at the five centres' clinics during the three clinic review weeks (see the section 'Generalisability', p. 11) (621 in 1997, 662 in 1998 and 616 in 1999); 762 (40%) were classified as having RA, the proportion with RA was consistent between the years and 267 (35%) of these were eligible for the study.

A similar percentage of patients was eligible for the study from the clinic review weeks in 1997 and 1998; 30% and 33% of RA patients and 12% and 13% of all patients, respectively. In 1999, 103 patients were eligible (42% of the RA patients). There was also an increase across the years in the proportion of all patients eligible for the BROSG study, from 12% in 1997 and 13% in 1998 to 17% in 1999.

There were approximately twice as many eligible female patients from each year compared with male patients (*Table 24*). Hence the BROSG trial results will be generalisable to at least one-third of current rheumatology clinic attenders with RA. In fact, the proportion of all clinic attenders to whom the trial can be generalised will be higher because, in any one week, patients with severe and unstable disease will be over-represented as they are seen more often.

Social deprivation scores

There is some evidence from the literature that patients from more socially deprived areas in the UK have higher HAQ scores.[57,58] We therefore looked at the Townsend deprivation score[59] by centre and for the whole trial (*Figure 7*). Although there was variation from centre to centre, with the patients from King's coming from more socially deprived areas and those from Macclesfield from less socially deprived areas, the profile for the whole study population was very similar to that for the whole of England.

Economic evaluation

The main types of resource use were hospital inpatient and outpatient services, primary and community care services, other health and social care services, prescribed medications and aids and appliances/adaptations. All the resource use data were collected by questionnaires completed by the patients for each assessment period. A number of problems with this method of data collection were identified. First, patients and staff were asked to complete a large number of record forms and assessments, leading to substantial burden in terms of data collection and reporting. A consequence of this was that patients only recorded positive resource use and did not report if they had not used a particular type of service in the preceding 4 months. In addition, not all patients completed all assessment forms at each assessment. Some patients did not attend for all assessments. Patients were asked to record the dates or time period over which services were used. Analysis of this information suggests that some patients recorded the services used in one assessment period in subsequent periods and/or reported resource use over two or more assessment periods in one subsequent period. These factors mean that it is not clear whether absence of reported resource use means that no services were used or that the data are missing. For the primary analysis it was assumed that there were no missing observations due to incomplete records at individual assessment periods (i.e. resource use was assumed to be zero if not recorded). In addition, it was assumed that, if an item of

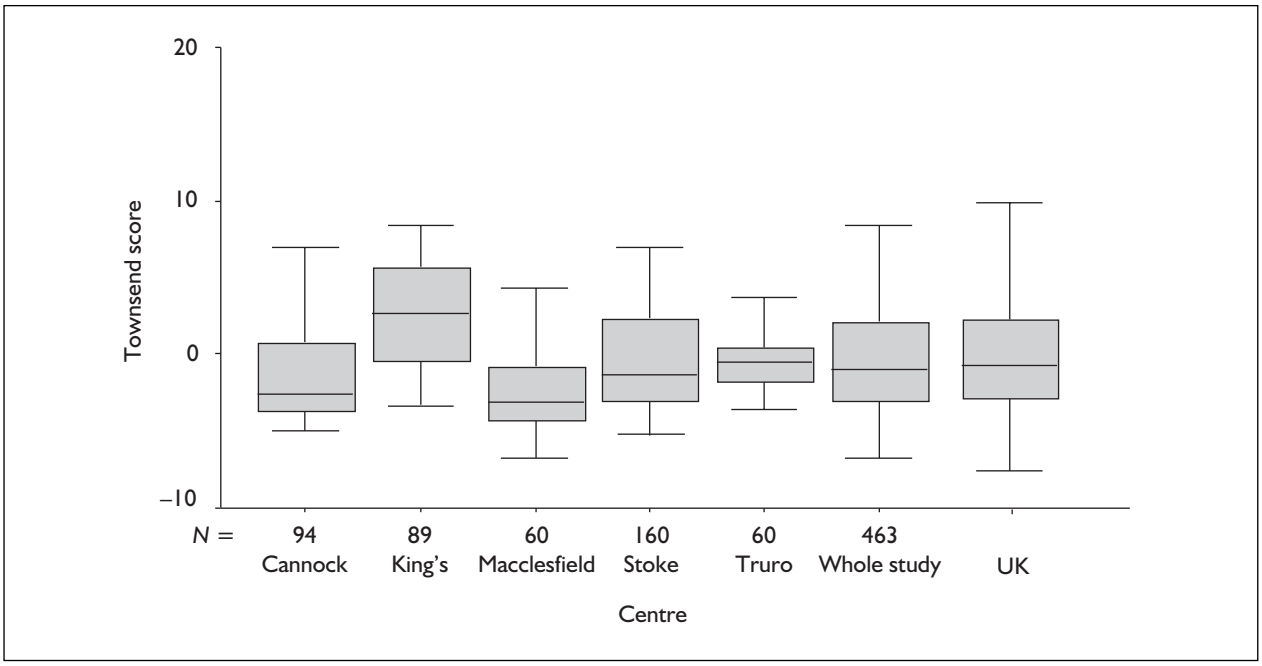

FIGURE 7 *Townsend score (social deprivation for the individual centres, the whole study group and the UK)*

TABLE 25 *Correlation between utility values and measures of health status*

Outcome measure	Utility value		
	Pearson correlation	*p*-Value (2-tailed)	*N*
Utility value	1		4358
HAQ score	–0.587	0.000	4211[a]
Disease duration (years)	–0.036	0.445	460[b]
Status (alive/dead)	0.88	0.000	4358[a]

[a] Number of observations from 466 patients over 10 assessment periods.
[b] Number of patients with baseline utility and duration of disease data.

resource use was recorded in more than one assessment and that the dates of use and description of use matched, the second record was a duplicate and was excluded from the analysis.

Health outcomes

There were statistically significant associations between the utility values generated by the EQ-5D and population weights and the HAQ scores at each assessment and whether the patient was alive or dead at each assessment (*Table 25*). This suggests that the utility measure reflected the relative values of the health states of the trial sample throughout the follow-up period. There was no statistically significant association between utility values generated by the EQ-5D and population weights and the duration of disease at baseline.

Table 26 summarises the level of problems of the trial sample in terms of mobility, self-care, usual activities, pain and anxiety/depression at baseline and 12, 24 and 36 months of follow-up. The majority of patients in both shared care (symptomatic) and hospital (aggressive treatment) groups had some or severe problems with mobility, self-care, usual activities and pain at baseline and over the 3 years of follow-up. No statistical analysis of differences between groups was conducted.

Throughout this section of the report, we refer to the symptomatic care as the shared care arm as most resource use was in primary care; and the aggressive treatment arm as the hospital arm as most resource use was initiated by secondary care.

TABLE 26 *EQ-5D health status scores in the two treatment arms*

Level of problem	Mobility		Self-care		Usual activities		Pain		Anxiety/ depression	
	SC (%)	HT (%)	SC (%)	HT (%)	SC (%)	HT (%)	SC (%)	HT (%)	SC (%)	HT (%)
Baseline										
None	23	21	46	47	22	22	7	6	67	63
Some	75	77	52	52	73	72	85	83	30	34
Severe	0	0	0	<1	3	5	6	11	1	1
Month 12										
None	23	23	46	47	22	22	7	6	67	63
Some	69	72	52	52	73	72	85	83	30	34
Severe	0	0	0	<1	3	5	6	11	1	1
Month 24										
None	22	21	37	30	18	20	5	6	52	53
Some	66	67	50	57	66	60	72	69	34	32
Severe	0	0	0	0	4	7	10	12	2	2
Month 36										
None	16	21	32	29	14	17	4	7	51	50
Some	69	65	52	56	65	64	70	68	33	32
Severe	0	0	<1	0	6	5	10	11	1	3

HT, hospital treatment; SC, shared care.

TABLE 27 *EQ-5D utility values by assessment period: population weights*

Assessment period	Shared care			Hospital treatment		
	N = 233	Mean	SD (range)	*N* = 233	Mean	SD (range)
Baseline	228	0.60	0.21 (–0.18 to 1)	232	0.57	0.23 (–0.18 to 1)
Month 4	225	0.58	0.26 (–0.24 to 1)	232	0.55	0.26 (–0.29 to 1)
Month 8	222	0.58	0.27 (–0.29 to 1)	230	0.54	0.29 (–0.29 to 1)
Month 12	217	0.57	0.25 (–0.18 to 1)	226	0.54	0.27 (–0.28 to 1)
Month 16	212	0.59	0.24 (–0.11 to 1)	218	0.56	0.26 (–0.24 to 1)
Month 20	213	0.60	0.25 (–0.17 to 1)	213	0.54	0.28 (–0.18 to 1)
Month 24	207	0.56	0.25 (–0.24 to 1)	211	0.54	0.27 (–0.24 to 1)
Month 28	203	0.56	0.26 (–0.24 to 1)	207	0.56	0.26 (–0.24 to 1)
Month 32	200	0.57	0.27 (–0.25 to 1)	202	0.55	0.26 (–0.25 to 1)
Month 36	195	0.57	0.24 (–0.13 to 1)	199	0.54	0.27 (–0.18 to 1)

Table 27 and *Figure 8* present patient utility values by allocation group and assessment period for those people who completed the scheduled follow-up or died, and exclude imputed values for patients with censored data. These indicate that the mean utility values displayed a downward trend over the follow-up period. However, the utility values at each assessment period were similar for the two groups.

The range of utility values indicates that some patients were in health states considered worse than death at each of the assessment periods and also that some patients were in full health. *Figure 9* illustrates the proportion of people in health states valued at worse than death (<0) and those at or near full health. The percentage of people in states valued at worse than death showed an upward trend over the follow-up period. Conversely, the proportion of people in states at or near full health showed a downward trend over the follow-up period. These results are consistent with the rise in HAQ scores seen in the clinical evaluation.

Table 28 presents the QALYs at 12, 24 and 36 months (including imputed values for missing observations and censored cases).

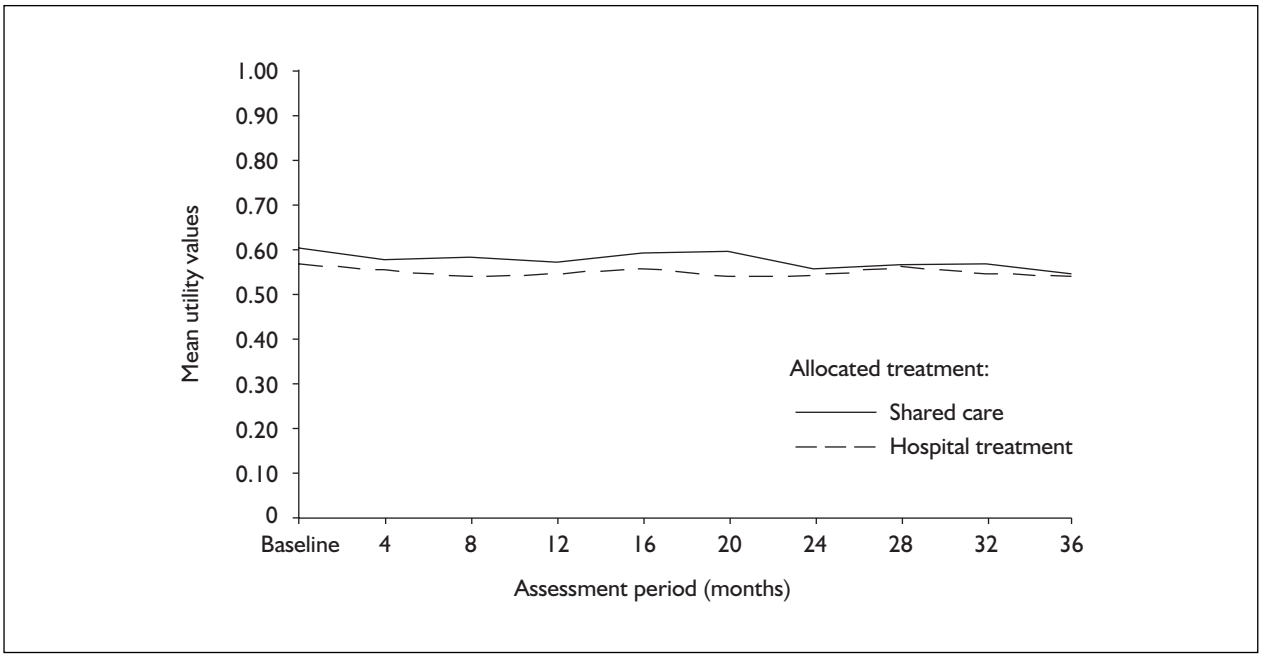

FIGURE 8 *Utility values by assessment period: population weights*

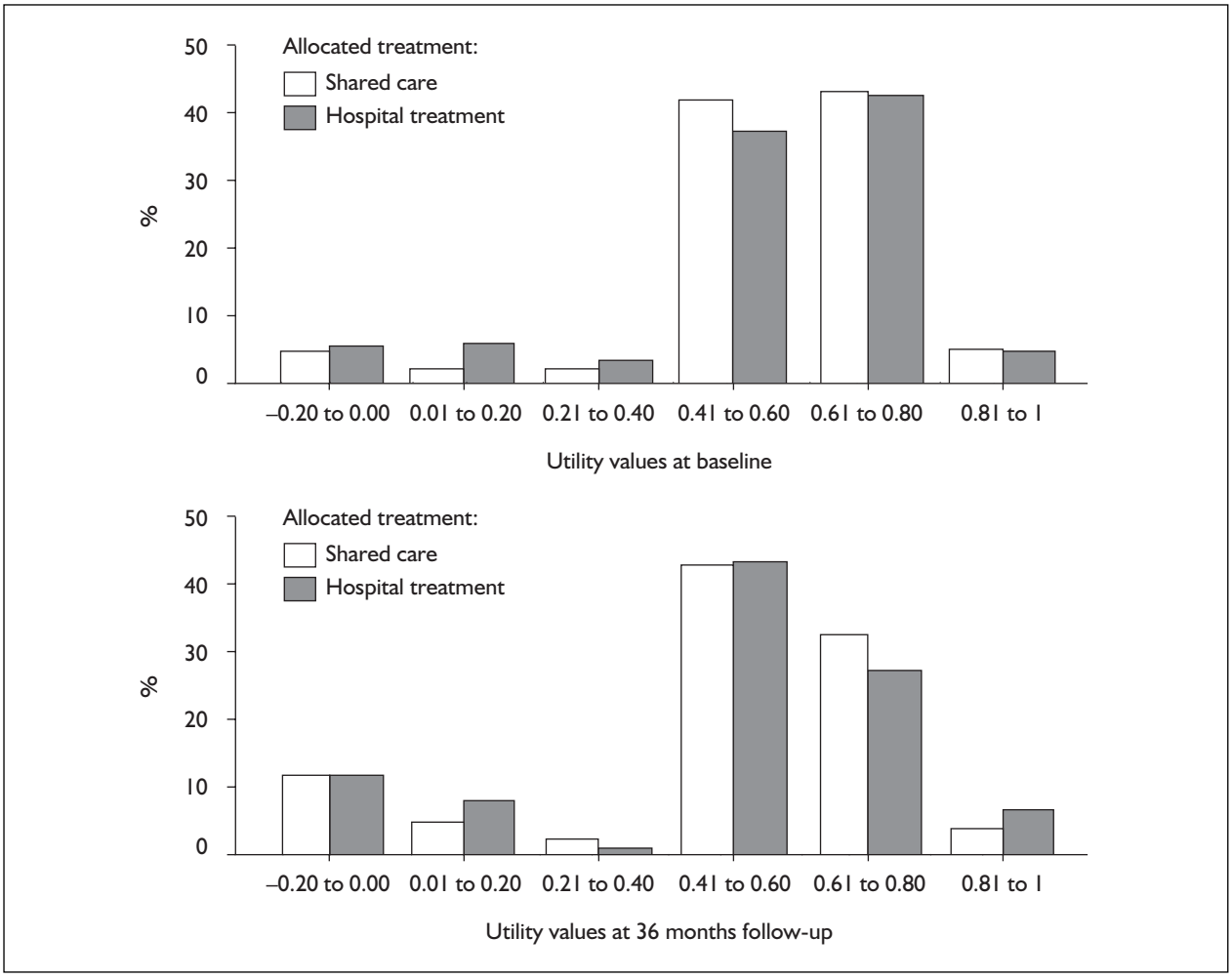

FIGURE 9 *Distribution of utility values at baseline and month 36*

TABLE 28 *Annual QALYs by treatment group at 12, 24 and 36 months, discounted at 3.5%*

Assessment period	Shared care (*N* = 233)	Hospital treatment (*N* = 233)
0–12 months		
Mean	0.60	0.57
SD	0.22	0.23
95% CI	0.57 to 0.63	0.54 to 0.60
12–24 months		
Mean	0.55	0.53
SD	0.20	0.23
95% CI	0.53 to 0.58	0.50 to 0.56
24–36 months		
Mean	0.52	0.50
SD	0.21	0.23
95% CI	0.49 to 0.54	0.47 to 0.53
0–36 months		
Mean	1.67	1.60
SD	0.56	0.60
95% CI	1.6 to 1.74	1.52 to 1.67

The results indicate that the shared care and hospital treatment group are associated with a similar level of QALYs at each time-point and have a similar distribution of total QALYs at 36 months.

