# Specialized Rheumatology Nurse Substitutes for Rheumatologists in the Diagnostic Process of Fibromyalgia: A Cost-Consequence Analysis and a Randomized Controlled Trial

MARIËLLE E. KROESE, JOHAN L. SEVERENS, GUY J. SCHULPEN, MONIQUE C. BESSEMS, FRANS J. NIJHUIS, and ROBERT B. LANDEWÉ

***ABSTRACT.*** ***Objective.*** To perform a cost-consequence analysis of the substitution of specialized rheumatology nurses (SRN) for rheumatologists (RMT) in the diagnostic process of fibromyalgia (FM), using both a healthcare and societal perspective and a 9-month period.

***Methods.*** Alongside a randomized controlled trial, we measured costs and consequences of a nurse-led diagnostic consult (SRN group, n = 97) versus a rheumatologist-led diagnostic consult [usual care (UC) group, n = 96]. Patients were followed for 9 months. Every second month a questionnaire on medical consumption and social participation was filled out. Satisfaction was measured 1 week after the first consultation. During followup, health status was measured by health-related quality of life (EQ-5D), functional status (Fibromyalgia Impact Questionnaire), fatigue (Checklist Individual Strength), and self-efficacy (Generalized Self-Efficacy Scale).

***Results.*** Patients in the SRN group were significantly more satisfied. Improvements in health status were similar in both groups after 9 months of followup. Total costs for healthcare consumption and patient and family costs were significantly lower in the SRN group (€1298 vs €1644; difference €346; 95% CI –€746 to –€2). Total societal costs were €3853 per patient for the SRN group and €5293 for the UC group after 9 months of followup (difference €1440; 95% CI –€3721 to €577).

***Conclusion.*** From both a healthcare and societal perspective, the nurse-led diagnostic process can be recommended. Patients in the SRN group were significantly more satisfied, improvements in health status were similar in both groups, and total societal costs were lower for the SRN group compared to the RMT group after 9 months' followup. Registered with Current Controlled Trials, no. ISRCTN77212411. (J Rheumatol First Release April 1 2011; doi:10.3899/jrheum.100753)

*Key Indexing Terms:*
FIBROMYALGIA
OUTCOME AND PROCESS ASSESSMENT
COSTS AND COST ANALYSIS
CLINICAL TRIAL

Fibromyalgia (FM) is a chronic pain disorder characterized by generalized musculoskeletal pain and concomitant symptoms such as fatigue, sleep disturbances, cognitive dysfunction, and depression. The prevalence has been estimated at 2% to 4% in the general population, forming 10% to 20% of rheumatologic consultations and 5% to 8% of primary care consultations[1,2].

Patients with FM rate their quality of life extremely low compared with other groups of patients[3,4,5,6]. FM diminishes social and occupational functioning[7]. The economic burden of FM is considerable because of reduced productivity or ability to work and a high use of healthcare resources[8,9,10,11,12,13,14,15].

Patients may repeatedly present to the general practition-

*From the Department of Integrated Care; Department of Health Organization, Policy, and Economics; Department of Internal Medicine, Division of Rheumatology, Maastricht University Medical Centre; CAPHRI School of Public Health and Primary Care, Maastricht University; the Foundation 'Regionale HuisartsenZorg Heuvelland,' Maastricht; and the Institute of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands.*

*Supported by the Maastricht University Medical Centre and Care Renewal Grants by courtesy of medical insurance companies in the regions.*

*M.E.A.L. Kroese, MSc, Department of Integrated Care and CAPHRI School of Public Health and Primary Care, Maastricht University Medical Centre; J.L. Severens, PhD, Professor, Department of Health Organization, Policy, and Economics and CAPHRI School of Public Health and Primary Care, Maastricht University Medical Centre and Institute of Health Policy and Management, Erasmus University Rotterdam; G.J.C. Schulpen, MD, PhD, Foundation 'Regionale HuisartsenZorg Heuvelland'; M.C.M. Bessems, Department of Integrated Care and CAPHRI School of Public Health and Primary Care, Maastricht University Medical Centre; F.J. Nijhuis, PhD, Professor, Department of Health Organization, Policy, and Economics and CAPHRI School of Public Health and Primary Care, Maastricht University Medical Centre; R.B.M. Landewé, MD, PhD, Professor, Department of Internal Medicine, Division of Rheumatology and CAPHRI School of Public Health and Primary Care, Maastricht University Medical Centre.*

*Address correspondence to M.E.A.L. Kroese, Department of Integrated Care, Maastricht University Medical Centre, PO Box 5800, 6202 AZ Maastricht, The Netherlands. E-mail: marielle.kroese@mumc.nl.*

*Accepted for publication February 4, 2011.*

er (GP) with various symptoms before a diagnosis of FM is made. This delay may result in repetitive drug prescriptions, multiple diagnostic tests, and referrals to medical specialists and other healthcare providers[16].

Little is known about the effect of labeling a patient with a diagnosis of FM. There are 2 schools of thought[16]. A diagnosis of FM may lead to increased illness behavior, dependence on healthcare providers, and increased health service costs[17,18]. A diagnosis of FM, however, may also reduce the number of referrals, use of healthcare providers, and costs[16,19].

The importance of a prompt diagnosis in patients who are at risk of developing persistent pain and pain-related behavior is increasingly recognized[20]. Early diagnosis and intervention may reassure the patient and reduce or prevent disability, which in turn will reduce societal and medical costs. Cost savings allowed by a diagnosis are estimated at €126 (2007 values) to €200 (2003 values) per patient per year[16,21].

Limitations in healthcare capacity and a high prevalence of FM may jeopardize an early approach. In Maastricht, in the southern part of The Netherlands, this problem was addressed by designing a nurse-led diagnostic process, in which trained, specialized rheumatology nurses (SRN) assist in the diagnostic process and simultaneously provide nursing care such as information, education, and support to this group of patients.

Over the last decade, the role of specialized nurses has evolved in undertaking such extended activities as patient assessments, formulating and carrying out plans of disease management, and making referrals to other health professionals[22,23].

In our previous study on the feasibility of substituting SRN for rheumatologists (RMT) in the diagnostic process of FM, we have shown that this approach is safe (no misclassifications), avoids waiting time, provides better patient satisfaction, and is cheaper from a health service perspective[24]. Insight into the full societal consequence of this nurse-led diagnostic process is important for health professionals, healthcare management, health policy decision makers, and third-party payers. Our study investigates the effect of a timely diagnosis for FM by an SRN on health outcomes, social participation, and costs from both a healthcare and societal perspective.

