COSTS AND QUALITY OF LIFE IN MULTIPLE SCLEROSIS

A CROSS-SECTIONAL STUDY IN THE USA

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SUMMARY

Treatment of multiple sclerosis (MS) has changed substantially during the past decade, as new biological disease-modifying treatments have been introduced in a field where only symptomatic pharmacological treatment had been available. The new treatments come at a high cost, between $ 8-12,000 per patient and year. Consequently, it must be expected that the part of total costs represented by drugs has increased, from essentially a very minor part in the nineties (2-5%) to a much larger proportion. However, no studies investigating this development from a societal perspective have so far been published.

Objective

The objective of this study was to investigate the current cost structure in MS and the effect of disease severity on costs and quality of life (utility) for patients treated with the new disease modifying drugs (DMDs) in the US.

Methods

The study follows closely the methodology used in three previous observational studies in Sweden, the United Kingdom and Germany. It is a descriptive bottom-up prevalence-based cost of illness study. The analysis was performed from the societal perspective and did not investigate costs for different payers. Costs were calculated as mean annual cost per patient in the sample, and mean costs for patients using a given resource. All unit costs are for 2004, or were inflated to 2004 using the CPI.

Demographic variables, information on disease severity and disease activity, resource utilization and utility were collected directly from a sub-sample of ~24,000 patients taking part in a regular follow-up since up to 8 years, the North American Committee on Multiple Sclerosis (NARCOMS) Patient Registry. A questionnaire was mailed to a 4,000 randomly selected sample and the target answer rate was 50%.

Results

1,989 (49.7%) of patients contacted returned the questionnaire, but 80 of them were returned empty and had to be excluded. This left a sample of 1,909 (47.7%) for analysis. The mean age of the sample was 49 years and three quarters were women. Their age at first symptoms was 30 years, and time since diagnosis was 13 years.

10.5% of patients had primary progressive, 47.6% relapsing-remitting and 33.3% secondary progressive disease. Less than 1% of patients did not answer the question, but 7.6% were unsure. 28.8% of patients indicated to have experienced a relapse during the past 3 months. 34.8% had mild, 42.7% had moderate and 22.1% had severe disease. Slightly less than one third (31.4%) was in early retirement due to MS.

Total costs are estimated at $ 47,215 per patient and year. The largest proportions of costs are indirect costs ($ 17,581 or 37.2%) and drugs ($ 18,628 or 39.5%). Of the latter, disease modifying drugs accounted for 86% of total drug cost and 34% of total costs ($ 16,050), while OTC medication amounted to $ 122. Informal care represented

9.8% ($ 4614) and services and investments, which were to a large extent paid for by patients themselves, amounted to $ 2707 per patient (5.7%).

Using the new (unpublished) US health status system, the mean utility in the sample was 0.698, with women having higher utility than men (0.709 versus 0.667). Patients who had experienced a relapse in the past 3 months had a utility of 0.648, compared to 0.742 for those who did not.

On the absence of published gender and age specific population values in the US, the UK tariff has been used to estimate the age and gender specific utility loss of MS patients compared to the normal population. The loss of quality-adjusted life years (QALYs) was estimated at 0.255 QALY/patient. Using a willingness to pay for a QALY of $ 60000, intangible costs were estimated at $ 15,315.

Costs increased and utility decreased with decreasing functional capacity. Patients with mild disease had a cost of $ 32,297 and a utility of 0.824; figures for patients with moderate MS were $ 50,293 and 0.679, and for patients with severe MS $ 64,492 and 0.533. The proportion of bed-ridden patients in the sample (EDSS 8.0 or more) was small compared to the expected prevalence. When the proportion was increased to 4%, costs for patients in the severe group increased slightly to $ 65,173 and utility decreased to 0.479. Thus, it appears that the effect of very severe disease is more pronounced on patients' quality of life than on costs.

Conclusions

The objective of this study was to investigate the overall costs for patients treated with the new MS therapies, and cost distribution among different resources after the introduction of the new MS treatments. In view of the high cost of these treatments, our results are not surprising, with MS drugs representing 34% of total costs. When the use of disease modifying drugs is adjusted to the estimated national average (52%), the share of costs represented by these drugs is 21%.

The findings are consistent with previous studies into the cost of MS: costs and utilities are significantly correlated with functional capacity (EDSS).

This study does not investigate the value of the investment in these treatments. Rather it provides the necessary input into a disease model where costs and utility are linked to disease progression, without treatment, or with different treatments.