Direct costs

Table 29 gives details of the average resource use and unit costs per item for those patients who reported the use of specific categories of health and social care. Full details of resource use and unit costs by individual types of service are given in Appendix 4. Similar numbers of patients in each allocation group reported using each of the categories of healthcare, with similar intensity and cost (*Table 29*).

Table 30 gives details of the undiscounted mean total cost per person for each of the allocation groups by category of cost. This cost does not include imputed cost estimates for missing observations or for people who did not complete scheduled follow-up. These data indicate that, over the 3 years of the trial, the costs of the shared care and hospital treatment groups were similar. However, the costs did not include the impact of people who did not complete the trial, which are shown in *Table 31*. The shared care patients incurred more costs for inpatient care and visits to primary care. The hospital arm incurred more costs for outpatient care and aids and appliances.

Table 31 summarises the cost data when discounted at 3.5% and imputed values were included for censored cases. As noted earlier, no imputation of costs was conducted for people with missing observations before completion of scheduled follow-up or withdrawal from the trial. The costs at each time-point were similar between the two groups. The data were characterised by large SDs and range for each group.

ICER

Table 32 presents the incremental QALYs, costs, ICER and net benefit statistic for shared care compared with hospital treatment. This indicates that shared care is associated with a trend towards higher QALYs and higher costs than hospital treatment. These differences result in a net cost of £1517 per QALY gained by shared care. The mean net benefit is positive, indicating that when the QALY gain is revalued over a threshold range of £0–£50,000 per QALY gained, the net value of the QALYs associated with shared care is higher than the net costs of shared care.

TABLE 29 *Average resource use and unit costs per patient reporting use of services*

Type of resource use	Shared care					Hospital treatment				
	N	Mean quantity	SD	Mean unit cost	SD	*N*	Mean quantity	SD	Mean unit cost	SD
Inpatient admissions (number)	91	2	1	–	–	90	2	1	–	–
Inpatient admissions (length of stay, days)	91	14	20	279	72	90	10	21	304	130
Outpatient visits	220	14	14	80	7	230	18	15	81	6
Primary care visits	221	21	18	26	13	225	19	19	24	13
Other healthcare professionals	175	9	9	15	11	184	9	11	14	6
Drug therapy	225	11	6	14	4	233	11	5	14	5
Aids and adaptations	124	3	2	55	163	122	4	2	55	100

TABLE 30 *Undiscounted cost of healthcare services in £ (2001), no imputation of costs for censored cases*

Type of service	Shared care			Hospital treatment		
	N	Mean	SD	*N*	Mean	SD
Inpatient care						
Month 0–12	226	556	2440	231	525	2788
Month 12–24	219	396	1470	222	457	3126
Month 24–36	211	665	2791	214	308	1206
Month 0–36	224	1575	4198	229	1261	4486
Outpatient care						
Month 0–12	226	281	332	231	385	373
Month 12–24	219	338	472	222	499	481
Month 24–36	211	416	625	214	544	562
Month 0–36	226	997	1148	231	1369	1203
Primary care						
Month 0–12	226	198	180	231	161	161
Month 12–24	219	166	194	222	132	177
Month 24–36	211	154	192	214	116	156
Month 0–36	226	502	431	231	395	337
Other healthcare						
Month 0–12	226	42	110	231	36	68
Month 12–24	219	27	60	222	35	136
Month 24–36	211	31	86	214	21	47
Month 0–36	225	98	158	230	90	165
Drug therapy						
Month 0–12	226	342	322	231	344	279
Month 12–24	219	576	500	222	539	430
Month 24–36	211	616	523	214	583	433
Month 0–36	226	1475	1170	231	1403	966
Aids and appliances						
Month 0–12	226	21	72	231	27	120
Month 12–24	219	22	154	222	29	178
Month 24–36	211	27	124	214	23	81
Month 0–36	224	68	204	230	76	248
Total cost						
Month 0–12	226	1440	2693	231	1478	2865
Month 12–24	219	1525	1875	222	1690	3435
Month 24–36	211	1909	3134	214	1596	1644
Month 0–36	226	4700	5137	231	4581	5297

The 95% CIs on the incremental QALYs, costs and the net benefit statistic cross zero, suggesting that shared care is not likely to be cost-effective in all cases. *Figure 10* presents the bootstrapped net QALY and cost values of shared care in a cost-effectiveness plane. This indicates that in a proportion of cases, patients receiving shared care will have lower QALYs than hospital care at lower or higher cost.

The probability that shared care is cost-effective is 0.89 (*Table 32*). The probability that shared care is cost-effective at different ceiling or threshold values of cost per QALY is illustrated by the cost acceptability curve in *Figure 11*. This indicates that, if decision-makers are prepared to pay £2000 or more to gain one QALY, then shared care will be cost effective in 50% of cases. If decision-makers are prepared to pay £13,000 or more to gain one QALY, then shared care will be cost-effective in over 80% of cases.

Sensitivity analyses

Tables 33 and *34* give the results of the sensitivity analysis. The results of the alternative analyses are discounted at the rate used in the primary analysis (3.5%). The results of the analyses to test the impact of the discount rate include the imputed values for missing observations and censored cases used in the primary analysis. The choice of discount rates was based on the ranges indicated by the UK Treasury rates specified for 2002.

TABLE 31 *Summary of discounted costs including imputed values for censored cases*

Assessment period	Shared care (*N* = 233)	Hospital treatment (*N* = 233)
0–12 months		
Mean	1409	1429
SD	2558	2756
95% CI	1079 to 1739	1073 to 1784
Range	0–32,262	14–37,224
12–24 months		
Mean	1423	1577
SD	1697	3130
95% CI	1204 to 1642	1173 to 1981
Range	0–12,473	0–40,469
24–36 months		
Mean	1711	1432
SD	2689	1421
95% CI	1364 to 2059	1248 to 1615
Range	0–26,329	0–12,745
0–36 months		
Mean	4543	4437
SD	4695	4900
95% CI	3937 to 5149	3805 to 5070
Range	0–35,384	0–46,278

TABLE 32 *Incremental QALYs, costs and relative cost-effectiveness of shared care compared with hospital treatment*

	Incremental QALYs	Incremental costs	ICER	Net benefit[a]
Mean	0.07	106	1517	3508
Standard error	0.05	445	–	2896 (SD)
95% CI[b]	–0.03 to 0.18	–768 to 979	–	–1770 to 9482
Range	–	–	–15,920,347 to 843,025	–5650 to 13,705
pCE[c]	–	–	–	0.89

[a] Bootstrap values when the incremental QALYs are revalued using ceiling thresholds between £0 and £50,000 per QALY.
[b] The 2.5 and 97.5 percentiles of the bootstrap values for the ICER.
[c] The probability that both the incremental QALYs of shared care are ≥ 0 **and** that the cost per QALY gained by shared care was less than a maximum ceiling ratio of £50,000 compared with hospital treatment.

There were differences in utility values between the groups at baseline. Although small, these may be important given the relatively small differences in overall QALYs between the groups. The impact of the baseline differences was tested in two sensitivity analyses (Appendix 5). In one, the QALYs were adjusted for the baseline differences in QALYs. In the second, both QALYs and costs were adjusted. A general linear main effects regression model was used, using treatment and baseline utility values as covariates to estimate the differences between the groups and 95% CIs on the difference. These data were then bootstrapped to generate the net benefit statistic and cost-effectiveness acceptability analysis.

In addition, the sensitivity analysis included estimation of the costs to include a standard value for the additional cost of the trial protocol visits, that is, visits determined by the design of the trial rather than the provision of services in routine care. The protocol-driven visits were excluded from the primary analysis. The sensitivity analysis tests the impact on the results of relaxing the assumption that the protocol induced visits would not be used in routine practice. The majority of patients did not report whether they had used these visits. For the shared care arm, this was costed as an additional £67 per month for a 1-hour home visit by a hospital-based clinical nurse specialist every 4 months[70] and for the

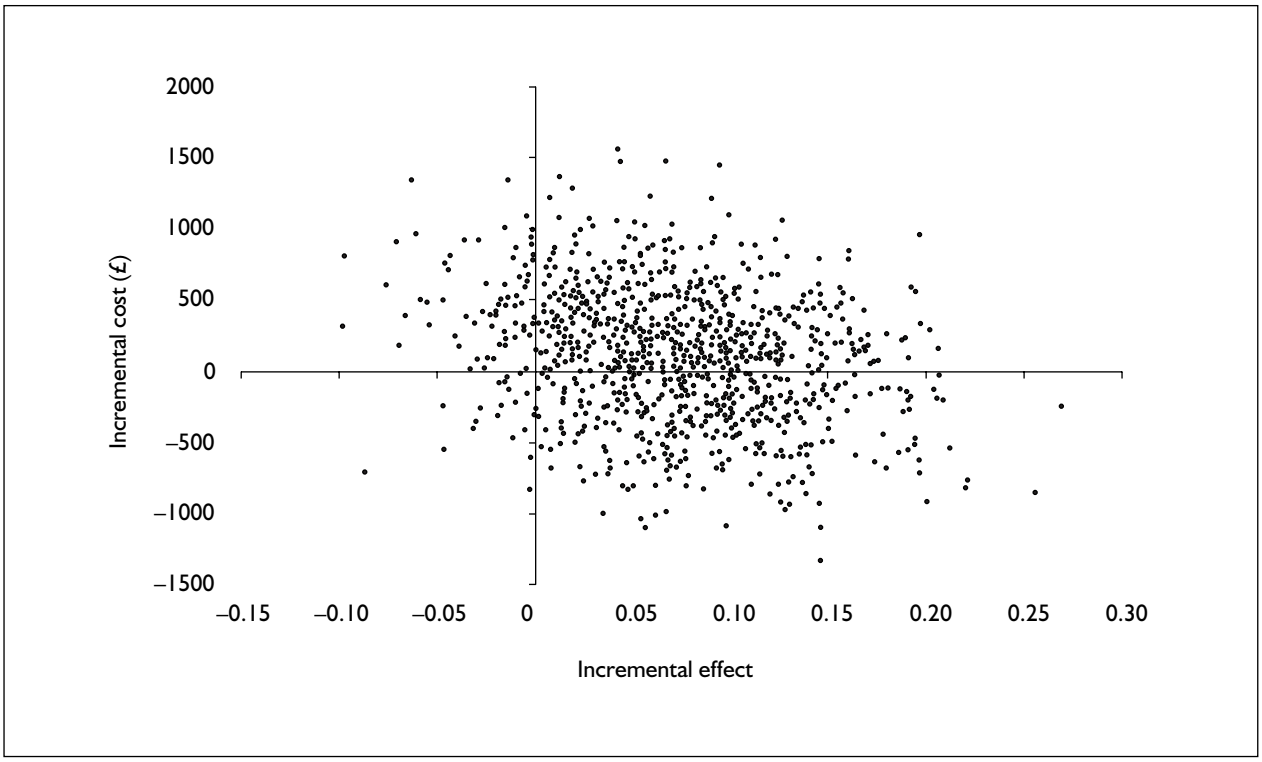

FIGURE 10 *Cost-effectiveness plane of the incremental cost and QALY of shared care versus hospital care*

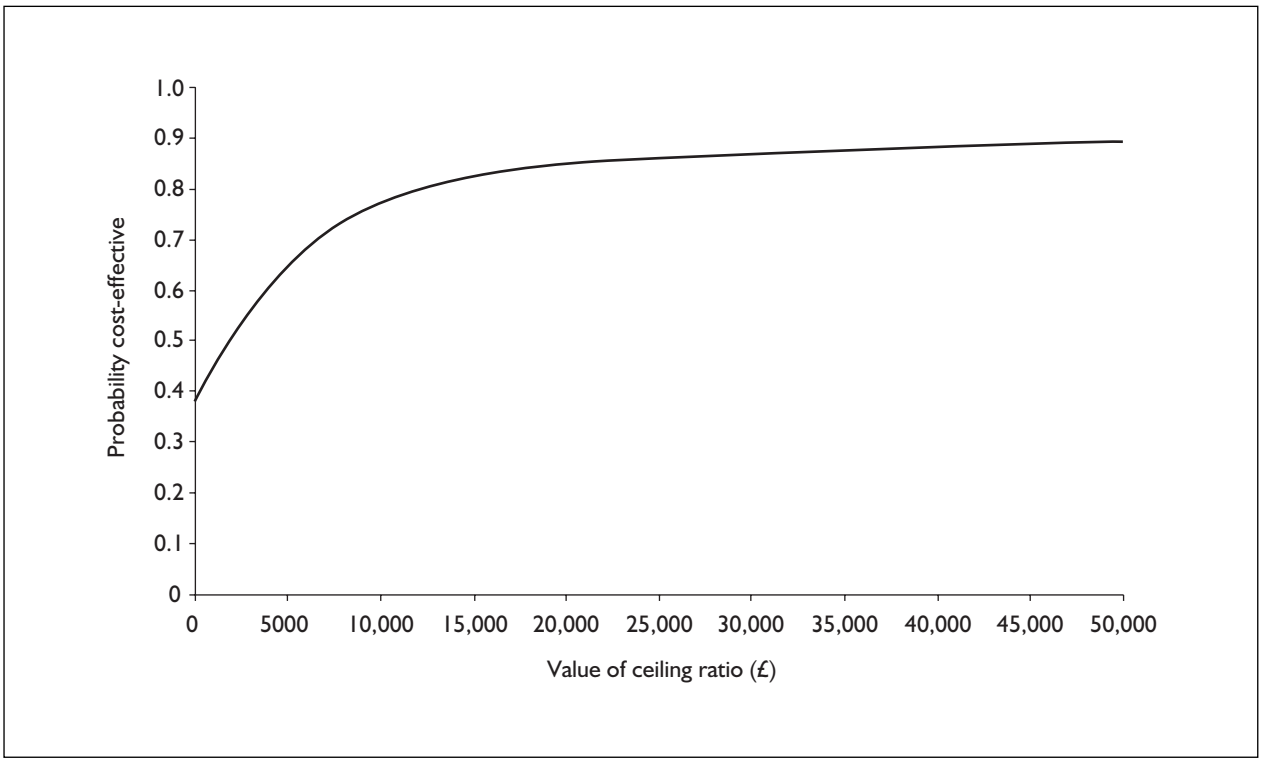

FIGURE 11 *Cost-effectiveness acceptability curve for shared care versus hospital treatment*