## MATERIALS AND METHODS

*Patients*. Between December 2003 and November 2005, we performed a 9-month pragmatic, prospective, randomized controlled trial with patients who were referred by their GP to the rheumatology outpatient clinic of the Maastricht University Hospital with a referral letter describing symptoms of FM. Inclusion criteria were suspicion of FM, first referral to the rheumatology outpatient clinic, age between 18 and 65 years, and the ability to read and write the Dutch language. Exclusion criteria were severe comorbidity and involvement in a legal procedure because of a disability pension. The protocol was approved by the local ethics committee of the University Hospital and University of Maastricht and all participants gave written informed consent. Current Controlled Trials no. ISRCTN77212411.

*Intervention*. The procedure of this RCT has been described in detail[24]. Patients were randomly assigned to either the nurse-led diagnostic consultation (SRN group) or to the regular physician-led diagnostic consultation [usual care (UC) group]. The SRN patients were seen within 3 weeks by experienced SRN (n = 2) who were trained in the diagnosis of FM. During the consultation, the SRN used a checklist in detecting symptoms of FM as well as conditions that should be excluded. Also, a routine blood test was done. In a standardized 5-min supervision session immediately following the SRN consultation, an RMT who was involved in the study was informed by the SRN about the medical history. Further, the RMT performed a brief physical examination, and confirmed or rejected the diagnosis made by the SRN.

Patients in the UC group were seen in a regular clinical visit by an RMT after a waiting period of about 3 months. This visit included extensive history-taking, physical examination, and additional tests if considered necessary by the RMT. In both groups, FM was diagnosed according to the American College of Rheumatology criteria[25].

*Study design*. A prospective cost-consequence analysis[26] was performed to be able to present an array of outcome measures alongside cost for the 2 procedures of diagnostic process. Such an analysis is opportune if it is not feasible or practical to value all costs and benefits in monetary terms[27]. In this situation, available monetary values can be augmented by other measures of cost and benefit such as waiting time and patient satisfaction[27]. Presenting the results of our economic evaluation in a disaggregated format allows readers and decision makers to select the information most relevant to their perspective, while the overview of all aspects reflects the societal perspective.

*Health assessments*. Outcome measures recorded were patient satisfaction, health-related quality of life (HRQOL), functional status, fatigue, self-efficacy, medical consumption, and social participation. Patient satisfaction was measured 1 week after the first consultation. HRQOL and participation were assessed by 2 monthly questionnaires. Functional status, fatigue, and self-efficacy were assessed at baseline (before randomization) and after 3 weeks, and at 3, 6, and 9 months of followup.

Patient satisfaction was measured with questions derived from the QUOTE (Quality of Care Through the Patient's Eyes)–Rheumatic Patients[28], where Q-values ≥ 1 reflect care aspects that could be improved. Further details have been described[24].

HRQOL was measured by the EuroQol-5D (EQ-5D), a self-administered, generic instrument that incorporates descriptions and valuations of health states[29]. The EQ-5D was developed and validated in a number of European countries, including The Netherlands[30,31,32], and has been used several times with patients with FM[4,6]. We used the British (for reasons of comparison to foreign studies) and the Dutch utility tariff, with results in possible utilities ranging from –0.59 and –0.33, respectively (worst imaginable health state), to 1 (best imaginable health state, equal to full health)[31,32,33,34]. The EQ-5D includes a visual analog scale (VAS) on which patients rate their current health state with endpoints of 100 (best imaginable health state) to 0 (worst imaginable health state). So the EQ-5D utility is a reflection of how society values the patient's health state, and the EQ-VAS is a reflection of how patients value their own health state.

Social participation was assessed by questions on productivity as well as unpaid activities. A self-developed questionnaire measured paid labor (e.g., hours of paid employment, hours of sick leave). Time spent on unpaid tasks, chores, leisure, and social activities in the past 2 months was measured by an adapted activity questionnaire based on the Utrechtse Activiteiten Lijst[35,36], a Dutch adaptation of the Craig Handicap Assessment Rating Technique[37]. The unpaid participation was divided into unpaid tasks and chores (hours per week spent on study, housekeeping, odd jobs around the house, and voluntary work) and leisure and social activities (hours per week spent on sports, club life, social activities, and other leisure activities).

Functional status was measured with the Fibromyalgia Impact Questionnaire (FIQ), a self-administered 10-item instrument that measures

physical functioning, number of days felt well, number of days unable to work because of FM symptoms, work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety, and depression[38]. All items of the FIQ were standardized on a scale ranging from 0 to 10, with 10 indicating greater impairment. The total FIQ score was calculated by adding up the 10 items (range 0–100)[39].

Fatigue was assessed by the Checklist Individual Strength (CIS-20), a 20-item self-report questionnaire[40]. Each item was scored on a 7-point Likert scale, and a CIS total score is calculated by adding up the score of the 20 items (range 20–140). Higher scores indicate more problems.

The Generalized Self-Efficacy Scale is a 10-item scale designed to assess optimistic self-beliefs to cope with a variety of difficult demands in life[41]. Responses are made on a 4-point scale and are summed to yield the final score, ranging from 10 to 40, with 10 indicating lower self-efficacy.

*Cost assessment*. Costs during the 9-month followup period were assessed from the societal perspective, including healthcare consumption, patient and family costs, and productivity costs. Two monthly cost diaries [t1 (before randomization) – t6] completed by the patients were used to estimate healthcare costs (e.g., consultations, medication, home care) and non-healthcare costs (e.g., home help, informal care, medical aids, health activities, and productivity costs). Table 1 shows the cost items defined and the price value used. Prices were generally obtained from Dutch standard prices that were defined to reflect societal costs and to standardize economic evaluations[42]. The calculation of costs of the diagnostic process has been described in detail[24]. We used the tariffs of the Dutch National Health Tariffs Authority of 2006. Overhead costs were not taken into consideration.

All costs were presented in 2007 prices and inflated where appropriate, using the general Dutch consumer price index rate (Centraal Bureau voor de Statistiek, Den Haag, Netherlands; website: www.cbs.nl). The costs of the diagnostic process were published in 2006 prices[24] and were also

*Table 1*. Costs per unit by categories, and sources of cost estimates.