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1 INTRODUCTION

1.1 Background

Treatment of multiple sclerosis (MS) has changed substantially during the past decade, as new biological disease-modifying drugs (DMDs) have been introduced in a field where only symptomatic pharmacological treatment had been available. The new treatments come at a substantial costs and as a result, it must be expected that the part of total costs represented by drugs has increased, from essentially a very minor part in the early nineties (2-5%)[1-6] to a much larger proportion. However, no studies investigating this development from a societal perspective have so far been published. One recent analysis of a large managed care claims database in the United States analysed charges of patients with relapsing-remitting MS and found drug costs to account for 75-80% of charges [7].

When the new treatments were first introduced, a number of cost of illness studies were performed across the world. Some of these had the objective to assess the total cost of MS in a given country, while others were performed to provide baseline information to assess the potential economic impact of the new drugs [4-6, 8, 9].

A European review of cost of illness studies performed prior to the widespread use of the new treatments [10] found that, despite large differences in health care systems, absolute and relative costs in the countries and methodologies used for the studies, studies agree in their overall findings:

- Costs outside the health care system, i.e. productivity losses (short term sick leave and early retirement), non-medical costs (investments, etc) and informal care by family or friends, dominate the costs of MS.
- Indirect costs represent a larger proportion of costs in patients with limited permanent disability (i.e. at lower EDSS levels).
- Males have higher total costs than females, driven by higher productivity losses.
- Inpatient care dominates direct costs (prior to the introduction of the new drugs).
- Costs rise with increasing severity of the disease. Taken individually, age, disease duration, level of disability (measured with the Expanded Disability Status Scale, EDSS [11]) all are positively correlated with costs, but there is also a clear co-linearity between these variables.
- Costs are higher overall for patients with SPMS than for those with RRMS. However, when controlling for EDSS this is less clear: Costs appear to be driven by the level of EDSS rather than by the type of MS, and for patients at the same level of EDSS and in the absence of a relapse, there is no significant difference in costs between the two types of MS [12].
- Costs increase during relapses, while utility (QoL) decreases.
- Qol and/or utility decreases with increasing disease severity.

In the United States, a number of studies have looked at costs from different payer perspectives and results vary therefore amongst studies. Stolp-Smith and colleagues estimated billed hospital and ambulatory care charges in the two main medical centers in the county, by severity of the disease, in a population-based study in Olmsted county [13]. Annual billings (1993) ranged from $ 2,463 for patients with an EDSS below 4.0 to $ 6,575 for those with an EDSS of 7.0 and above. Pope and colleagues [14] estimated charges (1995) from the perspective of private insurance, Medicare and Medicaid at $7,677, $ 13,048 and $ 11,391 respectively. Only one study estimated costs from a societal perspective, including services, equipment, informal care and productivity losses [6]. Total

costs (1994) were estimated at $ 34,103, of which 52% were indirect costs and 19% informal care costs and drugs represented less than 3%.

Cost of illness data were used in disease models that incorporate symptoms as well as progression, in order to estimate the short and medium term effects of reducing symptoms and the long term effects of slowing progression, both in terms of costs and quality of life (QoL). Such models were used in most European countries to support decisions on resource allocation to the new drugs, and many – but not all - of them are in the public domain [12, 15-24]. There has been considerable controversy regarding the results of these studies, as cost-effectiveness ratios spanned a large range, all the way from cost saving compared to previous treatment up to one million dollars per quality-adjusted life-year (QALY) gained. These differences are due to differences in the data used, the time horizon of the analysis, the patient groups included and the assumptions made for extrapolations to the long term, etc. Although they can rather easily be explained, they are not very obvious to non-specialists and therefore leading to considerable controversies.

At the time of introduction of new drugs, cost-effectiveness estimates are partly based on assumptions about their use. It is therefore important to update such analyses once a new treatment has been used for a number of years. Some authorities in Europe have started to request such re-evaluations, and one of the most prominent cases is the use of the new MS drugs in the United Kingdom. Indeed, the National Institute for Clinical Excellence (NICE) has recommended their use within the UK National Health Service in 2001, conditional upon collecting cost and outcome data to populate the hypothetical model used to reach the decision [25]. Similarly, many European countries have started MS registries to better follow patients, but it will take a number of years before the data will be available for analysis. Furthermore, the data needed for economic evaluation (resource utilisation, utility, etc) are generally not included and have to be researched in separate additional studies.