TABLE 33 *Sensitivity analysis of the point estimates of costs, effects and ICER*

Analysis	QALYs: mean (SD)		Costs: mean (SD)		ICER: SC – HT
	SC	HT	SC	HT	
Adjustment of QALYs for baseline utility values	1.64 (1.58 to 1.70)[a]	1.62 (1.57 to 1.68)[a]	4543 (4695)	4437 (4900)	7571
Adjustment of QALYs and costs for baseline utility values	1.64 (1.58 to 1.70)[a]	1.62 (1.57 to 1.68)[a]	4619 (4013 to 5226)[a]	4361 (3754 to 4967)[a]	18,500
No imputation of missing observations or censored data	1.67 (0.52)	1.58 (0.58)	4389 (4797)	4278 (4947)	1261
No imputation of censored data	1.63 (0.56)	1.54 (0.60)	4389 (4797)	4278 (4947)	1233
Censored QALY data imputed by last observation carried forward, weighted for survival probability (Cox regression)	1.61 (0.58)	1.55 (0.65)	4543 (4695)	4437 (4900)	1767
0% discount rate QALYs and costs	1.72 (0.58)	1.65 (0.62)	4879 (5038)	4755 (5208)	1737
1.5% discount rate QALYS, 3.5% costs	1.70 (0.57)	1.63 (0.62)	4543 (4695)	4437 (4900)	1494
1.5% discount rate QALYs, 6% costs	1.70 (0.57)	1.62 (0.62)	4325 (4475)	4231 (4670)	1329
6% discount rate QALYs and costs	1.63 (0.55)	1.56 (0.59)	4325 (4475)	4231 (4670)	1376
Costs exclude costs of drug therapy	1.67 (0.56)	1.60 (0.60)	3169 (4295)	3128 (4648)	596
Costs include costs of protocol visits	1.67 (0.56)	1.60 (0.60)	5067 (4717)	4627 (4871)	6328
Costs include protocol visits and exclude costs of drug therapy	1.67 (0.56)	1.60 (0.60)	3662 (4223)	3253 (4620)	5885

HT, hospital treatment; SC, shared care.
[a] 95% CI.

TABLE 34 *Sensitivity analysis of net benefit and probability that shared care was cost-effective*

Analysis	Net benefit of shared care[a]	Probability shared care was cost-effective
Adjustment of QALYs for baseline utility values	591	0.60
Adjustment of QALYs and costs for baseline utility values	445 (–4111 to 4799)	0.58
No imputation of missing observations or censored data	3741 (–4361 to 12,089)	0.83
No imputation of censored data	2135 (–4656 to 9730)	0.70
Censored QALY data imputed by last observation carried forward, weighted for survival probability (Cox regression)	2276 (–3445 to 8038)	0.79
0% discount rate QALYs and costs	3578 (–2002 to 9154)	0.90
1.5% discount rate QALYs, 3.5% costs	3603 (–2894 to 9094)	0.89
1.5% discount rate QALYs, 6% costs	3564 (–2069 to 9440)	0.89
6% discount rate QALYs and costs	3341 (–2048 to 8527)	0.89
Costs exclude costs of drug therapy	3568 (–1922 to 9080)	0.91
Costs include costs of trial intervention	2969 (–2377 to 8360)	0.84
Costs include trial intervention and exclude costs of drug therapy	3078 (–2166 to 8472)	0.87

[a] 95% CIs in parentheses.

hospital treatment arm this was costed at £84 for an additional visit to the rheumatology outpatient clinic every 4 months. This cost was added to the total costs for each patient only if they did not report the specialist nurse home visit (shared care) or a visit to the rheumatology clinic (hospital treatment).

The sensitivity analyses (Appendix 5) used the same analytic approach as the primary analyses, but altered the values of the key variables specified in each of the analyses described above. The values for all other parameters not being tested in the sensitivity analysis were those used in the primary analysis. As with the primary analysis, each sensitivity analysis estimated the net benefit of shared care and used cost acceptability analysis (using a £0–£50,000 range of cost per QALY threshold values, in increments of £1000) to estimate mean net benefit and the probability that shared care was cost-effective. Overall, the results of the sensitivity analyses indicate that the trend towards higher QALYs and costs with shared care is not affected by the assumptions tested. However, the probability that shared care is cost-effective is lower if the data are adjusted for differences in baseline utility values ($p = 0.58$), the costs of protocol-driven visits are included ($p = 0.84$) or when censored data are not imputed ($p = 0.70$).

However, incomplete and inconsistent reporting of resource use means that the cost data are likely to be underestimates of actual costs in routine practice. If there were no differences between the allocation groups in the unit cost, frequency and/or intensity of service use that was not recorded, then the finding that shared care is likely to be more cost-effective than hospital treatment will be valid. Alternatively, if there are differences in the unit cost, frequency and/or intensity of unrecorded service use, then the findings of the evaluation may be biased and the robustness of the conclusions about relative costs will be uncertain.

Chapter 4
Discussion

Problems encountered

Recruitment

Recruitment to the study took place over 17 months rather than the 12 months originally planned. In addition, the final number recruited (466) was less than the original target (480). However, this did not add to the cost of the study since the contracts for the nurses at each centre did not have to be extended and the loss to follow-up was less than expected so the power of the study was not reduced. All the centres felt, at the end of 17 months, that they had probably recruited all eligible (and consenting) patients from their practice. This adds to the external generalisability of the study.

Incomplete data

For a variety of reasons, very few patients had complete data at all time-points throughout the study. The combination of an economic evaluation (which included very detailed patient diaries and a number of extra questionnaires) with a full clinical assessment (and blood tests in the hospital arm) meant that there was a great deal of scope for one or more items to be omitted at any one attendance. In addition, patients in the aggressive treatment arm may have missed scheduled appointments. A great effort was made to bring as many people as possible back for the final assessment.

Compliance with randomisation and with the treatment algorithms

This was a pragmatic trial and the only person who was blinded was the nurse who performed the joint examination at the time of the annual assessments. No patients actually changed treatment arm during the course of the study (although, in error, one patient was not allocated to the arm to which she had been randomised). If a decision was made to change DMARD therapy in patients in the shared care arm then they did have extra hospital visits while the new treatment was started and stabilised, but they then returned to shared care management. This style of management was expected as part of the protocol.

However, the actual management of the two treatment arms was more similar than we originally anticipated. There were two main reasons for this. One was that the patients in the symptomatic (shared care) arm had their treatment changed more often than might have been expected; 55.9% of patients in this arm had at least one change in DMARD therapy during the study. This may have been initiated by the nurse at one of the 4-monthly home visits, by the rheumatologist at the annual assessment or by the GP on another occasion. Some of these changes were simply an increase in the dose of an existing DMARD. There was no evidence that these changes were being initiated because an aggressive management policy was being followed – the GP, nurse and consultant did not have access to measurements of the ESR or CRP at the time that treatment changes were made and (given what happened in the aggressive arm) it is unlikely that they changed the treatment if they saw one or two inflamed but asymptomatic joints. The fact that these treatment changes were made in the shared care arm is reassuring as it means that, provided that stable RA patients are reviewed regularly by a rheumatology nurse and seen annually by a consultant, any need to change treatment is likely to be detected.

The second reason why the management in the two groups was similar was because treatment was not changed as often as it should have been in the aggressive treatment arm; 24% of patients in the aggressive treatment arm satisfied the criteria for changing treatment on two consecutive occasions and yet no change was made. Both rheumatologists and patients found it hard to consider a complete change in treatment for only minor evidence of RA disease activity. The median number of tender joints and swollen joints at baseline was only three. None of these patients would have satisfied the conventional entry criteria for active disease for RA clinical trials of new therapies. This problem was perhaps enhanced by the fact that the patients recruited to the study had stable disease and may have been on the same therapy for many years despite ongoing mild disease activity. In retrospect, it might be easier to test the hypothesis that complete suppression of disease activity improves outcome in RA by recruiting patients with active RA who have to change their DMARD therapy, and just continuing to add in new therapy until the disease is completely suppressed.

Finally, some patients in the aggressive treatment arm never had any indication to change their treatment. They clearly did not benefit from more frequent hospital assessment. Further analysis will explore whether it is possible to predict which patients will remain completely stable over the medium term.

Clinical outcome

This trial compared the outcome following 3 years of either symptomatic or aggressive therapy. The outcome in the two treatment arms was the same for all outcome measures except the physician global assessment and OSRA disease activity. Nevertheless, both treatment groups showed a significant deterioration in health as measured by both the HAQ and EQ-5D during the treatment period. The mean adjusted increase in HAQ score over the trial period was 0.05 units per year (95% C1 0.04 to 0.07) (see the section 'Efficacy analysis', p. 32). In a 5-year longitudinal study of 245 RA patients, Gardiner and colleagues reported a mean increase in HAQ of 0.03 units/year.[60] Their study included both early and established RA. Wolfe also reported a mean increase of 0.03 units/year.[61] However, he pointed out that, as in this trial, individual RA patients have different patterns of change in HAQ – by no means always linear. Hence we can conclude that, overall, the patients in this trial showed a decline in physical function at a similar rate to that reported in the literature.

This is perhaps surprising because the patients enrolled in the BROSG trial had 'mild, stable' RA. The term 'mild' here is used to describe patients with low disease activity. The median number of swollen joints was three (IQR1, 6) at the beginning of the study and two (IQR 0, 4.5) at the end of the study. The median ESR was 19 (IQR 10, 32) at the beginning of the study and 18 (IQR 10, 32) at the end. These patients would not be eligible for entry into the great majority of RA clinical trials (*Table 35*).

TABLE 35 *Average entry criteria for RA clinical trials*

≥ 6 swollen joints ≥ 6 tender joints ESR ≥ 28 mm/h And/or early morning stiffness >45 minutes
Summarised by Sokka and Pincus.[62]

Other authors have also drawn attention to the fact that the majority of patients attending clinics for treatment for RA have disease which is neither sufficiently active for enrolment in a clinical trial nor in remission.[62,63]

Our understanding of the long-term prognosis and the best way of managing this large group of RA patients is poor.[60] The results of the present trial indicate that these patients do continue slowly to deteriorate despite current therapy regimes. They also indicate that attempts to suppress disease activity further were unsuccessful. The conclusion must be either that current management (focusing on symptom control) is the best that can be achieved or that much more aggressive therapy is needed to suppress the disease activity completely.

Economic evaluation

Overall, the primary economic analysis and sensitivity analyses of the cost and QALY data indicate that symptomatic treatment is likely to be more cost-effective than hospital treatment in 58–90% of cases. There were differences in the health status and associated utility values between the two groups at baseline, with those in the symptomatic treatment group having higher utility values. To assess whether this difference was important and could have biased the results, the sensitivity analysis included an analysis of data adjusted for baseline utility values. These indicated that the symptomatic treatment was still likely to be cost-effective, but with a lower probability of 58–60%. Healthcare visits that were mandated by the trial protocol rather than the need for care in routine practice were excluded from the analysis and national average unit cost data for England were used, to facilitate transferability of the results to settings outside the trial in England. Even if the protocol-defined visits were actually part of the intervention and included in the costs, the probability that shared care is cost-effective is still high, albeit reduced slightly from 89 to 84%.

There has been relatively little work on the costs of RA, either within or outside the context of clinical trials. The mean annual costs per patient to the health service in this trial were around £1500. If we assume that around one-third of all adults with RA in the UK fall into the category of 'mild, stable RA', then this group incurs direct care costs of around £193 million per year.

As noted previously, there were a number of problems with incomplete and inconsistent reporting of resource use. This means that the costs estimated here may be underestimates of actual costs in routine practice. If there were no differences between the treatment groups in the frequency and/or intensity of service use that was not recorded and the cost of those services, then the finding that shared care is likely to be more cost-effective than hospital treatment will be valid. However, if such differences exist, then the findings of the evaluation may be biased and the robustness of the conclusions about relative costs is uncertain. Other recently published studies reported a lower cost of $1702 per person per year in the USA, or approximately £1100 (using the exchange rate at the time of the study). The differences between the costs found in this trial may be due to differences in the RA population evaluated (in terms of location of care, availability of services, age and disease severity), underestimation of the costs in this study, overestimation of costs in other studies or some combination of these factors.

There is evidence that greater disease severity is associated with higher direct costs.[64,65] However, comparison with studies that present cost information by mean HAQ score does not indicate that the lower costs found in this trial were because the sample had less severe disease or that there were clear differences in the average age of patients.[64,66] The distribution of costs by category of resource use differed widely between the studies. Overall, inpatient costs typically accounted for the highest percentage of total cost, in contrast to this trial where inpatient costs were 27–37% depending on time period. Overall, for the 3-year study period, inpatient costs and drug costs each accounted for 31% of the total cost. In relative terms, the drug costs for this study represented a higher proportion of total costs than found elsewhere. These factors, combined with high rates of information recorded for inpatient and outpatient stay and the main drug category of DMARDS (between 90 and 97%), indicate that the main costs found in this trial may be relatively robust, but lower than those reported elsewhere.

EQ-5D data were recorded for the majority of patients enrolled in the trial. The estimated utility values and QALYs derived from the EQ-5D scores were similar to those reported in other studies of people with RA.[64,67]

In most trials, the conclusions are based on evidence of clinical effectiveness. In this trial, both treatment options were equally effective. The conclusions here are, therefore, driven by the economic evaluation, which has shown that shared care/symptom control would be more cost-effective than entirely hospital-based treatment in 60–90% of cases.

This trial is one of the largest studies to use the EQ-5D in RA. We have shown that it correlates well with the HAQ. Both the HAQ and EQ-5D results indicate that, although we describe these patients as having 'mild, stable' RA in terms of their disease activity, they were nevertheless significantly disabled as measured by a median HAQ score of 1.38 at study entry and around 7% of patients being in states considered to be worse than death (*Figure 9*).

Internal and external validity

As indicated, this trial showed good internal and external validity. The centres felt that they had recruited the great majority of RA patients who satisfied the entry criteria, follow-up rates were high and loss to follow-up did not seem to be predicted by any of the measured baseline variables. The five centres were widely distributed round the country and represented a range of practice settings. The overall pattern of social deprivation in the trial represented that of the whole UK (*Figure 7*).

Implications for future rheumatological practice

The fundamental hypothesis of the trial that aggressive treatment (i.e. complete suppression of all evidence of disease activity) in patients with established RA would slow disease progression has not been answered. There are three reasons for this: the patients enrolled in the trial had relatively mild and stable RA, the patients in the aggressive treatment arm did not have their disease completely suppressed (and because treatment was not changed as often as it should be, we do not know whether it would have been possible to suppress disease activity completely) and patients in the symptomatic arm had their treatment changed more often than had been anticipated.

Nevertheless, it must be noted that patients in both arms deteriorated. During the last 3 years, a revolution has occurred in the management of RA with the introduction of biologic agents.[11] Only 15 patients (3%) would have satisfied the

NICE guidelines for anti-TNFα treatment at any point during the trial. However, the patients in the trial deteriorated despite conventional treatment with DMARD therapy. It is a challenging thought that such deterioration might have been prevented by the biological agents. It is important to remember that mild, stable, established RA is not a benign condition and this trial indicates that such patients need to remain under regular hospital review.