| Cost Categories | Source of Estimate | Cost per Unit, € (2007) |
|---|---|---|
| Hospital | | |
| Diagnostic process of fibromyalgia | Dutch National Health Tariffs authority[24] | Various |
| Outpatient | Oostenbrink[42] | 110.83/visit[a] |
| Specialized nurse | Oostenbrink[42] | 84.38/visit[a] |
| General practitioner | | |
| Practice | Oostenbrink[42] | 21.98/contact[b] |
| Home | Oostenbrink[42] | 42.75/contact |
| Telephone | Oostenbrink[42] | 10.69/contact |
| Out-of-hours services (practice) | Dutch National Health Tariffs Authority | 65.02/contact[a] |
| Out-of-hours services (telephone) | Dutch National Health Tariffs Authority | 25.00/contact |
| Healthcare professionals | | |
| Physical therapist | Oostenbrink[42] | 24.68/contact[b] |
| Mensendieck and Cesar therapy | Oostenbrink[42] | 24.95/contact[b] |
| Occupational therapist | Oostenbrink[42] | 24.95/contact[b] |
| Psychologist | Oostenbrink[42] | 76.31/contact[b] |
| Social worker | Dutch National Health Tariffs Authority | 55.61/contact[b] |
| Activity therapy | Dutch National Health Tariffs Authority | 55.61/contact[b] |
| Dietician | Oostenbrink[42] | 27.06/contact[b] |
| Alternative medicine | Patient-reported costs | Various[b] |
| Medication | | |
| Prescribed drugs | Pharmacotherapeutic compass 2007[63] | Various/DDD |
| OTC drugs | Patient-reported costs | Various |
| Day care | Oostenbrink[42] | 128.03/day |
| Professional domestic care | Oostenbrink[42] | 22.96/h |
| Informal care | | |
| Various | Oostenbrink[42] | 8.78/h |
| Paid housekeeper | Oostenbrink[42] | 8.78/h |
| Meal service | Estimated market price | 7.00/day |
| Expenses for health activities | Patient-reported costs | Various |
| Expenses for medical aids | Patient-reported costs or estimated market price[c] | Various |
| Productivity costs | Oostenbrink[42] | Men |
| | Standard hourly wage by age for mean and women | 15–24 yrs: €20.49 |
| | | 25–34 yrs: €32.74 |
| | | 35–44 yrs: €40.86 |
| | | 45–54 yrs: €45.37 |
| | | 55–65 yrs: €47.82 |
| | | Women |
| | | 15–24 yrs: €20.07 |
| | | 25–34 yrs: €29.88 |
| | | 35–44 yrs: €33.60 |
| | | 45–54 yrs: €34.21 |
| | | 55–65 yrs: €36.41 |

[a] Including €5.02 travel expenses (mean distance to hospital 7 km): 14 × 0.17/km + €2.65 (parking)[42]; [b] Including €0.61 travel expenses (mean distance to GP/PT 1.8 km): 3.6 × 0.17/km; [c] by various websites, e.g., www.thuiszorgwinkel, www.medireva.nl. OTC: over the counter; DDD: daily defined dose.

indexed. For 8 patients in the RMT group, costs for the diagnostic process could not be calculated because they canceled their appointment. Therefore, the mean costs of the diagnostic process of the remaining 88 patients were used.

Productivity costs were calculated by using the human capital limited approach (HClim). This approach estimates the value of all potentially lost production, in contrast with the friction cost method, in which productivity costs are only counted as long as it takes to replace someone[43,44]. The difference between the HClim and the HC extended approach (HCext) is that in HClim, disease-related work disability at baseline is not taken into account, while in HCext, work disability at baseline is included in the estimation of productivity costs[45]. We chose HClim because FM leads to disease-related work disability for a substantial number of patients. In the cost diary, patients reported their official working hours per week and the number of days and hours of absenteeism. Because FM is highly prevalent in middle-aged women, paid work was valued at age-dependent and sex-dependent standard hourly costs, ranging from €17 to €41 per hour (including 80% production elasticity)[42]. Costs associated with paid labor were calculated for each patient as the difference between the official working hours reported and the number of hours actually worked, valued at the patient's value per hour.

*Sample size*. The power calculation was based upon the acceptability of a 3-month waiting time for a first visit led by a rheumatologist, as described[24].

*Statistical analysis*. All analyses were conducted on the basis of intention-to-treat. Descriptive statistics were used for demographic and clinical variables and included percentages, means, and standard deviations.

Because of the rather large number of missing values in the cost and social participation data at t3 to t5 (31%–42%), we used a nonparametric multiple imputation method, which replaces each missing value with a set of "m" plausible values to generate 5 replacement values (m = 5) for each of the missing cells in these datasets, using multiple linear regression models. Means presented for cost and social participation are an average of the means from the 5 datasets created.

Average total costs were calculated for patients in each group. Given that cost data are often positively skewed, a nonparametric bootstrap method was used to obtain uncertainty intervals for the mean differences in costs[46].

Because of the random assignment, differences in health outcome at baseline were considered to occur by chance[47]. For consistency, health outcome data at 9 months of followup were treated in the same way as the cost data: a multiple imputation method was used to generate 5 replacement values for each of the missing cells and the nonparametric bootstrap was applied to calculate uncertainty intervals.

Statistical analysis was performed using SPSS 17.0 (SPSS, Chicago, IL, USA). Bootstrapping was performed using Excel.

## RESULTS

*Patient characteristics*. A total of 193 patients were randomized (97 to the SRN group and 96 to the UC group). Comparison of patient characteristics showed no meaningful differences between the SRN and the UC group. The majority of the patients were women. The mean (SD) age was 44.1 (11.1) and 44.7 (11.9) years in the SRN and UC groups, respectively. The mean (SD) duration of complaints at presentation was 6.1 (7.2) years in the SRN group and 5.7 (6.8) years in the UC group. Most patients (86% in the SRN and 79% in the UC group) indicated additional health problems.

Resource use 2 months prior to randomization is described in Table 2. The UC group reported more GP contacts (3.3 vs 2.5), but fewer physical therapy consultations (1.8 vs 2.9). A majority of the patients used prescribed medications (58.8% in the SRN and 52.1% in the UC group). Mean costs for prescribed medications were €34.1 in the SRN group and €25.5 in the UC group. Use of over-the-counter medications was higher in the SRN group (47.4% vs 39.6%). Costs for (paid and unpaid) help and medical aids were higher in the UC group (help: €62 vs €34; medical aids: €25.0 vs €3.6). In the SRN group, more money was spent on health activities (€20.7 vs €10.4).

More patients in the SRN group had a job (47.4% vs 36.8%), especially a full-time job (22.7% vs 11.7%) and fewer of those patients received a disability insurance benefit (22.7% vs 34.7%). The percentage of patients with sick pay was 21.6% in the SRN group and 25.0% in the UC group. The SRN group had more contractual hours (15.1 vs 11.7 per week), worked a higher number of hours (12.2 vs 8.2 per week), and reported a lower number of sick leave hours during the 2 months prior to randomization (25.4 vs 35.2).

*Health outcomes*. Table 3 shows the results on waiting time and patient satisfaction of the 2 approaches, as published[24]. The mean waiting time after randomization was 2.8 weeks in the SRN group and 12.1 weeks in the UC group ($p \leq 0.0001$). In the UC group, 8 patients canceled their appointments because of a too-long waiting time. Patients in the SRN group were significantly more satisfied than patients in the UC group with regard to nearly all items.

The changes in health status during the 9 months of followup are presented in Table 4. The UC group scored lower than the SRN group at baseline and at 9 months of followup on nearly all health outcomes. The improvements are fairly similar across the 2 groups.

*Healthcare and productivity costs*. The costs of the diagnostic process have been published[24] and are presented in Table 3. Mean total costs of the diagnostic process were lower in the SRN group than in the RMT group (€219 per patient vs €282 per patient; 95% uncertainty interval €–103 to €–20).

The use of healthcare resources during the 9 months of followup is summarized in Table 2. The resource use is generally higher in the UC group. The UC group reported significantly more contacts with GP, medical specialists, and other paramedical professionals and significantly more hours of paid housekeeping help.

Table 5 shows a comparison of paid and unpaid activities between the SRN group and the UC group. After 9 months of followup, a slight decrease in contractual hours and a small increase in actually worked hours is seen in both groups. Also, a substantial decrease in sick leave is observed, especially in the UC group. The decrease of absenteeism in the UC group occurred only in the last month of followup, resulting in higher costs for absenteeism in this group (€–1109; 95% uncertainty interval €–3581 to €–1094).

*Table 2*. Average resource use per patient 2 months before baseline and during 9 months' followup (mean) and difference in resource use during 9 months' followup between UC group and SRN group. Boldface type indicates significant difference.

| Cost Components | UC Group, n = 96 | | SRN Group, n = 97 | | Difference (95% UI) |
|---|---|---|---|---|---|
| | 2 Mo Before Baseline | During 9 Mo Followup | 2 Mo Before Baseline | During 9 Mo Followup | Resource Used During 9 Mo Followup |
| Healthcare consumption | | | | | |
| Total GP contacts | 3.3 | 6.1 | 2.5 | 4.6 | **–1.5 (–2.6 to –0.2)** |
| Outpatient specialist care contacts | 0.6 | 0.8 | 0.3 | 0.5 | **–0.3 (–0.6 to 0.0)** |
| Physical therapy contacts | 1.8 | 9.8 | 2.9 | 8.0 | –1.8 (–4.6 to 1.4) |
| Psychological therapy contacts | 0.4 | 1.8 | 0.4 | 1.7 | –0.1 (–1.1 to 1.0) |
| Other therapy contacts | 0.5 | 3.4 | 0.3 | 1.9 | **–1.5 (–2.9 to –0.3)** |
| Multidisciplinary day care (no. contacts) | 0.0 | 0.9 | 0.0 | 0.6 | –0.3 (–1.4 to 0.6) |
| Home help (h/wk) | 0.1 | 0.7 | 0.1 | 0.8 | 0.1 (–0.5 to 0.7) |
| Patient and family costs | | | | | |
| Paid housekeeping help (h/wk) | 0.3 | 2.7 | 0.2 | 1.5 | **–1.2 (–2.5 to –0.1)** |
| Unpaid help from family/ friends (h/wk) | 0.2 | 4.2 | 0.0 | 2.5 | –1.7 (–4.1 to 0.4) |
| Meal provision (no. meals) | 0.0 | 0.5 | 0.3 | 1.7 | 1.2 (–0.1 to 3.3) |

UC: usual care; SRN: specialized rheumatology nurses; UI: uncertainty interval based on bootstrap replications; GP: general practitioner.

*Table 3*. Cost consequence of diagnostic procedure (means): comparison between UC group and SRN group. Boldface type indicates significant difference.

| Cost Components | Usual Care, n = 96* | | SRN Group, n = 97 | | Difference (95% UI**) |
|---|---|---|---|---|---|
| | Units | Costs (€) | Units | Costs (€) | |
| Waiting time, wks | 12.1 | | 2.8 | | **–9.3 (–10.0 to –8.4)** |
| No. "no shows" | 8 | | 0 | | –8 |
| No. FM diagnoses (%) | 66 (75) | n = 88 | 89 (92) | | 23 (17) |
| | 70 (73) | n = 96 | | | 19 (19) |
| | n = 88 | | | | |
| Total consultations (RMT and/or SRN) | 3.1 | | 2.5 | | **–0.6 (–1.1 to 0.0)** |
| Total length of consultation (min) | 124 | | 144 | | 21 (–2 to 42) |
| Costs of consultations with RMT and/or SRN | | 210 | | 162 | **–48 (–75 to –22)** |
| Costs of blood tests | | 23 | | 44 | **21 (12 to 30)** |
| Costs of function tests | | 48 | | 14 | **–34 (–54 to –13)** |
| Total costs | | 281 | | 219 | **–62 (–103 to –20)** |
| Patient satisfaction*** | n = 85 | | n = 94 | | |
| Take seriously | 0.17 | | 0.00 | | **–0.17 (–0.47 to 0.00)** |
| Know problems very well | 1.86 | | 1.58 | | –0.28 (–1.29 to 0.71) |
| Take enough time for me | 0.74 | | 0.00 | | **–0.74 (–1.26 to –0.33)** |
| Take care that I can tell story | 0.95 | | 0.11 | | **–0.84 (–1.52 to –0.29)** |
| Tell findings at the end of consultation | 0.85 | | 0.25 | | –0.60 (–1.30 to 0.01) |
| Pay attention to (psycho)social aspects of illness | 2.42 | | 0.48 | | **–1.94 (–2.71 to –1.19)** |
| Give clear information about disorder | 1.47 | | 0.24 | | **–1.23 (–1.99 to –0.49)** |
| Give useful advice | 4.96 | | 1.59 | | **–3.37 (–4.53 to –2.23)** |
| Acceptable waiting time | 1.54 | | 0.20 | | **–1.34 (–1.74 to –0.95)** |

* 8 patients canceled the diagnostic consultation at the outpatient clinic. ** UI: uncertainty interval based on bootstrap replications. *** Quality effect by QUOTE: Quality of Care Through the Patient's Eyes measurement instrument. Higher values indicate less satisfaction; values ≥ 1 reflect care aspects that could be improved. UC: usual care; SRN: specialized rheumatology nurse; RMT: rheumatologist.