Research implications

Around 2 years ago, the biological agents – a new class of drug specifically designed to block key mediators of the RA inflammatory pathway – were introduced for the treatment of RA. They are already proving tremendously successful. NICE guidelines[11] recommend that anti-TNF agents be considered in patients with active RA who have failed on two or more DMARDs. They have not been tested in patients with relatively inactive RA such as were included in this trial.

Research priorities

1. A trial to establish whether disease progression can be retarded in patients with mild, stable established RA using biological agents. There is evidence from the TEMPO Trial that the combination of MTX and etanercept can halt radiological progression in patients with active established RA.[68] Would the same effect be seen in patients with relatively inactive disease?
2. Further work to refine the model of shared care which was found to be cost-effective in this trial. For example, is 4-monthly contact with a nurse (based in either hospital or primary care) essential? Could the contact be replaced by a telephone call or a postal questionnaire?
3. Further studies to develop a robust and fail-safe system of DMARD monitoring which is primary care based. If patients are going to be managed in shared care with annual review by a rheumatologist, then the DMARD monitoring should also be able to detect non-attendance for blood tests, should be able to prevent prescriptions from being issued if monitoring is not taking pace, should be able to detect abnormal results and bring them to the prescriber's attention and should protect the nurse or doctor from having to check large numbers of normal results. Such a system should be computerised and link into both GP and hospital systems. The rheumatologist should be available to provide advice in the case of abnormal results.
4. Further studies to predict response to DMARDs.
5. Further studies to establish whether there is a minimum disease activity level below which disease progression does not occur.[69]

Conclusions

This trial has shown that patients with mild, stable, established RA comprise around one-third of rheumatology clinic attenders with RA. These patients continue to deteriorate with respect to their physical function, the structural damage in their joints (as seen on X-ray) and their quality of life. All patients in this trial received DMARD therapy and/or steroids if needed to control their symptoms. Adding to or changing DMARD therapy in order to abolish all clinical evidence of joint inflammation and minimise laboratory evidence of inflammation did not make any difference to the rate of deterioration in these patients. This was partly because clinicians and/or patients were reluctant to change their therapy when there was only minimal evidence of active disease. However, given that the policy could not be fully implemented in the context of a clinical trial, it is unlikely to be any more successful in routine practice. The shared care/symptomatic arm was more cost-effective. We therefore conclude that, until a more effective way of controlling mild but ongoing inflammation is found, the best way to manage patients with mild, stable, established RA is in the shared care setting. Patients should be seen annually by the hospital rheumatology team and should have contact with a rheumatology specialist nurse around every 4 months. They should have ready access to the hospital rheumatology service when they need it, including access to a telephone help-line. Provided that these arrangements are in place, patients with mild, established RA are able to initiate changes in treatment when their symptoms deteriorate.

In conclusion, this trial has provided important information on the management of patients with mild, established RA. It has also raised questions as to whether the outcome of these patients could be improved by using a different treatment strategy.

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Contribution of authors

Deborah Symmons (Professor of Rheumatology and Muscloskeletal Epidemiology) was involved in the conception and design of the trial. She also supervised the analysis and the interpretation of the data and drafted and revised the report. Karen Tricker (Research Fellow) was the clinical trial coordinator for the majority of the time following recruitment to the trial. Chris Roberts (Senior Lecturer in Medical Statistics) was the trial statistician. Linda Davies (Reader and Director of Health Economics Research) was the trial health economist. Peter Dawes (Consultant Rheumatologist) was involved in the conception and design of the study. He also recruited patients to the trial and was involved in the review of the report. David Scott (Consultant Rheumatologist) was involved in the conception and design of the study. He also recruited patients to the trial and was involved in the review of the report.

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Appendix 1

Choosing a second-line drug

For the purposes of this trial, DMARDs will be considered in three categories (*Table 36*).

TABLE 36 *DMARD categories*

Category 1	Category 2	Category 3
Sulfasalazine Antimalarials	Intramuscular gold Methotrexate	Penicillamine Azathioprine Leflunomide[a]

[a] New drug licensed during the study.

The clinician has a number of options which include the following:

0. Do nothing
1. Category 1 drug
2. Category 2 drug
3. Category 3 drug
4. Increase steroids to max. 7.5 mg
5. Increase steroids to max. 10 mg
6. Start oral steroids
7. Intramuscular steroids
8. Intravenous steroids
9. Ciclosporin
10. Cyclophosphamide

Begin by deleting all those drugs to which the patient has previously failed to respond, developed serious adverse reactions or which are contraindicated (e.g. MTX in patients with high alcohol consumption). If any drug remains, apart from the one(s) which the patient is currently taking, apply the appropriate algorithm (see below).

Algorithm 1: treatment choices for patients in the shared-care arm

TABLE 37 *Algorithm 1*

Current 2nd line	Problem	Solution[a,b]
None		1 → 2
Category 1	Adverse reaction Inefficacy	Stop drug → 0 → 1 → 2 → 3 → 4 → 6 Increase dose → stop drug → 2 → 3 → 4 → 6 → 1
Category 2	Adverse reaction Inefficacy	Stop drug → 0 → 2 → 3 → 4 → 6 → 1 Increase dose → stop drug → 2 → 3 → 4 → 6 → 1
Category 3	Adverse reaction Inefficacy	Stop drug → 2 → 4 → 6 → 1 → 3 Increase dose → stop drug → 2 → 4 → 6 → 1 → 3
Oral steroids	Inefficacy	4 → 2 → add AZA

[a] The number refers to the options list above. Consider options in order. Record reasons for rejecting each solution, e.g. no drug available in category.
[b] If no suitable solution can be found and the patient still has symptomatic disease, the patient will have to be brought back into the hospital system.

Algorithm 2: treatment choices for patients in the hospital arm

TABLE 38 *Algorithm 2*

Current 2nd line	Problem	Solution[a]
None		1 → 2 → 6
Category 1	Adverse reaction Inefficacy[b]	Stop drug → 1 → 2 → 3 → 5 → 6 • Partial response: increase dose → add in → 1 → 5 → stop drug → • No response: increase dose → stop drug → 2 → 3 → 5 → 6 → 9
Category 2	Adverse reaction Inefficacy[b]	Stop drug → 2 → 3 → 5 → 6 → 9 • Partial response: increase dose → add in → 1 → 5 → 6 → stop drug → • No response: increase dose → stop drug → 2 → 3 → 5 → 6 → 9
Category 3	Adverse reaction Inefficacy[b]	Stop drug → 2 → 3 → 5 → 6 • Partial response: increase dose → 5 → 6 → stop drug → • No response: increase dose → stop drug → 2 → 5 → 6 → 1 → 9
Combination	Adverse reaction Inefficacy[b]	Stop most likely drug and review • Partial response: increase dose of drug(s) → 5 → 6 → stop both drug • No response: increase dose of drug(s) → stop both drugs → 2 → 3 → 5 → 6 → 9
Prednisolone	Inefficacy[b]	5 → 2 add AZA → 9
CYP	Adverse reaction Inefficacy[b]	Stop drug 5 → 6 → add MTX → stop drug
No available options	Active disease	Consider 10

[a] The number refers to the options list above. Consider options in order. Record reasons for rejecting each solution, e.g. no drug available in category.

[b] Consider option 7 if symptomatic or raised CRP and therapy has been changed within the last 6 months or if further change considered premature. Consider option 8 if patient experiences an acute flare or to try to regain disease control while starting new therapy.

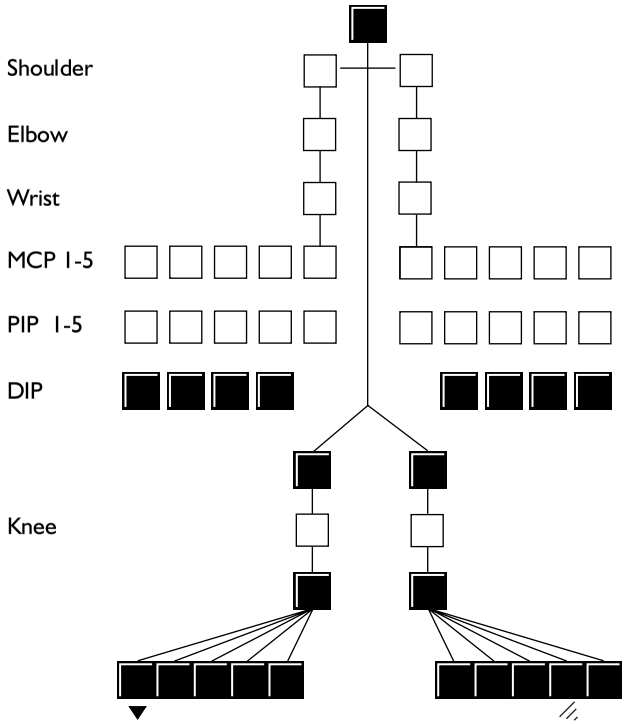
Appendix 2

Joint examination manikin

Date: ☐☐☐☐☐☐

28-JOINT TENDER AND SWOLLEN JOINT COUNT

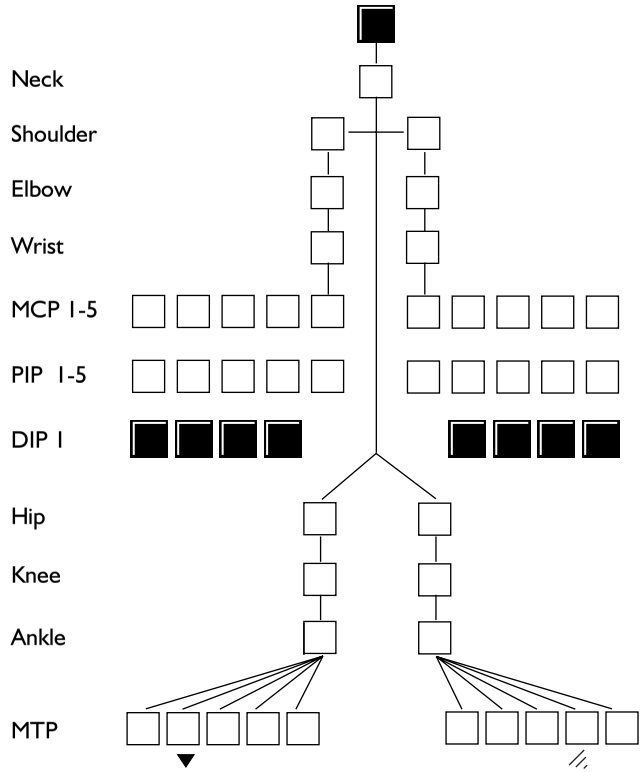
Which joints are tender (T), swollen (S) or both (B) now:



Assessment Number: ☐☐

ORTHOPAEDIC PROCEDURES AND JOINT DEFORMITY

Which joints are deformed (D) or have been operated on (O):



Trial Number: ☐☐☐☐☐

Appendix 3

Patient satisfaction questionnaire

Date: ☐☐☐☐☐☐ Assessment Number: ☐☐

We are interested in your *honest* opinions, whether they are positive or negative. Please answer **all** the questions. We also welcome your comments and suggestions (on back of questionnaire). Thank you very much, we appreciate your help.

1. How would you rate the quality of service you receive?

(*please tick **one** box*)

- Excellent ☐
- Good ☐
- Fair ☐
- Poor ☐

2. To what extent has our treatment met your needs?

(*please tick **one** box*)

- Almost all my needs have been met ☐
- Most of my needs have been met ☐
- Only a few of my needs have been met ☐
- None of my needs have been met ☐

3. In an overall, general sense, how satisfied are you with the service you have received?

(*please tick **one** box*)

- Very satisfied ☐
- Mostly satisfied ☐
- Indifferent or mildly dissatisfied ☐
- Quite dissatisfied ☐

4. If you were to be asked to help again, would you participate?

(*please tick **one** box*)

- No, definitely not ☐
- No, I don't think so ☐
- Yes, I think so ☐
- Yes, definitely ☐

Appendix 4

Resource use and cost data

TABLE 39 *Inpatient admissions, average length of stay and unit cost per person with an inpatient stay*

Department	Unit cost	Shared care					Hospital				
		N	Mean no. of admissions	SD	Mean LOS (days)	SD	*N*	Mean no. of admissions	SD	Mean LOS (days)	SD
A&E	300[a]	1	1	0	5	0	1	1	0	9	0
Cardiology	445[a]	8	1	0	7	6	5	1	0	9	10
ENT	477[a]	1	1	0	2	0	1	2	0	2	0
Medical	273[b]	7	1	1	28	40	8	1	0	7	5
Maternity	333[a]	1	1	0	2	0	0	0	0	0	0
Orthopaedic	319[a]	36	1	1	14	18	34	2	1	11	15
Renal	190[c]	2	1	0	10	12	0	0	0	0	0
Rheumatology	234[a]	22	1	0	11	6	15	1	1	21	37
Surgical	315[a]	8	1	0	12	14	7	1	0	8	8
Urology	297[a]	0	0	0	0	0	2	1	0	2	0
Neurology	263[a]	2	1	0	6	6	0	0	0	0	0
Plastic surgery	446[a]	1	1	0	16	0	0	0	0	0	0
Gastroenterology	249[a]	0	0	0	0	0	1	1	0	2	0
ITU	1193[b]	0	0	0	0	0	1	1	0	32	0
Day surgery	315[d]	6	1	0	1	0	5	1	0	1	0
Dermatology	229[a]	1	2	0	40	0	0	0	0	0	0
Geriatric	140[a]	1	1	0	6	0	0	0	0	0	0
Rehabilitation/convalescent	186[a]	1	1	0	5	0	1	1	0	14	0
Thoracic	232[a]	1	1	0	3	0	0	0	0	0	0
Orthopaedic day	319[d]	10	1	0	1	0	13	1	0	1	0
Rheumatology day	184[b]	15	1	0	1	0	17	1	0	1	0
Urology day	315[c]	1	2	0	2	0	1	1	0	1	0
Haematology day	211[c]	1	1	0	1	0	0	0	0	0	0
Gastroenterology day	176[c]	4	1	0	1	0	2	2	1	2	1
Opthalmology day	632[c]	0	0	0	0	0	4	1	0	1	0
Dermatology day	75[c]	1	2	–	2	0	0	0	0	0	0
Orthodontist day	129[c]	1	1	0	1	0	1	1	0	1	0
A&E day	55[b]	2	1	0	1	0	1	1	0	1	0
Rehabilitation day	186[a]	0	0	0	0	0	1	1	0	1	0
Cardiology day	104[c]	0	0	0	0	0	1	1	0	1	0
Gynaecology day	89[c]	0	0	0	0	0	1	1	0	1	0
Neurology day	335[b]	1	1	0	1	0	0	0	0	0	0
Colonoscopy	179[c]	1	1	0	1	0	0	0	0	0	0
Hernia repair	988[c]	0	0	0	0	0	1	1	0	1	0
Pain management	126[c]	1	1	0	1	0	0	0	0	0	0

A&E, accident and emergency; ENT, ear, nose and throat; ITU, intensive treatment unit; LOS, length of stay.
[a] CIPFA (2001) [*Financial year (2000/2001)*].
[b] PSSRU (2002) [*Financial year (2000/2001)*].
[c] Average Reference Costs (2001) [*Financial year (2000/2001)*] of procedures carried out in that department available at http://www.doh.gov.uk/nhsexec/refcosts.htm.
[d] CIPFA (2001) [*Financial year (2000/2001)*], cost per patient day of patient using a bed for that department.

TABLE 40 *Number and unit cost of hospital outpatient visits per patient using outpatient care*

	Shared care			Hospital treatment			
Department	***N***	**Mean visits**	**SD**	***N***	**Mean visits**	**SD**	**Unit cost (£)**
Not known	43	2	4	64	2	1	82[b,d]
A&E	11	1	1	9	1	0	74[a]
Cardiology	12	1	1	18	2	2	82[a]
ENT	4	2	1	6	2	1	68[a]
Medical	12	1	0	10	2	1	82[b]
Gynaecology	7	2	1	5	2	1	77[a]
Maternity	1	1	0	0	0	0	66[a]
Orthopaedic	67	4	3	67	3	3	71[a]
Renal/nephrology	4	2	2	4	3	1	90[a]
Rheumatology	214	10	13	222	15	14	84[a]
Surgical	19	1	1	13	1	0	76[a]
Urology	1	2	0	3	1	0	74[a]
Neurology	3	2	1	6	2	1	123[a]
Plastic surgery	2	2	1	0	0	0	58[a]
Haematology	28	4	6	47	4	3	73[a]
Gastroenterology	4	1	1	9	1	0	80[a]
Opthalmology	22	4	7	21	2	2	56[a]
Dermatology	10	2	2	6	3	1	58[a]
Othodontist	1	2	0	0	0	0	65[c]
Dentistry	9	2	1	0	0	0	60[c]
Podiatry	9	2	1	11	2	1	18[c]
Diabetic	2	2	1	4	2	1	82[c]
Endocrinology	1	5	0	1	1	0	82[c]
Dietician	0	0	0	1	1	0	65[c]
General Practice	0	0	0	1	1	0	82[b]
Genito-urinary	0	0	0	1	1	0	91[a]
Mammography	4	1	1	2	2	0	104[c]
Nuclear medicine	1	1	0	3	1	1	31[a]
Obstetrics	1	1	0	0	0	0	85[a]
Occupational therapy	5	1	1	4	1	1	166[c]
Oncology	2	1	0	2	2	1	116[a]
Othotics	0	0	0	2	3	1	18[c]
Generic outpatients	4	3	1	9	1	0	82[b]
Pathology and radiology	27	1	1	34	2	1	31[a]
Physiotherapy	7	3	3	7	2	1	75[c]

[a] CIPFA (2001) [*Financial year (2000/2001)*].
[b] PSSRU (2002) [*Financial year (2000/2001)*].
[c] Average Reference Costs (2001) [*Financial year (2000/2001)*] of procedures carried out in that department available at http://www.doh.gov.uk/nhsexec/refcosts.htm.
[d] Generic outpatient visit cost.

TABLE 41 *Number, length and unit cost of primary care services per person using primary care by type of staff (financial year 2000–2001)*

Type of service	Allocation group	*N*	Mean no. of visits	SD	Total minutes	SD	Mean unit cost (£)[a]
Practice nurse	Shared care	155	12	13	200	261	0.51[b]
	Hospital treatment	159	13	17	199	348	0.51[b]
GP	Shared care	215	8	6	155	148	2.18[c]
	Hospital treatment	215	7	6	116	111	2.18[c]
Chiropodist	Shared care	44	9	11	211	239	0.32[d]
	Hospital treatment	46	7	6	171	175	0.32[d]
District nurse	Shared care	12	8	13	206	358	0.95[e]
	Hospital treatment	7	4	2	65	58	0.95[e]
Physiotherapist	Shared care	7	4	5	103	167	0.62[f]
	Hospital treatment	3	3	3	80	88	0.57[f]
Phlebotomist	Shared care	2	9	4	68	11	0.50[g]
	Hospital treatment	5	3	3	61	48	0.53[g]
Practice nurse + GP	Shared care	0	0	0	0	0	0[h]
	Hospital treatment	4	2	1	40	32	2.62[h]
GP + nurse	Shared care	1	2	0	40	0	2.62[i]
	Hospital treatment	1	3	0	120	0	2.62[i]
Dietician	Shared care	1	4	0	40	0	0.53[j]
	Hospital treatment	1	1	0	30	0	0.53[j]
Dentist	Shared care	1	1	0	35	0	1.19[k]
	Hospital treatment	0	0	0	0	0	0[k]
Optician	Shared care	2	1	0	20	0	2.12[l]
	Hospital treatment	0	0	0	0	0	0[l]
Consultant	Shared care	0	0	0	0	0	0[m]
	Hospital treatment	1	1	0	20	0	2.12[m]
Herbalist	Shared care	0	0	0	0	0	0[n]
	Hospital treatment	1	1	0	90	0	1.14[n]
Daughter	Shared care	0	0	0	0	0	0[o]
	Hospital treatment	1	1	0	5	0	0.65[o]
Not known	Shared care	91	5	5	121	126	1.19[p]
	Hospital treatment	86	4	5	84	78	1.14[p]
Total		1061					

[a] All unit costs were derived from national average data from Netten and Curtis[70] (financial year 2000/2001). Subsequent footnotes refer to that reference.
[b] Practice nurse – mean cost per minute in clinic/home visit; includes wages, salary oncosts, qualifications, overheads, capital overheads.
[c] GP – mean cost per minute in surgery/home visit; includes net remuneration, practice expenses, qualifications, ongoing training, capital costs, overheads.
[d] Community chiropodist – mean cost per minute; includes wages, salary oncosts, overheads, capital overheads.
[e] District nurse – mean cost per minute in clinic/home visit; includes wages, salary oncosts, qualifications, overheads, capital overheads.
[f] Community physiotherapist – mean cost per minute in clinic/home visit; includes wages, salary oncosts, qualifications, overheads, capital overheads.

continued

TABLE 41 *Number, length and unit cost of primary care services per person using primary care by type of staff (financial year 2000–2001) (cont'd)*

[g] Phlebotomist – costed as practice nurse – mean cost per minute in clinic/home visit; includes wages, salary oncosts, qualifications, overheads, capital overheads.
[h] Combined cost per minute of surgery/home visit of GP and practice nurse; includes wages, salary oncosts, qualifications, overheads, capital overheads.
[i] Combined cost per minute of surgery/home visit of GP and practice nurse; includes wages, salary oncosts, qualifications, overheads, capital overheads.
[j] Costed as hospital dietician – mean cost per minute in clinic/home visit; includes wages, salary oncosts, qualifications, overheads, capital overheads.
[k] Mean imputed cost from primary care visits by trial arm.
[l] Costed as GP visit – mean cost per minute in clinic; includes net remuneration, practice expenses, qualifications, ongoing training, capital costs, overheads.
[m] Costed as GP visit – mean cost per minute in surgery/home visit; includes net remuneration, practice expenses, qualifications, ongoing training, capital costs, overheads.
[n] Mean imputed cost from primary care visits by trial arm.
[o] Costed as practice nurse visit – mean cost per minute in clinic/home visit; includes wages, salary oncosts, qualifications, overheads, capital overheads.
[p] Mean imputed cost from primary care visits by trial arm.

TABLE 42 *Number, length and unit cost of primary care services per person using primary care, by location of care*

Location of care	Allocation group	*N*	Total minutes	SD	Mean no. of visits	SD	Unit cost (£)[a]
GP surgery	Shared care	217	288	304	16	14	1.51[b]
	Hospital treatment	221	237	282	15	16	1.49[b]
Community clinic	Shared care	38	214	259	9	11	0.45[c]
	Hospital treatment	43	132	110	6	5	0.43[c]
Home	Shared care	55	105	205	5	8	2.44[d]
	Hospital treatment	53	136	429	6	15	2.28[d]
Private practice	Shared care	3	110	35	4	1	0.32[e]
	Hospital treatment	2	50	14	2	0	0.32[e]
Department	Shared care	1	100	0	5	0	0.50[e]
	Hospital treatment	2	35	7	2	1	1.22[e]
Day case	Shared care	1	20	0	1	0	2.12[e]
	Hospital treatment	0	0	0	0	0	0[e]
Dentist	Shared care	1	35	0	1	0	1.19[e]
	Hospital treatment	0	0	0	0	0	0[e]
Home (telephoned)	Shared care	1	5	0	1	0	1.67[f]
	Hospital treatment	0	0	0	0	0	0
Not known	Shared care	232	119	126	5	5	1.18[e]
	Hospital treatment	191	85	78	4	5	1.12[e]

[a] Unit costs were derived from national average data (PSSRU, 2002), from Netten and Curtis.[70] Subsequent footnotes refer to that reference.
[b] Mean unit cost per minute – GP surgery visit; includes overheads and capital.
[c] Mean unit cost per minute – community clinic visits; includes overheads and capital.
[d] Mean unit cost per minute – home visits.
[e] Costed as GP surgery visits – mean unit cost per minute; includes overheads and capital.
[f] Mean unit cost per minute – GP, home telephoned; includes overheads and capital.

TABLE 43 *Use and unit costs of other healthcare professionals and procedures per person using other health and social care and not reported elsewhere*

	Shared care					Hospital treatment					
Type of healthcare professional	***N***	**Total minutes**	**SD**	**Mean visits**	**SD**	***N***	**Total minutes**	**SD**	**Mean visits**	**SD**	**Unit cost (£)[a]**
Physiotherapist	93	224	284	7	7	99	190	340	7	12	0.63[b]
Chiropodist	93	125	122	6	6	113	127	151	5	6	0.32[c]
Occupational therapist	65	106	133	3	3	65	77	91	2	3	0.72[d]
Orthotist	36	58	39	2	1	43	92	88	3	3	0.32[e]
Acupuncture	2	360	339	10	11	1	30	0	1	0	0.33[f]
Occupational health	5	77	77	2	1	4	90	83	3	2	0.45[g]
Nurse	1	600	0	20	0	1	30	0	1	0	0.30[h]
Hydrotherapist	1	29	0	1	0	4	118	61	4	2	0.33[f]
District nurse	2	255	318	9	11	0	0	0	0	0	0.95[i]
Practice nurse	1	15	0	1	0	1	405	0	15	0	0.50[j]
Dietician	3	118	57	3	2	0	0	0	0	0	0.53[k]
Hand therapist	1	405	0	12	0	0	0	0	0	0	0.63[l]
Herbalist	1	174	0	6	0	1	360	0	7	0	0.33[f]
Appliance officer	1	45	0	3	0	5	40	30	2	1	0.32[e]
Aromatherapist	1	570	0	10	0	1	60	0	1	0	0.33[f]
Orthopaedics	1	90	0	3	0	2	60	42	2	1	0.32[e]
Bone density	2	27	3	1	0	3	48	16	1	1	0.50[m]
Reflexologist	1	29	0	1	0	1	135	0	5	0	0.33[f]
Osteopath	0	0	0	0	0	1	135	0	5	0	0.33[f]
Podiatrist	1	20	0	1	0	3	29	2	1	0	0.32[e]
Optician	0	0	0	0	0	3	27	0	1	0	0.51[n]
Herbalist homeopathic	0	0	0	0	0	1	210	0	3	0	0.33[f]
Insole fitter	0	0	0	0	0	1	120	0	2	0	0.32[e]
Cardiac rehabilitation	1	90	0	1	0	0	0	0	0	0	1.50[o]
Chiropodist/appliance officer	0	0	0	0	0	1	35	0	1	0	0.32[e]
Chiropracter	1	29	0	1	0	0	0	0	0	0	0.33[f]
Clinical nurse specialist	1	30	0	1	0	0	0	0	0	0	0.45[p]
Dental hygienist	0	0	0	0	0	1	27	0	1	0	0.51[n]
ECG technician	0	0	0	0	0	1	45	0	1	0	0.51[n]
Homeopathic nursing sister	0	0	0	0	0	1	60	0	1	0	0.33[f]
Pain clinic	1	29	0	1	0	0	0	0	0	0	0.30[q]
Radiologist	0	0	0	0	0	1	30	0	1	0	0.50[m]
Social services occupational therapy	1	30	0	1	0	0	0	0	0	0	0.73[r]
Social worker	0	0	0	0	0	1	27	0	1	0	0.32[s]
Splint technician	1	45	0	1	0	0	0	0	0	0	0.32[e]
Stoma nurse	0	0	0	0	0	1	27	0	1	0	0.45[p]
Ultrasound	1	29	0	1	0	0	0	0	0	0	0.63[t]
Worth Wall clinic	0	0	0	0	0	1	27	0	1	0	0.30[q]

continued

TABLE 43 *Use and unit costs of other healthcare professionals and procedures per person using other health and social care and not reported elsewhere (cont'd)*

[a] All unit costs were derived from national average data from Netten and Curtis.[70] Subsequent footnotes refer to that reference, except *f*.
[b] Physiotherapist – mean cost per minute in hospital treatment/clinic/home visit; includes wages, salary oncosts, overheads, capital overheads.
[c] Costed as community chiropodist – mean cost per minute; includes wages, salary oncosts, overheads, capital overheads.
[d] Occupational therapist – mean cost per minute in hospital treatment/clinic/home visit; includes wages, salary oncosts, qualifications, overheads, capital overheads.
[e] Costed as community chiropodist – mean cost per minute; includes wages, salary oncosts, overheads, capital overheads.
[f] www.Exeter.ac.uk/FACT (2003) (average cost per hour of complementary medicine).
[g] Costed as nurse specialist; includes wages, salary oncosts, qualifications, overheads, capital overheads.
[h] Staff nurse – mean cost per minute in hospital treatment; includes wages, salary oncosts, qualifications, overheads, capital overheads.
[i] District nurse – mean cost per minute in clinic/home visit; includes wages, salary oncosts, qualifications, overheads, capital overheads.
[j] Practice nurse – mean cost per minute in clinic/home visit; includes wages, salary oncosts, qualifications, overheads, capital overheads.
[k] Dietician – mean cost per minute in hospital treatment/clinic/home visit; includes wages, salary oncosts, qualifications, overheads, capital overheads.
[l] Costed as physiotherapist – mean cost per minute in hospital treatment/clinic/home visit; includes wages, salary oncosts, qualifications, overheads, capital overheads.
[m] Costed as radiographer – mean cost per minute in hospital treatment; includes wages, salary oncosts, qualifications, overheads, capital overheads.
[n] Mean unit cost per minute – GP surgery visit; includes overheads and capital.
[o] Costed as consultant visit – mean cost per minute in hospital treatment; includes wages, salary oncosts, qualifications, overheads, capital overheads.
[p] Clinical nurse specialist – mean cost per minute in hospital treatment/community clinic/home; includes wages, salary oncosts, qualifications, overheads, capital overheads.
[q] Costed as staff nurse visit – mean cost per minute in hospital treatment; includes wages, salary oncosts, qualifications, overheads, capital overheads.
[r] Costed as community occupational therapist – mean cost per minute in clinic/home; includes wages, salary oncosts, qualifications, overheads, capital overheads.
[s] Community social worker – mean cost per minute in clinic/home; includes wages, salary oncosts, qualifications, overheads, capital overheads.
[t] Costed as senior house officer visit – mean cost per minute in hospital treatment; includes wages, salary oncosts, qualifications, overheads, capital overheads.

TABLE 44 *Number and average net ingredient costs (£) of frequently used drugs by BNF chapter*

	Shared care					Hospital treatment				
BNF chapter	***N***	**Mean NIC[a]**	**SD**	**Mean use**	**SD**	***N***	**Mean NIC[a]**	**SD**	**Mean use**	**SD**
1. Gastrointestinal system	95	22	12	16	13	103	23	13	15	12
2. Cardiovascular system	118	14	7	37	40	121	15	9	27	24
3. Respiratory system	41	15	9	16	21	51	15	10	19	31
4. Central nervous system	178	13	7	21	17	183	13	6	19	16
5. Infections	88	8	9	3	4	96	8	11	4	6
6. Endocrine system	112	15	12	20	19	103	16	13	17	14
7. Obstetrics, gynaecology and urinary tract disorders	7	12	9	13	11	8	16	14	7	9
8. Malignant disease and immunosuppression	2	19	0	12	3	1	19	0	26	0
9. Nutrition and blood	94	6	7	17	14	131	5	6	15	12
10. Musculoskeletal and joint disease	218	14	5	39	24	230	15	7	41	26
11. Eye	39	19	10	17	28	32	21	10	11	14
12. Ear, nose and oropharynx	11	4	4	4	4	9	6	5	3	3
13. Skin	41	5	5	6	8	38	4	4	5	7
14. Immunological products and vaccines	2	5	0	1	0	5	6	1	2	1

NIC, net ingredient cost.