*Table 4*. Health outcome measurements after 9 months' followup per patient. Boldface type indicates significant difference.

| Outcome Measure | UC Group, n = 96 | | | SRN Group, n = 97 | | |
|---|---|---|---|---|---|---|
| | Baseline | 9 Mo Followup | 95% UI* | Baseline | 9 Mo Followup | 95% UI* |
| EQ-5D UK tariff | 0.35 | 0.43 | 0.08 (–0.01 to 0.16) | 0.43 | 0.49 | 0.06 (–0.03 to 0.14) |
| EQ-5D Dutch tariff | 0.43 | 0.47 | 0.04 (–0.05 to 0.13) | 0.51 | 0.54 | 0.03 (–0.05 to 0.11) |
| EQ-VAS | 47.7 | 47.4 | –0.3 (–5.0 to 4.4) | 49.2 | 49.8 | 0.6 (–4.6 to 5.6) |
| FIQ total | 59.9 | 58.4 | –1.5 (–5.9 to 3.0) | 57.0 | 56.1 | –0.9 (–5.4 to 3.4) |
| CIS-20 total | 99.0 | 93.9 | –5.1 (–11.1 to 1.4) | 90.4 | 90.7 | 0.3 (–6.5 to 7.1) |
| CIS-20 fatigue severity | 47.3 | 42.5 | **–4.8 (–7.0 to –2.4)** | 44.4 | 41.9 | –2.5 (–5.4 to 0.2) |
| Self-efficacy | 26.5 | 26.2 | –0.3 (–1.6 to 1.0) | 27.4 | 26.7 | –0.7 (–2.1 to 0.8) |

* UI: uncertainty interval based on bootstrap replications. UC: usual care; SRN: specialized rheumatology nurses; EQ-VAS: EuroQol visual analog scale; FIQ: Fibromyalgia Impact Questionnaire; CIS-20: Checklist Individual Strength.

*Table 5*. Amount of paid and unpaid participation per patient (mean h/week): comparison between UC group and SRN group.

| Outcome Measure | UC Group, n = 96 | | | SRN Group, n = 97 | | |
|---|---|---|---|---|---|---|
| | Baseline | 9 Mo Followup | 95% UI* | Baseline | 9 Mo Followup | 95% UI* |
| Official working hours | 11.9 | 10.4 | –1.5 (–5.4 to 2.6) | 15.2 | 14.3 | –0.9 (–5.1 to 3.3) |
| Hours actually worked | 8.3 | 10.4 | 2.1 (–1.3 to 5.8) | 12.2 | 13.3 | 1.1 (–3.0 to 5.2) |
| Absent hours (mean, last 2 mo) | 36.6 | 9.4 | **–27.2 (–44.6 to –11.6)** | 26.1 | 13.7 | 12.4 (–26.8 to 1.0) |
| Absent hours (HClim; sum 9 mo followup) | | 99.5 | | | 76.1 | –23.4 (–86.6 to 32.2) |
| Cost of absenteeism from work (HClim; €) | | 3674 | | | 2565 | –1109 (–3581 to 1094) |
| Unpaid participation | | | | | | |
| Education | 1.6 | 2.3 | 0.7 (–1.1 to 2.4) | 1.0 | 1.8 | 0.8 (–0.4 to 2.1) |
| Housekeeping | 23.4 | 22.2 | –1.2 (–7.4 to 4.5) | 23.0 | 20.5 | –2.5 (–8.1 to 2.9) |
| Odd jobs around the house | 2.6 | 3.2 | 0.6 (–0.7 to 1.9) | 3.1 | 4.0 | 0.9 (–0.5 to 2.3) |
| Volunteer work | 1.0 | 1.6 | 0.6 (–0.4 to 1.6) | 0.5 | 1.0 | **0.5 (0.0 to 1.0)** |
| Sport | 1.5 | 2.2 | 0.7 (–0.1 to 1.3) | 1.7 | 2.4 | **0.7 (0.0 to 1.5)** |
| Club life | 0.4 | 0.9 | **0.5 (0.1 to 0.9)** | 0.7 | 0.9 | 0.2 (–0.3 to 0.6) |
| Leisure time | 7.0 | 7.0 | 0.0 (–2.3 to 2.1) | 7.3 | 5.7 | –1.6 (–3.2 to 0.2) |
| Social activities | 2.9 | 3.6 | 0.7 (–0.1 to 1.7) | 3.5 | 4.0 | 0.5 (–0.4 to 1.4) |
| Other activities | 0.2 | 1.0 | **0.8 (0.0 to 2.1)** | 0.2 | 0.4 | 0.2 (–0.1 to 0.6) |
| Unpaid tasks and chores | 28.7 | 29.2 | 0.5 (–5.5 to 6.8) | 27.7 | 27.3 | –0.4 (–5.8 to 5.0) |
| Leisure and social activities | 11.9 | 13.8 | 1.9 (–0.9 to 4.6) | 13.2 | 13.1 | –0.1 (–2.4 to 2.2) |

* UI: uncertainty interval based on bootstrap replications. UC: usual care; SRN: specialized rheumatology nurses; HClim: human capital limited approach.

Concerning unpaid activities, the UC group spent, in contrast to the SRN group, slightly more hours on unpaid tasks and chores and leisure and social activities.

Table 6 presents the mean healthcare and societal costs per patient during 9 months of followup. Cost differences were nearly all in favor of the SRN group. Costs of the diagnostic process and GP contacts were significantly lower in the SRN group compared to the UC group. Expenses for health activities, conversely, were higher in the SRN group compared to the UC group. Total costs excluding absenteeism were significantly lower in the SRN group (€1298 vs €1644; 95% uncertainty interval €–746 to €–2). Mean total costs from a societal perspective were €3853 per patient for the SRN group and €5293 for the UC group after 9 months of followup. Productivity costs accounted for two-thirds of the total societal costs and had a big effect on the incremental costs. The mean cost difference was €1440 per patient (95% uncertainty interval €–3721 to €577) in favor of the SRN group.

## DISCUSSION

We investigated the health and economic consequences of substituting SRN for RMT in the diagnostic process of FM. Patients in the SRN group were significantly more satisfied, but differences in health status between the 2 groups during 9 months of followup were small and insignificant. Mean total costs from a societal perspective (including absenteeism) were €1440 per patient lower in the SRN group than in the UC group after 9 months of followup (95% uncertainty interval €–3721 to €577).