[a] The net ingredient cost was estimated for each individual preparation from prescription cost analysis data for England (http://www.doh.gov.uk/stats/pca2000.htm).

TABLE 45 *Number and average net ingredient costs (£) of frequently used drugs by type of drug*

	Shared care					Hospital treatment				
Drug type[a]	***N***	**Mean NIC[b]**	**SD**	**Mean use[c]**	**SD**	***N***	**Mean NIC[b]**	**SD**	**Mean use[c]**	**SD**
H_2-receptor antagonists	45	16	3	13	11	50	17	4	12	11
Proton pump inhibitors	43	39	9	13	10	47	39	9	14	11
NSAIDs (including aspirin dose >300 mg)	187	11	5	19	12	191	11	5	20	13
Drugs to suppress rheumatic disease process	193	17	8	25	16	219	18	10	26	16
Tear deficiency, ocular lubricants, astringents	32	20	8	18	23	28	21	8	9	11
Topical corticosteroids	25	3	2	4	6	25	4	2	6	8
Thiazides and related diuretics	35	24	3	14	10	35	23	5	11	8
Loop diuretics	29	4	1	11	10	15	4	1	10	7
Beta-adrenoceptor blocking drugs	36	6	9	15	12	44	7	8	15	11
Drugs affecting the renin–angiotensin system	33	21	5	16	11	24	21	5	11	7
Calcium channel blockers	34	18	4	17	10	36	20	7	11	9
Anti-platelet drugs including aspirin <300 mg	51	2	6	14	10	35	1	1	12	8
Bronchodilators – adrenoceptor agonists	26	16	9	11	13	29	19	10	14	17
Inhaled corticosteroids	20	22	11	12	9	30	20	11	9	11
Tricyclic and related antidepressant drugs	23	17	1	12	11	27	16	4	9	9
Non-opioid analgesics (excluding aspirin)	159	12	6	15	11	169	12	6	15	10
Opioid analgesics	36	16	8	13	15	29	17	7	12	10
Antibiotics (not otherwise specified)	33	6	0	2	2	33	6	0	3	3
Penicillins	51	5	3	2	2	62	5	3	2	2
Glucocorticoid therapy	47	2	1	11	11	44	2	2	14	13
Female sex hormones	41	23	8	15	10	42	23	7	14	9
Bisphosphonates	23	34	2	12	6	23	35	5	10	8
Iron-deficiency anaemias	27	18	5	7	8	29	18	4	10	11
Drugs used for megaloblastic anaemias	73	1	1	14	10	102	1	1	13	10
Calcium and magnesium	21	16	2	13	8	23	15	1	10	7

[a] Drugs categorised according to BNF paragraph.
[b] The net ingredient cost was estimated for each individual preparation from prescription cost analysis data for England (http://www.doh.gov.uk/stats/pca2000.htm).
[c] Mean use refers to the average number of times a drug was reported as used by a patient.

TABLE 46 *Use and unit costs of aids and adaptations*

Type of appliance	Trial code	*N*	Mean number	SD	Unit cost (£)
Not known (patient reported cost)	Shared care	1	1	0	3.00[a]
	Hospital treatment	3	1	0	67.32[a]
Crutches – elbow	Shared care	4	1	1	25.00[b]
	Hospital treatment	5	1	0	25.00[b]
Crutches – axillary	Shared care	0	0	0	0
	Hospital treatment	1	1	0	25.00[b]
Walking stick	Shared care	14	1	1	20.00[a]
	Hospital treatment	13	1	1	20.00[a]
Wheelchair	Shared care	1	1	0	1400.00[a]
	Hospital treatment	1	1	0	1400.00[a]
Hand splint	Shared care	62	3	1	23.50[b]
	Hospital treatment	59	3	1	23.50[b]
Special shoes	Shared care	38	2	1	48.63[a]
	Hospital treatment	35	2	1	49.08[a]
Special clothing	Shared care	2	3	1	27.90[a]
	Hospital treatment	2	1	0	27.90[a]
Special chair	Shared care	4	1	0	599.00[a]
	Hospital treatment	10	1	0	530.30[a]
Special crockery	Shared care	1	3	0	20.00[a]
	Hospital treatment	2	2	1	20.00[a]
Special cutlery	Shared care	7	1	0	15.29[a]
	Hospital treatment	8	2	1	22.14[a]
Special utensils	Shared care	11	1	0	14.04[a]
	Hospital treatment	14	1	0	13.14[a]
Tap-turner	Shared care	9	2	1	11.11[a]
	Hospital treatment	10	2	1	13.00[a]
Special door handles	Shared care	2	2	1	26.15[c]
	Hospital treatment	2	1	0	26.15[c]
Raised toilet seat	Shared care	10	1	0	10.00[b]
	Hospital treatment	7	1	0	10.00[b]
Bath rails	Shared care	6	1	0	10.00[d]
	Hospital treatment	7	1	0	10.00[d]
Kitchen adaptations	Shared care	1	1	0	0[e]
	Hospital treatment	2	1	0	0[e]
Pen adaptations	Shared care	2	3	1	4.80[a]
	Hospital treatment	2	1	0	9.00[a]
Automatic bath set	Shared care	0	0	0	0
	Hospital treatment	1	1	0	700.00[a]
Bath apparatus	Shared care	3	1	0	92.00[f]
	Hospital treatment	0	0	0	0
Bath boards	Shared care	1	1	0	34.00[b]
	Hospital treatment	2	1	0	34.00[b]
Bath seat	Shared care	1	1	0	280.00[d]
	Hospital treatment	1	1	0	280.00[d]
Bottle opener	Shared care	0	0	0	0
	Hospital treatment	5	1	1	1.99[a]
Can opener	Shared care	1	1	0	14.00[a]
	Hospital treatment	0	0	0	0
Electric can opener	Shared care	1	1	0	12.00[a]
	Hospital treatment	1	1	0	12.00[a]
Chair lift	Shared care	0	0	0	0
	Hospital treatment	1	1	0	1570.00[a]
Chair raise	Shared care	1	4	0	26.00[b]
	Hospital treatment	2	1	0	26.00[b]
Neck collar	Shared care	7	1	0	8.43[g]
	Hospital treatment	5	1	0	8.43[g]
Commode	Shared care	1	1	0	187.00[b]
	Hospital treatment	0	0	0	0

continued

TABLE 46 *Use and unit costs of aids and adaptations (cont'd)*

Type of appliance	Trial code	*N*	Mean number	SD	Unit cost (£)
Dressing aids	Shared care	5	1	0	15.00[a]
	Hospital treatment	7	2	1	14.86[a]
Eye drop dispenser	Shared care	0	0	0	0
	Hospital treatment	1	1	0	6.95[a]
Finger splints	Shared care	2	1	0	20.00[h]
	Hospital treatment	1	4	0	20.00[h]
Foot stool	Shared care	0	0	0	0
	Hospital treatment	5	1	1	63.83[h]
Insoles	Shared care	10	2	0	8.25[b]
	Hospital treatment	4	2	0	8.25[b]
Iron press	Shared care	1	1	0	4.00[d]
	Hospital treatment	0	0	0	0
Jar opener	Shared care	2	3	2	2.00[d]
	Hospital treatment	3	1	1	1.87[d]
Key rings	Shared care	1	1	0	4.00[b]
	Hospital treatment	0	0	0	0
Shoe horn	Shared care	0	0	0	0
	Hospital treatment	4	1	0	2.00[a]
Reacher	Shared care	1	1	0	4.99[a]
	Hospital treatment	1	1	0	4.99[a]
Kitchen knife	Shared care	1	1	0	17.00[a]
	Hospital treatment	0	0	0	0
Motorised carriage	Shared care	0	0	0	0
	Hospital treatment	1	1	0	1800.00[a]
Neck pillow	Shared care	1	1	0	24.99[a]
	Hospital treatment	0	0	0	0
Outside rails	Shared care	1	1	0	12.00[c]
	Hospital treatment	1	1	0	12.00[c]
Elbow protectors	Shared care	1	1	0	21.00[b]
	Hospital treatment	0	0	0	0
Perch seat	Shared care	1	1	0	69.00[b]
	Hospital treatment	1	1	0	69.00[b]
Pillow raiser	Shared care	1	1	0	25.00[a]
	Hospital treatment	2	1	0	25.00[a]
Shoe inserts	Shared care	1	4	0	17.95[b]
	Hospital treatment	3	2	0	17.95[b]
Sock aid	Shared care	0	0	0	0
	Hospital treatment	1	1	0	9.00[b]
Special mattress	Shared care	1	1	0	100.00[a]
	Hospital treatment	1	1	0	100.00[a]
Stair lift	Shared care	1	1	0	2257.00[g]
	Hospital treatment	0	0	0	0
Stair rail	Shared care	1	1	0	50.00[i]
	Hospital treatment	3	1	1	50.00[i]
Bathroom stool	Shared care	1	1	0	54.00[b]
	Hospital treatment	0	0	0	0
Surgical stockings	Shared care	0	0	0	0
	Hospital treatment	2	2	0	11.10[a]
TENS machine	Shared care	1	1	0	60.00[a]
	Hospital treatment	2	1	0	60.00[a]
Toilet rail	Shared care	0	0	0	0
	Hospital treatment	2	1	0	99.00[b]
Trolley	Shared care	0	0	0	0
	Hospital treatment	1	1	0	110.00[b]
Walking frame	Shared care	4	1	0	66.00[b]
	Hospital treatment	1	1	0	66.00[b]
Shower seat	Shared care	2	1	0	341.50[a,b]
	Hospital treatment	5	1	0	70.40[a]

continued

TABLE 46 *Use and unit costs of aids and adaptations (cont'd)*

Type of appliance	Trial code	*N*	Mean number	SD	Unit cost (£)
Splint repair	Shared care	0	0	0	0
	Hospital treatment	1	1	0	23.50[j]
House modification	Shared care	4	1	0	0[e]
	Hospital treatment	0	0	0	0[e]

[a] Average cost reported by the patient (2001) in the resource use questionnaire.
[b] Average cost from Millercare Mobility Specialists (2003).
[c] Average cost from www.promedics.co.uk (2003).
[d] Average cost reported by patient as cost to NHS (2001) in the resource use questionnaire.
[e] The cost of these adaptations cannot be estimated accurately. Contact was made with Manchester City Council; however prices vary considerably given that grants are available up to £50,000 (2003).
[f] The average cost of bath rails, bath boards, bathroom stool, bath seat and shower seat was used as the average cost of bath apparatus.
[g] Average from www.mobility.co.uk (2003).
[h] Average from www.brookmobility.co.uk (2003).
[i] Average from www.benfitsnowshop.co.uk (2003).
[j] Assumed to be cost of a new splint.

Appendix 5

Sensitivity analysis

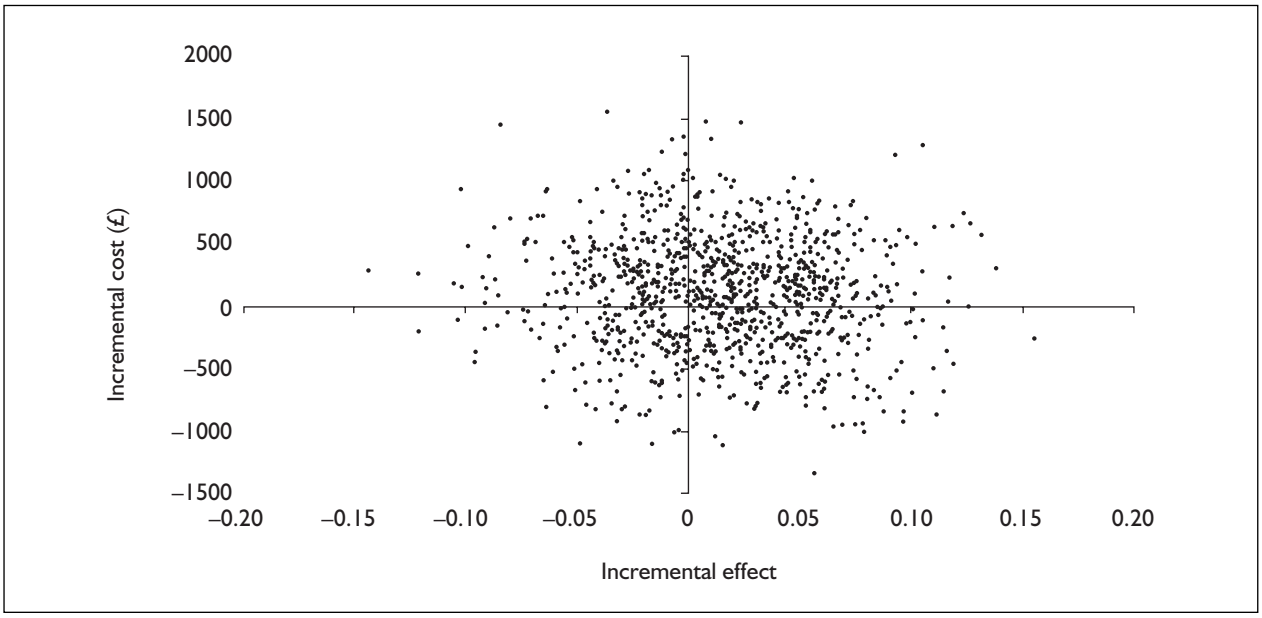


FIGURE 12 *Cost-effectiveness plane QALYs adjusted for baseline utility*

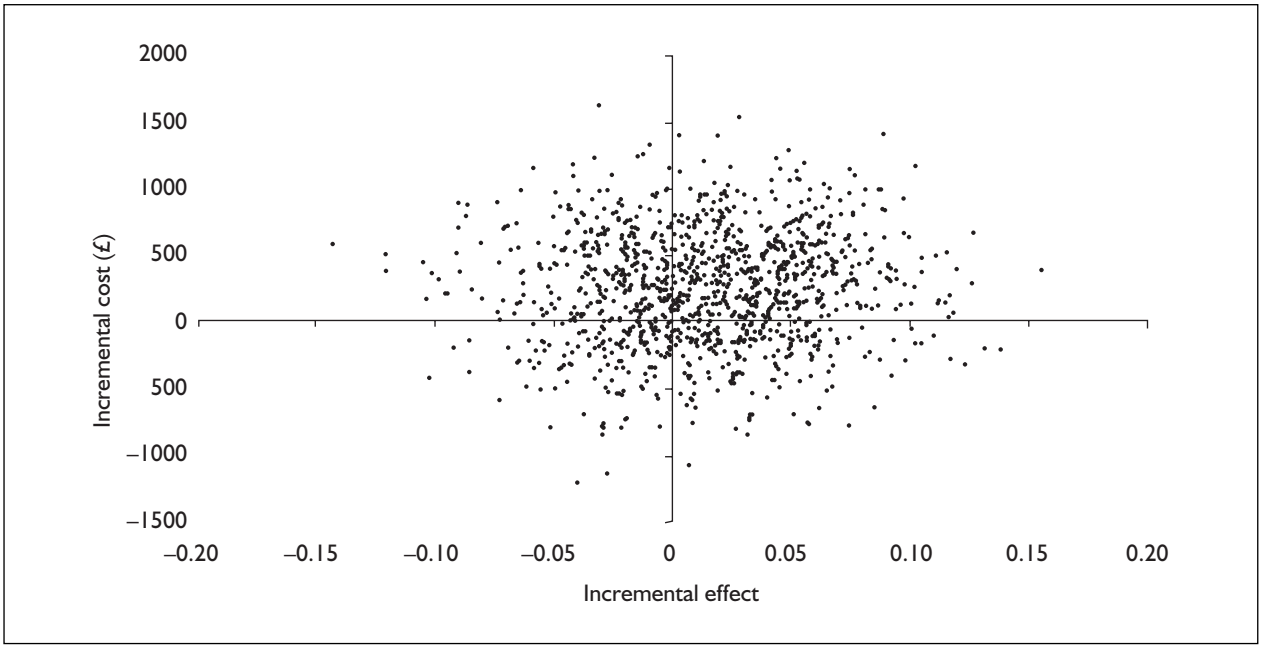


FIGURE 13 *Cost-effectiveness plane QALYs and costs adjusted for baseline utility*