We could not prove that a timely diagnosis had a positive effect on health outcomes and social participation in terms

*Table 6*. Mean costs of healthcare consumption during 9 months' followup per patient (€). Boldface indicates significant difference.

| Cost Components | UC Group, n = 96 | SRN Group, n = 97 | Difference (95% UI)* |
|---|---|---|---|
| Healthcare consumption | | | |
| Total costs diagnostic process | 287 | 223 | **–64 (–103 to –26)** |
| Total GP contacts | 123 | 83 | **–40 (–76 to –1)** |
| Outpatient specialist care contacts (excluding contacts in Table 2) | 103 | 63 | **–40 (–79 to 0)** |
| Therapist contacts | 436 | 355 | –81 (–224 to 70) |
| Prescribed medications | 148 | 115 | –33 (–80 to 7) |
| OTC medications | 30 | 24 | –6 (–20 to 8) |
| Multidisciplinary day care | 98 | 62 | –36 (–169 to 82) |
| Patient and family costs | | | |
| Home help (paid/unpaid) | 295 | 216 | –79 (–276 to 109) |
| Meal provision | 15 | 16 | 1 (–12 to 20) |
| Expenses for health activities | 82 | 118 | 36 (–6 to 86) |
| Expenses for medical aids | 19 | 19 | 0 (–20 to 23) |
| Total costs (excluding absenteeism from work) | 1644** | 1298** | **–346 (–746 to –2)** |
| Absenteeism from work (HClim) | 3674 | 2565 | –1109 (–3581 to 1094) |
| Total societal costs | 5293** | 3853** | –1440 (–3721 to 577) |

* UI: uncertainty interval based on boostrap replications. ** Total costs deviate from the sum of cost items because of boostrap random variation. UC: usual care; SRN: specialized rheumatology nurses; GP: general practitioner; OTC: over the counter; HClim: human capital limited approach.

of hours spent. However, medical and productivity costs were significantly lower in the SRN group. Since the timespan of our analysis was only 9 months, a longer followup may be necessary to confirm these effects.

Our results suggest that healthcare use in terms of contacts with GP, medical specialists, and physical and psychological therapists and in medication costs was similar in both groups before and after diagnosis. The literature is not in agreement on the effects on healthcare use of making a diagnosis. Annemans, *et al* suggest that making a diagnosis leads to a decrease of resource use and costs, which is confirmed by other studies[16,48,49]. However, Hughes, *et al* found that following diagnosis, visits for most symptoms and healthcare use markers declined, but within 2–3 years most visits rose to levels the same as or higher than those at diagnosis[21]. On the other hand, Maugars, *et al* described a decrease in referrals and tests after diagnosis, and an increase in drug use and GP visits for the first 2 years after diagnosis[48]. White, *et al* illustrated that healthcare costs rose immediately after diagnosis[50]. In our study, we saw an increase after diagnosis in contacts with other therapists, paid housekeeping help, informal care, multidisciplinary daycare, and expenses for health activities.

Notwithstanding a considerable decrease in sick leave hours in both intervention groups, productivity costs based on absenteeism accounted for two-thirds of the total societal costs in our study. This is much higher than described in previous studies, in which about 20%–33% of the total societal costs of FM are related to productivity costs[10,14,51,52,53]. This could be due to the way that productivity costs were calculated. Huscher, *et al* showed that indirect costs differ by a factor of 3, based on whether the human capital approach or the friction costs approach is used[54].

The percentage of indirect costs (74% and 77% of the total societal costs for the SRN group and the RMT group, respectively) is in line with other studies[10]. In Boonen, *et al*[51], also based on patient diaries, the annual direct medical costs were €1311 (2002 values), which is in line with our results converted to total annual costs (€1233 and €1633 in the SRN and the RMT groups, respectively). Also, the total annual costs per patient are comparable: €7813 (2002 values) in Boonen, *et al*[51], €5137 (converted to annual costs) in the SRN group, and €7057 in the RMT group (converted to annual costs). Although Annemans, *et al*[16] showed that the total costs for FM, reported by Boonen, *et al*[51] and 12 other studies, are quite similar, a direct comparison of Dutch data with data from other countries should be done cautiously[55].

Our study has several difficulties. First, the choice for a cost-consequence analysis has disadvantages. Ideally, all outcomes should be integrated into 1 overall index of benefit. This is important when comparing different interventions or comparing the results of a study with other studies or other diseases in all facets. A cost-minimization analysis was not relevant in our study, as it assumes outcomes to be equivalent, which was not the case. In a cost-effectiveness analysis, consequences of programs are measured in the most appropriate natural effects or physical units, while in a cost-utility analysis, the consequences of interventions are adjusted by health state preference or utility weights. In our situation, with utility as one of the consequences and outcomes, we found no difference between improvement in quality of life in the intervention groups. Besides, these analyses, from a societal perspective, include all costs, irrespective of who bears them. A cost-benefit analysis measures costs in monetary terms as well as consequences of an intervention, which was not feasible for most of our consequences and therefore not a useful option.

In our study it is difficult to integrate the outcomes into 1 overall measure of benefit since they concern both consequences at the patient level (e.g., satisfaction, health status) and at the healthcare system level (e.g., waiting time, number of no-shows). A cost-consequence analysis overcomes this problem by presenting information on both costs and outcomes in a disaggregated form, allowing decision makers to make the necessary value judgments (implicitly weighing the relative importance of the outcomes) and tradeoffs that are relevant from their particular perspective. However, in our study costs from both healthcare and societal perspectives as well as consequences seem to point in the same direction, so we can formulate one overall conclusion and related recommendation.

Second, notwithstanding randomization, we found baseline differences for the EQ-5D index score, CIS-20, the percentage of employed patients, and hours of absenteeism. Concerning the between-group differences in work situation at baseline, costs of absenteeism at baseline were calculated and the difference was not found to be statistically significant. Adjustment for cost differences at baseline is not necessary in this situation, as the cost differences at baseline for other than productivity costs are very small and go in both directions. Besides, the recommendation of Van Asselt, *et al* for dealing with cost differences at baseline concerns baseline differences in total costs and not baseline differences in components of costs[56]. However, the finding that productivity costs were €1109 lower in the SRN group should be interpreted cautiously. Using the most conservative adjustment, this amount should be reduced, with the difference in productivity costs at baseline (€445).

Third, some data were missing from our study. We have carefully checked whether these missing values were random. Patients with lower scores in HRQOL at baseline were generally more likely to be missing from the data at some point. Since patients with FM seem to have lower scores than patients who do not have FM, and the SRN group contained more patients with FM, the HRQOL scores of the SRN group could be an underestimation. Therefore, the incremental difference between the RMT group and the SRN group could also be a conservative difference. Although we also found more missing values in patients who did not have FM and therefore in the RMT group, we assume the effect on the scores is limited because of the small number of missing patients who did not have FM on the total of the group.

Fourth, an unknown number of patients in the RMT group underwent medical consultations in another hospital because of waiting time. The visits to RMT and SRN are, as far as reported, included in the costs of outpatient specialist care contacts, but we have no data on diagnostic tests performed and therefore those costs could not be included. This lack of information could have caused an underestimation of the medical consumption in the RMT group. This situation is closely connected with the next point. Nearly all cost data are based on cost diaries, which may not necessarily reflect actual patterns of use because of problems with patient recall. However, patient-reported healthcare consumption data are considered to be relatively reliable regarding formal care[57] and if biased, we do not expect systematic reporting differences between the groups in our study.