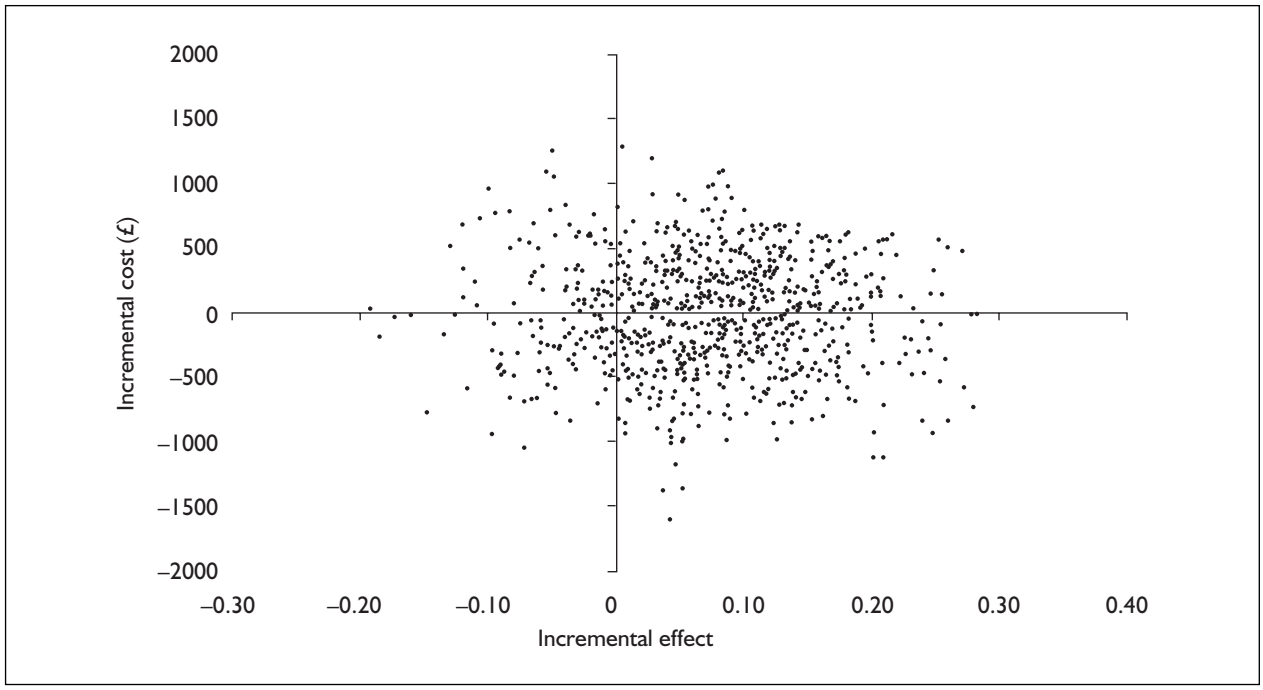


FIGURE 14 *Cost-effectiveness plane for no imputation of missing or censored data*

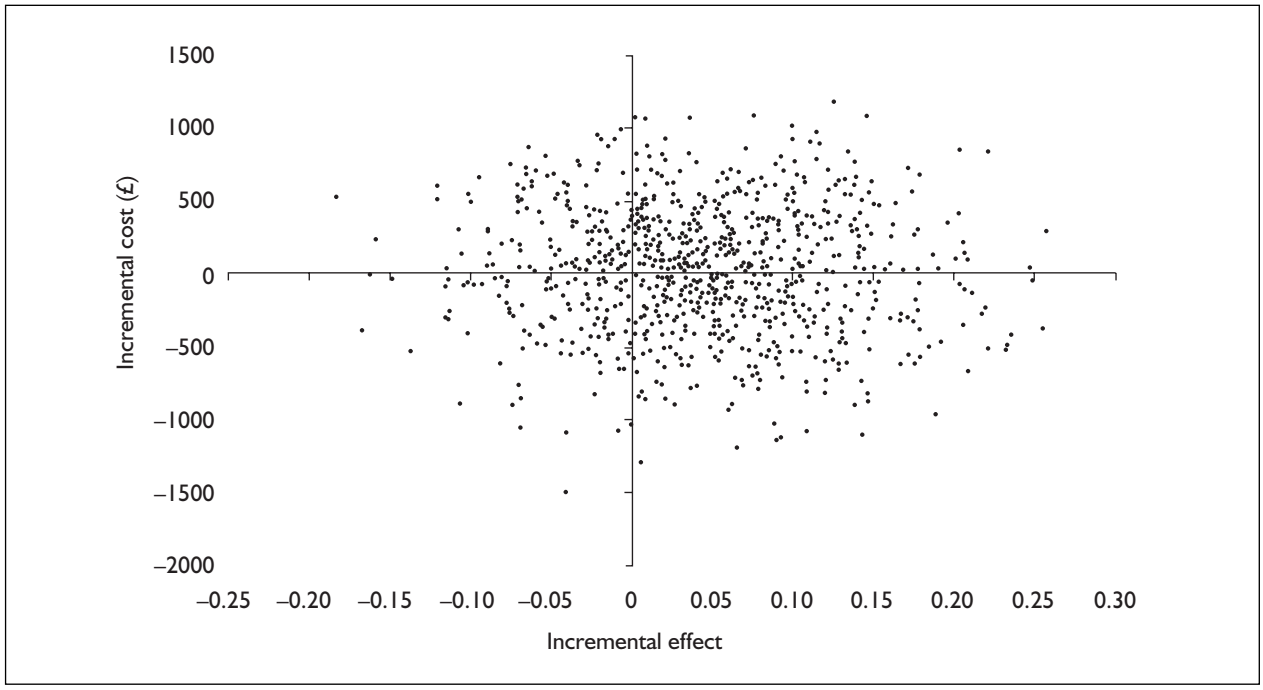


FIGURE 15 *Cost-effectiveness plane for no imputation of censored data*

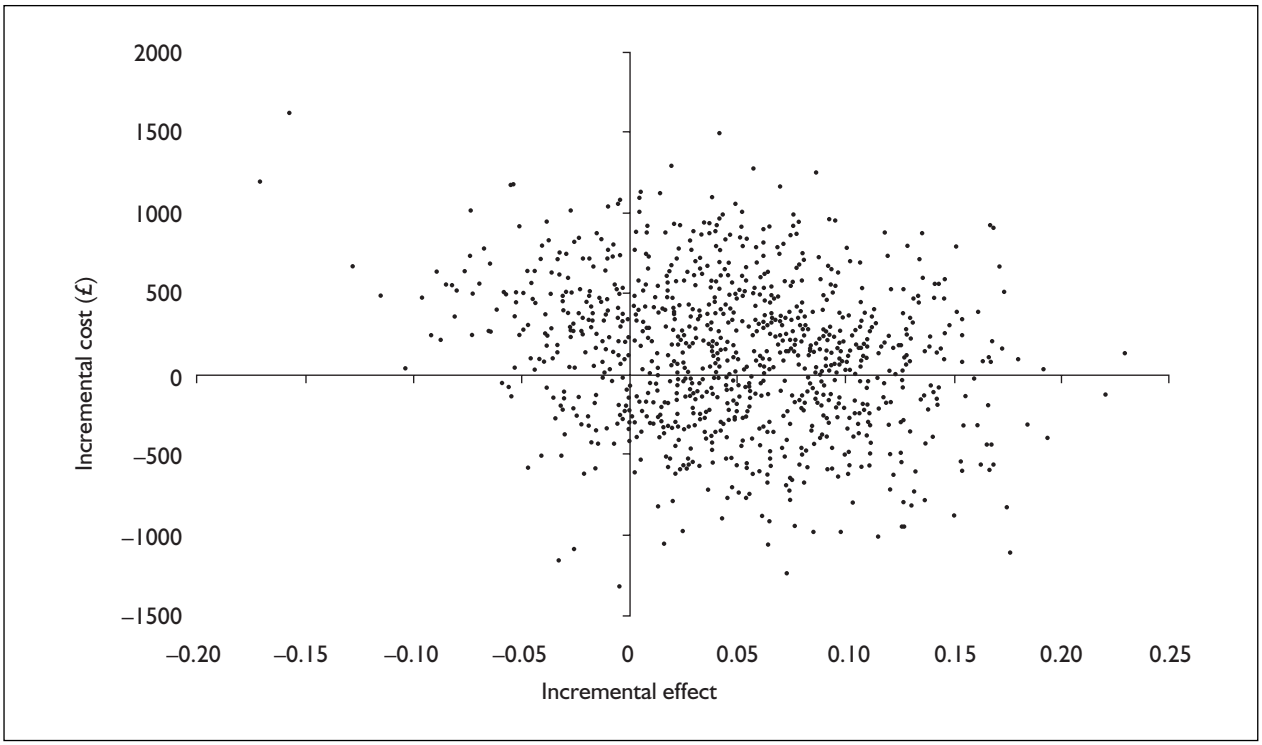


FIGURE 16 *Cost-effectiveness plane for censored QALY data imputed by last observation carried*

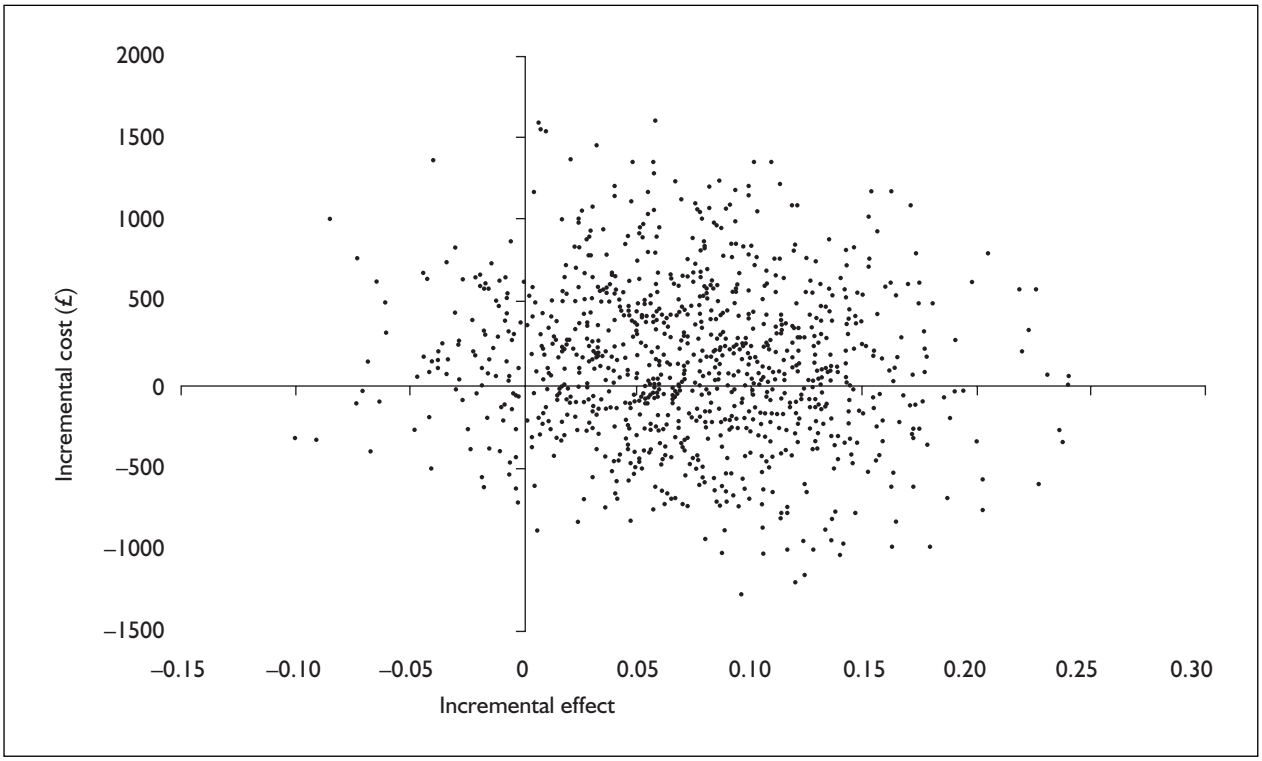


FIGURE 17 *Cost-effectiveness plane for 0% discount rate QALYs and costs*

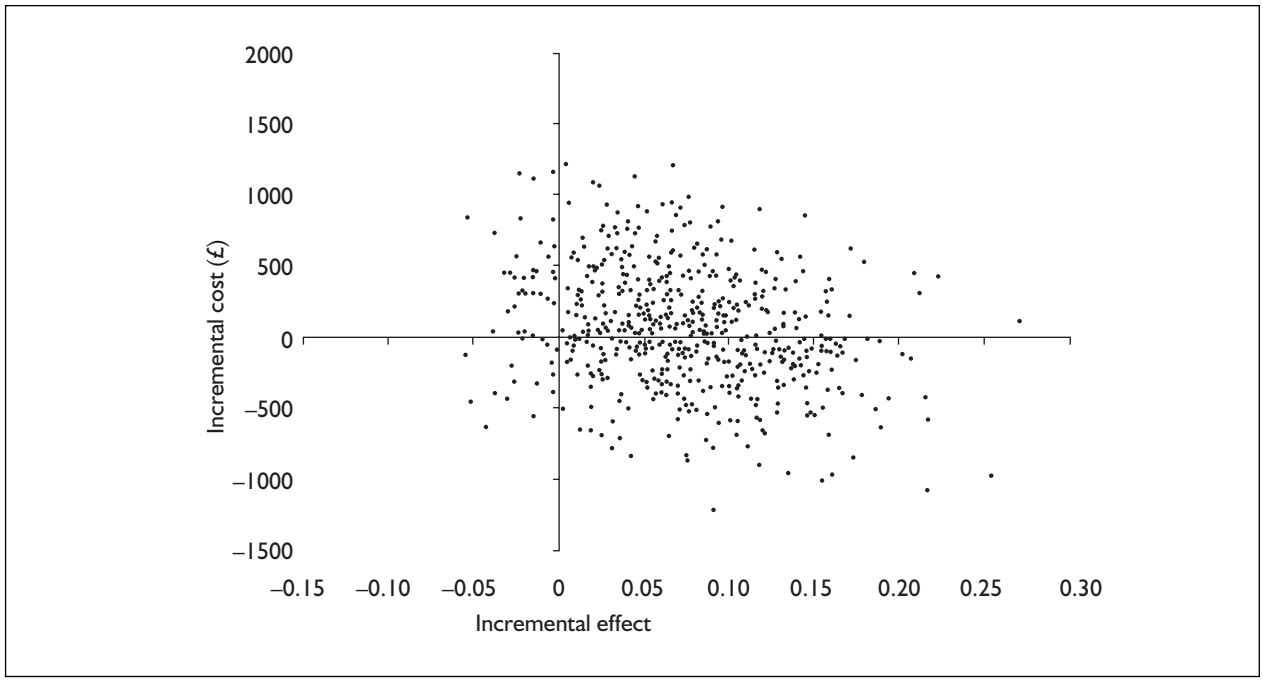


FIGURE 18 *Cost-effectiveness plane for 1.5% discount rate QALYs and 3.5% costs*

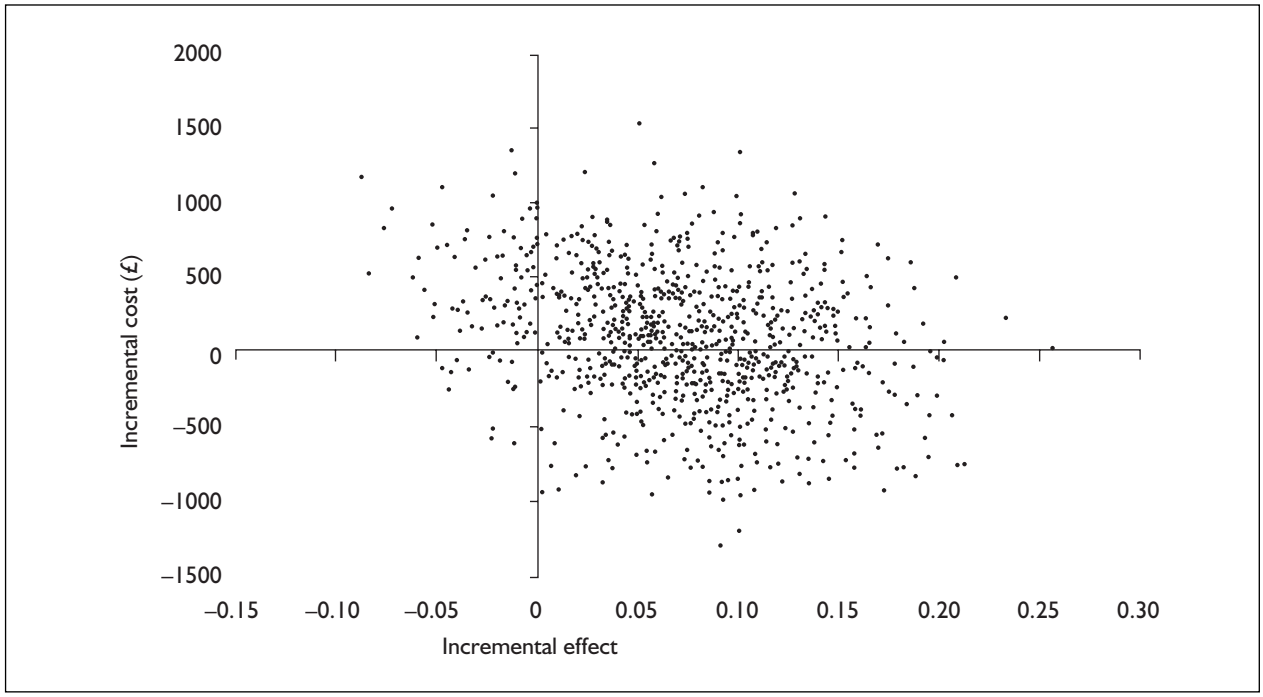


FIGURE 19 *Cost-effectiveness plane for 1.5% discount rate QALYs and 6% costs*

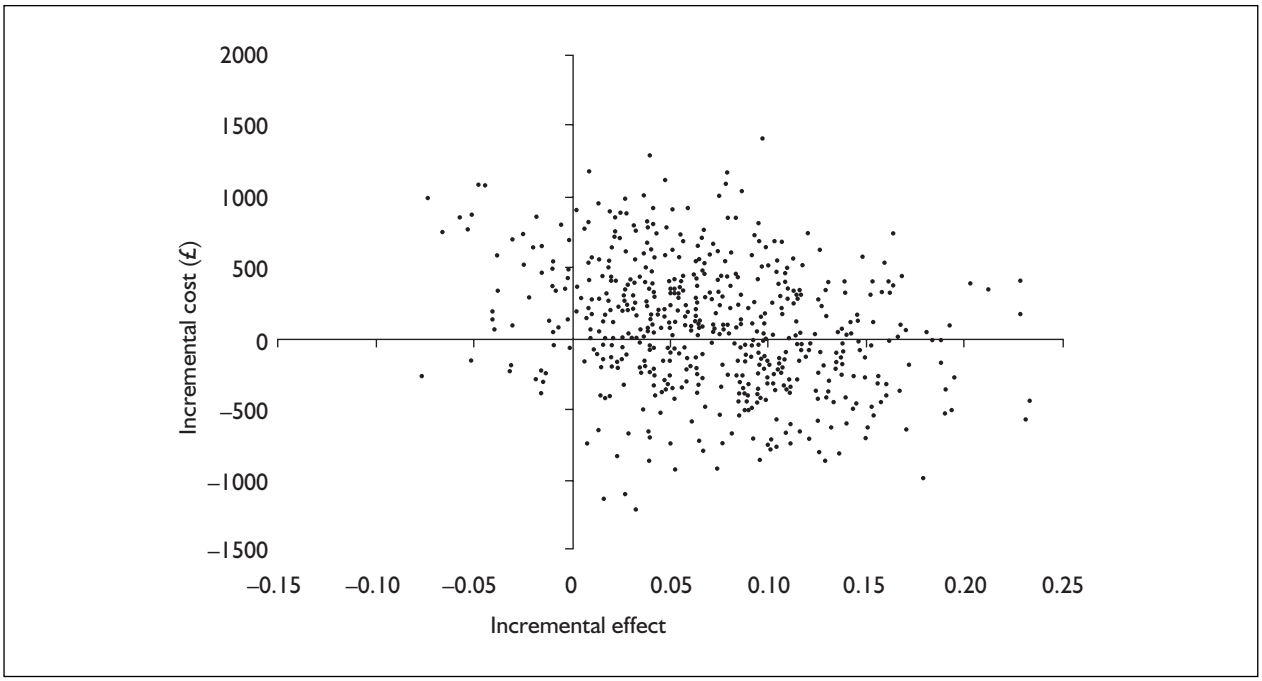


FIGURE 20 *Cost-effectiveness plane for 6% discount rate QALYs and costs*

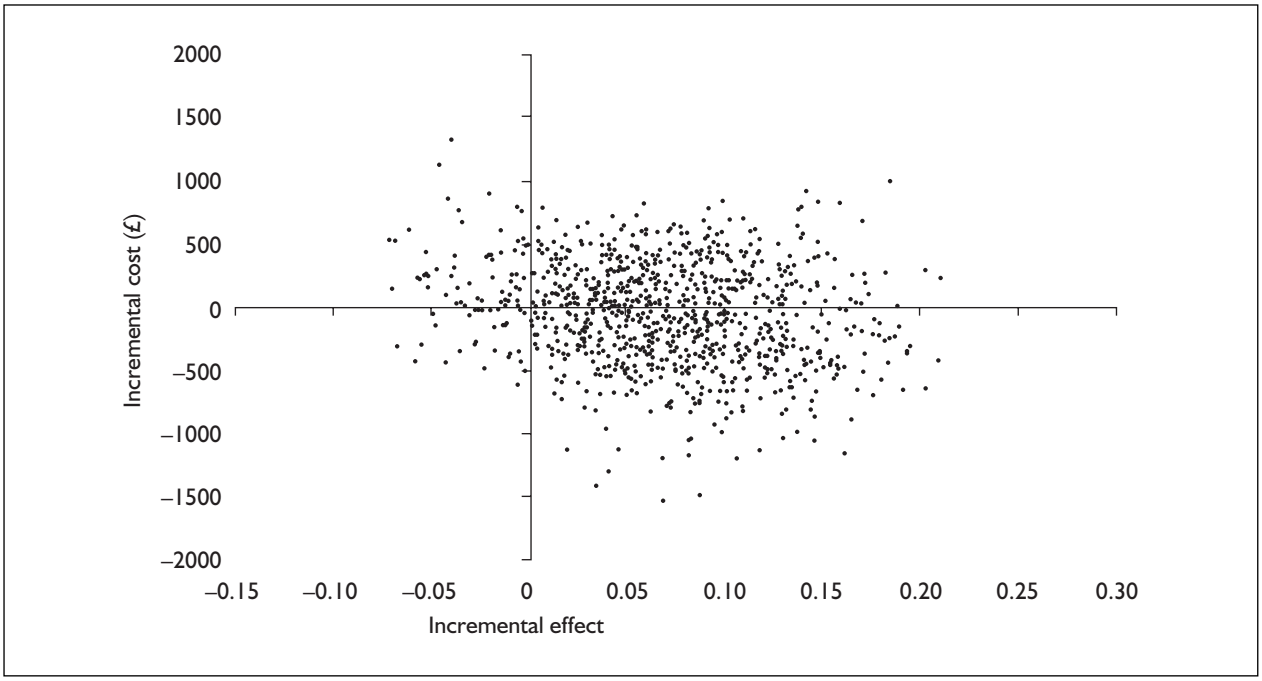


FIGURE 21 *Cost-effectiveness plane for costs excluding costs of drug therapy*

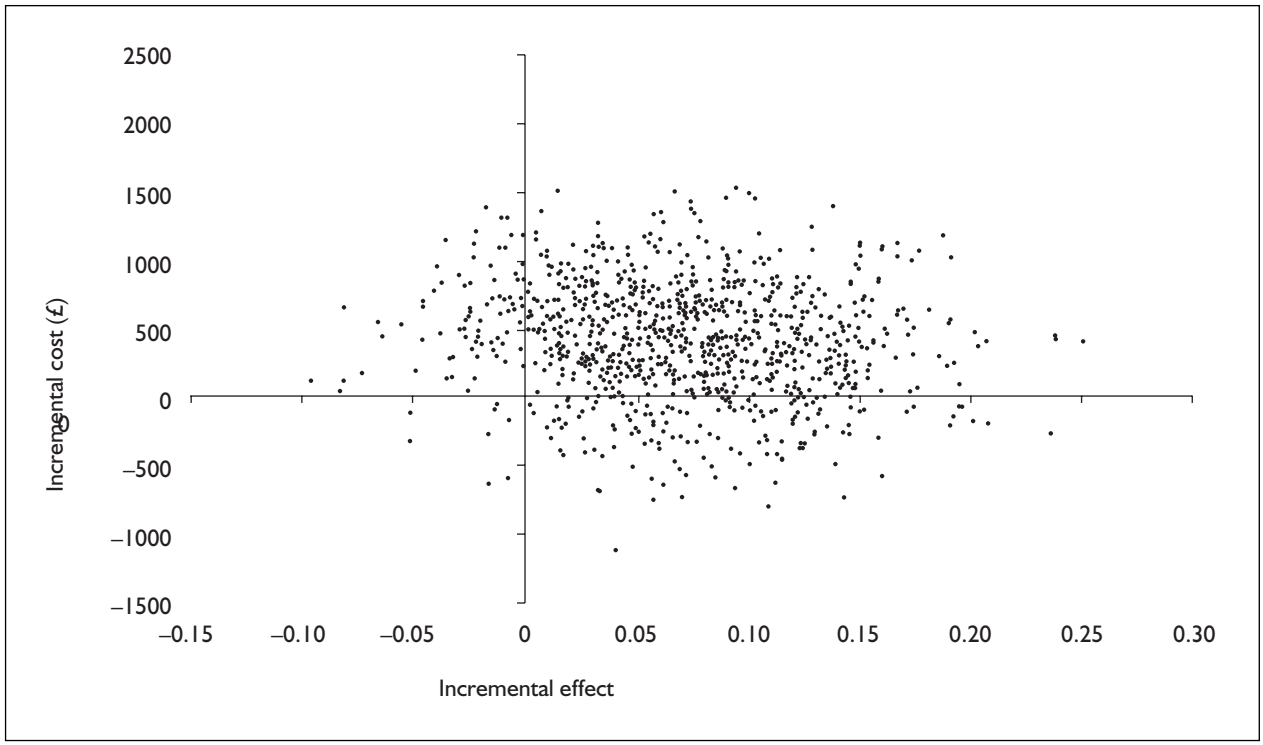


FIGURE 22 *Cost-effectiveness plane for costs including costs of protocol visits and excludes cost of drug therapy*

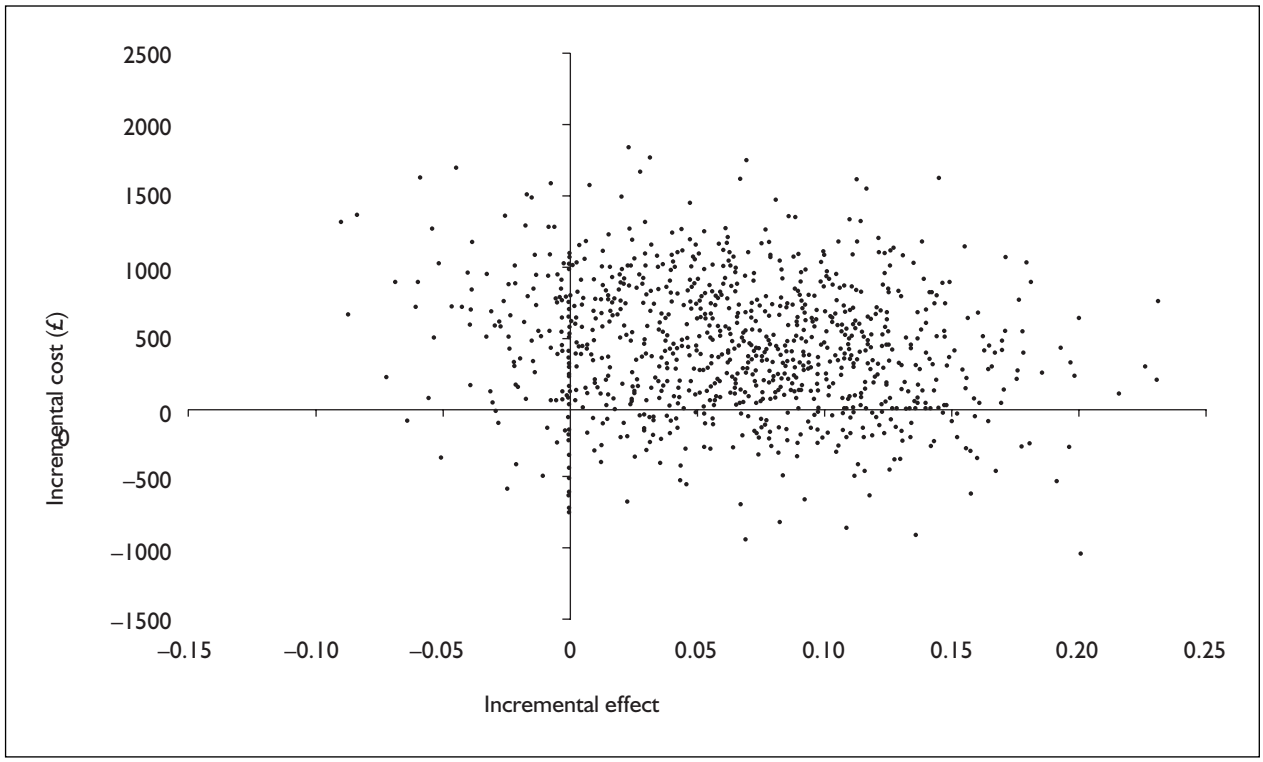


FIGURE 23 *Cost-effectiveness plane for costs including costs of protocol visits*

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We look forward to hearing from you.

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