In addition, the estimated productivity costs did not include costs associated with reduced productivity on the job (presenteeism) or with replacement costs[58,59]. In a future study, it is worth taking into account these costs because one of the consequences of FM is work loss, and those patients who do not lose their jobs still obviously experience difficulties in their working life as a direct result of FM[60,61]. Next, in our study we could not assess a possible difference in placebo effect of the nurse-led diagnostic process versus usual care. Within a cost-consequence analysis, however, the aim is to assess a difference in effectiveness, including a possible placebo effect instead of clinical efficacy as in clinical trials.

An important disadvantage of the nurse-led diagnostic process was the fact that more than 8% of the patients in the SRN group refused to participate because they indicated that they would only accept a rheumatologist consultation. However, given our analytic approach based upon intention-to-treat, this issue is incorporated in our findings and conclusion. This is a study based upon Dutch data, and the generalizability of our conclusion, and especially the issue of compliance to consultation by a nurse specialist, should be carefully considered, for instance by explicit assessment of transferability issues[62].

Finally, given the incremental approach of our analysis, we did not consider overhead costs of hospital facilities; those were considered to be sunk costs, retrospective costs that have already been incurred and cannot be recovered. When an FM clinic is to be initiated, it is important to be aware that such costs might be relevant. One should note as well that our results were obtained in a trial setting and possibly can differ from real-life data, as is commonly the case in a protocolized trial. Therefore, we advise monitoring the outcomes after the implementation of such a nurse-led diagnostic process.

The nurse-led diagnostic process can be recommended from a healthcare and societal perspective. Patients in the SRN group were significantly more satisfied, and no differential changes in health status were observed between the 2 groups during 9 months of followup. Total healthcare consumption costs and patient and family costs were significantly lower in the SRN group. Also, costs from a societal perspective (including absenteeism) were lower in the SRN group compared to the RMT group.

## REFERENCES


1. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38:19-28.
2. Vanhoof J, Declerck K, Geusens P. Prevalence of rheumatic diseases in a rheumatological outpatient practice. Ann Rheum Dis 2002;61:453-5.
3. Bernard AL, Prince A, Edsall P. Quality of life issues for fibromyalgia patients. Arthritis Care Res 2000;13:42-50.
4. Picavet HS, Hoeymans N. Health related quality of life in multiple musculoskeletal diseases: SF-36 and EQ-5D in the DMC3 study. Ann Rheum Dis 2004;63:723-9.
5. Verbunt JA, Pernot DH, Smeets RJ. Disability and quality of life in patients with fibromyalgia. Health Qual Life Outcomes 2008;6:8.
6. Wolfe F, Hawley DJ. Measurement of the quality of life in rheumatic disorders using the EuroQol. Br J Rheumatol 1997;36:786-93.
7. Arnold LM, Crofford LJ, Mease PJ, Burgess SM, Palmer SC, Abetz L, et al. Patient perspectives on the impact of fibromyalgia. Patient

Educ Couns 2008;73:114-20.
8. Berger A, Dukes E, Martin S, Edelsberg J, Oster G. Characteristics and healthcare costs of patients with fibromyalgia syndrome. Int J Clin Pract 2007;61:1498-508.
9. Penrod JR, Bernatsky S, Adam V, Baron M, Dayan N, Dobkin PL. Health services costs and their determinants in women with fibromyalgia. J Rheumatol 2004;31:1391-8.
10. Robinson RL, Birnbaum HG, Morley MA, Sisitsky T, Greenberg PE, Claxton AJ. Economic cost and epidemiological characteristics of patients with fibromyalgia claims. J Rheumatol 2003;30:1318-25.
11. Sicras-Mainar A, Rejas J, Navarro R, Blanca M, Morcillo A, Larios R, et al. Treating patients with fibromyalgia in primary care settings under routine medical practice: a claim database cost and burden of illness study. Arthritis Res Ther 2009;11:R54.
12. Silverman S, Dukes EM, Johnston SS, Brandenburg NA, Sadosky A, Huse DM. The economic burden of fibromyalgia: comparative analysis with rheumatoid arthritis. Curr Med Res Opin 2009;25:829-40.
13. White KP, Speechley M, Harth M, Ostbye T. The London Fibromyalgia Epidemiology Study: direct health care costs of fibromyalgia syndrome in London, Canada. J Rheumatol 1999;26:885-9.
14. White LA, Birnbaum HG, Kaltenboeck A, Tang J, Mallett D, Robinson RL. Employees with fibromyalgia: medical comorbidity, healthcare costs, and work loss. J Occup Environ Med 2008; 50:13-24.
15. Wolfe F, Anderson J, Harkness D, Bennett RM, Caro XJ, Goldenberg DL, et al. A prospective, longitudinal, multicenter study of service utilization and costs in fibromyalgia. Arthritis Rheum 1997;40:1560-70.
16. Annemans L, Wessely S, Spaepen E, Caekelbergh K, Caubere JP, Le Lay K, et al. Health economic consequences related to the diagnosis of fibromyalgia syndrome. Arthritis Rheum 2008; 58:895-902.
17. Ehrlich GE. Pain is real; fibromyalgia isn't. J Rheumatol 2003;30:1666-7.
18. Hadler NM. "Fibromyalgia" and the medicalization of misery. J Rheumatol 2003;30:1668-70.
19. White KP, Nielson WR, Harth M, Ostbye T, Speechley M. Does the label "fibromyalgia" alter health status, function, and health service utilization? A prospective, within-group comparison in a community cohort of adults with chronic widespread pain. Arthritis Rheum 2002;47:260-5.
20. Keefe FJ, Rumble ME, Scipio CD, Giordano LA, Perri LM. Psychological aspects of persistent pain: current state of the science. J Pain 2004;5:195-211.
21. Hughes G, Martinez C, Myon E, Taieb C, Wessely S. The impact of a diagnosis of fibromyalgia on health care resource use by primary care patients in the UK: an observational study based on clinical practice. Arthritis Rheum 2006;54:177-83.
22. Goh L, Samanta J, Samanta A. Rheumatology nurse practitioners' perceptions of their role. Musculoskeletal Care 2006;4:88-100.
23. Hill J. Rheumatology nurse specialists — do we need them? Rheumatology 2007;46:379-81.
24. Kroese MEAL, Schulpen GJC, Bessems MCM, Severens JL, Nijhuis FJ, Geusens PP, et al. Substitution of specialized rheumatology nurses for rheumatologists in the diagnostic process of fibromyalgia: a randomized controlled trial. Arthritis Care Res 2008;59:1299-305.
25. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160-72.
26. Mauskopf JA, Paul JE, Grant DM, Stergachis A. The role of cost-consequence analysis in healthcare decision-making. Pharmacoeconomics 1998;13:277-88.
27. McIntosh E, Donaldson C, Ryan M. Recent advances in the methods of cost-benefit analysis in healthcare. Matching the art to the science. Pharmacoeconomics 1999;15:357-67.
28. van Campen C, Sixma HJ, Kerssens JJ, Peters L, Rasker JJ. Assessing patients' priorities and perceptions of the quality of health care: the development of the QUOTE-Rheumatic-Patients instrument. Br J Rheumatol 1998;37:362-8.
29. The EuroQol Group. EuroQol — a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208.
30. Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53-72.
31. Lamers LM, McDonnell J, Stalmeier PF, Krabbe PF, Busschbach JJ. The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies. Health Econ 2006;15:1121-32.
32. Lamers LM, Stalmeier PF, McDonnell J, Krabbe PF, van Busschbach JJ. Kwaliteit van leven meten in economische evaluaties: het Nederlands EQ-5D-tarief [Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff]. Ned Tijdschr Geneeskd 2005;149:1574-8.
33. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35:1095-108.
34. Weinstein MC, Torrance G, McGuire A. QALYs: the basics. Value Health 2009;12 Suppl 1:S5-9.
35. Post M. Resultaatmeting in de dwarslaesierevalidatie. In: van Asbeck FWA, editor. Handboek dwarslaesierevalidatie. Houten: Bohn Stafleu van Loghum; 2007:365-76.
36. Schonherr MC, Groothoff JW, Mulder GA, Eisma WH. Participation and satisfaction after spinal cord injury: results of a vocational and leisure outcome study. Spinal Cord 2005;43:241-8.
37. Whiteneck GG, Charlifue SW, Gerhart KA, Overholser JD, Richardson GN. Quantifying handicap: a new measure of long-term rehabilitation outcomes. Arch Phys Med Rehabil 1992;73:519-26.
38. Burckhardt CS, Clark SR, Bennett RM. The Fibromyalgia Impact Questionnaire: development and validation. J Rheumatol 1991;18:728-33.
39. Bennett R. The Fibromyalgia Impact Questionnaire (FIQ): a review of its development, current version, operating characteristics and uses. Clin Exp Rheumatol 2005;5 Suppl 39:S154-62.
40. Vercoulen JHHM, Alberts M, Bleijenberg G. De Checklist Individual Strength (CIS). Gedragstherapie 1999;32:131-6.
41. Schwarzer R, Jerusalem M. Generalized self-efficacy scale. In: Weinman J, Wright S, Johnston M, editors. Measures in health psychology: a user's portfolio. Causal and control beliefs. Windsor, UK: NFER-Nelson; 1995:35-7.
42. Oostenbrink JB, Bouwmans CAM, Koopmanschap MA, Rutten FFH. Handleiding voor kostenonderzoek. Methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. Rotterdam: Instituut voor Medical Technology Assessment, Erasmus MC in opdracht voor College voor zorgverzekeringen; 2004.
43. Koopmanschap MA, Rutten FF, van Ineveld BM, van Roijen L. The friction cost method for measuring indirect costs of disease. J Health Econ 1995;14:171-89.
44. Rice DP, Cooper BS. The economic value of human life. Am J Public Health Nations Health 1967;57:1954-66.
45. van Asselt AD, Dirksen CD, Arntz A, Severens JL. Difficulties in calculating productivity costs: work disability associated with borderline personality disorder. Value Health 2008;11:637-44.
46. Thompson SG, Barber JA. How should cost data in pragmatic randomised trials be analysed? BMJ 2000;320:1197-200.
47. Altman DG, Dore CJ. Randomisation and baseline comparisons in clinical trials. Lancet 1990;335:149-53.
48. Maugars Y, Annemans L, Roué-Le Lay K, André E, Caubere JP,

Taieb C. Fibromyalgia: the avoided cost of the non-diagnosed patient in France. Ann Rheum Dis 2008;Suppl II:258.
49. Taieb C, Lamotte M, Maugars Y, Le Lay K. Health economic comparison of outpatient management of fibromyalgia before and after diagnosis in five European countries. Ann Rheum Dis 2009;Suppl 3:690.
50. White LA, Robinson RL, Yu AP, Kaltenboeck A, Samuels S, Mallett D, et al. Comparison of health care use and costs in newly diagnosed and established patients with fibromyalgia. J Pain 2009;10:976-83.
51. Boonen A, van den Heuvel R, van Tubergen A, Goossens M, Severens JL, van der Heijde D, et al. Large differences in cost of illness and wellbeing between patients with fibromyalgia, chronic low back pain, or ankylosing spondylitis. Ann Rheum Dis 2005;64:396-402.
52. Robinson RL, Birnbaum HG, Morley MA, Sisitsky T, Greenberg PE, Wolfe F. Depression and fibromyalgia: treatment and cost when diagnosed separately or concurrently. J Rheumatol 2004;31:1621-9.
53. Zijlstra TR, Braakman-Jansen LMA, Taal E, Rasker JJ, van de Laar MAFJ. Cost-effectiveness of spa treatment for fibromyalgia: general health improvement is not for free. Rheumatology 2007;46:1454-9.
54. Huscher D, Merkesdal S, Thiele K, Zeidler H, Schneider M, Zink A. Cost of illness in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and systemic lupus erythematosus in Germany. Ann Rheum Dis 2006;65:1175-83.
55. Knies S, Severens JL, Ament AJHA, Evers SMAA. Using cost-effectiveness results from abroad for local policy decisions. Eur J Hosp Pharm Pract 2008;14:51-4.
56. van Asselt AD, van Mastrigt GA, Dirksen CD, Arntz A, Severens JL, Kessels AG. How to deal with cost differences at baseline. Pharmacoeconomics 2009;27:519-28.
57. van den Brink M, van den Hout WB, Stiggelbout AM, van de Velde CJ, Kievit J. Cost measurement in economic evaluations of health care: whom to ask? Med Care 2004;42:740-6.
58. Koopmanschap M, Burdorf A, Jacob K, Meerding WJ, Brouwer W, Severens H. Measuring productivity changes in economic evaluation: setting the research agenda. Pharmacoeconomics 2005;23:47-54.
59. Severens JL, Laheij RJF, Jansen JBMJ, van der Lisdonk EH, Verbeek ALM. Estimating the cost of lost productivity in dyspepsia. Aliment Pharmacol Ther 1998;12:919-23.
60. Annemans L, Le Lay K, Taieb C. Societal and patient burden of fibromyalgia syndrome. Pharmacoeconomics 2009;27:547-59.
61. Bennett RM, Jones J, Turk DC, Russell IJ, Matallana L. An internet survey of 2,596 people with fibromyalgia. BMC Musculoskelet Disord 2007;8:27.
62. Knies S, Ament AJ, Evers SM, Severens JL. The transferability of economic evaluations: Testing the model of Welte. Value Health 2009;12:730-8.
63. Dutch Health Care Insurance Board. Pharmacotherapeutic compass. Diemen, Netherlands: 2007.