1.2 Study objectives

In the United States, the new treatments have been available for longer and are widely used, and longitudinal data exist. However, cost-effectiveness analyses have not been required and all published studies are from Europe. Guidelines for evaluation of treatments have been published by the Academy of Managed Care Pharmacy (AMCP) and there is growing interest in cost-effectiveness analysis.

We therefore performed a cross-sectional study in a large representative sample of MS patients in the USA treated with DMDs to

- provide information on the current cost structure in MS
- investigate the effect of disease severity on costs and QoL (utility)
- provide resource and utility data for cost-effectiveness modelling.

2 Materials and Methods

2.1 Study Method

This study follows closely the methodology used in the three observational studies in Sweden, the United Kingdom and Germany [4, 8, 9]. It is a descriptive cost of illness study, based on the human-capital theory and relates all cost to the disease (MS). As MS is a chronic disease with an average duration of around 40 years, a prevalence- rather than incidence-based approach was used, estimating the cost per patient and year. This allows calculating the cost for all patients with the disease in a given year in a geographically defined area and relating the estimates to measures of annual health care expenditure in the area.

Data collection strategies for cost of illness studies can be "top-down" (i.e. using aggregate figures on resource consumption related to diagnoses from registries, national statistics or other published sources), or "bottom-up" (i.e. estimating costs in a sample of patients and extrapolating to the national level). Both approaches have advantages and drawbacks, the major drawbacks being data interpretation and missing data in the top-down approach and difficulties relating to the selection of a representative sample in the bottom-up approach. As the purpose of this study was to include all costs, regardless of where they occur, the bottom-up approach was used.

The objective of the study was to estimate costs related to MS, not costs for patients with the disease, and only MS-specific resource consumption was therefore included. It is possible that patients with severe MS consume more resources also for other diseases and thus have overall higher costs. In these cases it is generally difficult to separate what part of total costs relates to the disease that is being investigated and what part to co-morbidities. For patients with MS, this is thought to be less of a problem, as the consequences of the disease are rather well defined, and in addition patients are in an age group where co-morbidities are generally limited. We therefore chose to instruct patients to only include MS-related costs rather than perform a comparative study. Whetten-Goldstein and colleagues have compared the consumption of MS patients to the average national consumption and estimated the excess utilization [6]. However, the comparison appears not to have been controlled for age, and costs in the control group may therefore have been overestimated.

Demographic variables, information on disease severity and disease activity, resource utilization and utility were therefore collected directly from a sub-sample of patients taking part in a regular follow-up since up to 8 years, the North American Committee on Multiple Sclerosis (NARCOMS) Patient Registry.

NARCOMS is a project of the Consortium of Multiple Sclerosis Centers (CMSC) that commenced patient enrollment in 1996 in order to facilitate research in MS and patient recruitment for clinical trials. Individuals with MS across the United States are invited to enroll in the registry through direct mailings, MS centers, support groups and the NARCOMS Registry web page. Enrollment involves completing a questionnaire and mailing it or submitting it online to the registry administration office. Most registrants update core data semi-annually. Information provided by participants has been approved for use for research purposes by the Human Investigation Committees of the Yale School of Medicine and Barrow Neurological Institute.

Information regularly collected includes demographic data, health insurance status, MS related history, disability status and treatment history. Disability status is reported using two validated patient self-report measures. The Patient Determined Disease Steps (PDDS) [26] is a scale based on disease steps, which has a correlation of 0.958 with the EDSS and evaluates disease progression over time. The Performance Scales [27] measure handicap in eight neurological domains: mobility, hand function, vision, fatigue, cognition, bladder/bowel, sensory and spasticity (test-retest reliability coefficient for the total score was 0.89, and for the eight subscales it ranged from 0.65 to 0.91). The scales have 0-6 levels in measuring mobility, and 0-5 levels for the rest of the functions.

2.2 Patients

Suitable patients were selected from the NARCOMS database of >24'000 patients. The selection criteria were based on the double objective of obtaining a sample

- that represented as much as possible a prevalence sample
- where patients at all disease levels were represented in sufficient numbers to allow analyses of costs and utility by disease severity
- treated with one of the new DMDs (Avonex®, Betaseron®, Copaxone®, Rebif®) at the last follow-up

The earlier European studies had shown that samples of at least 700-1200 patients were required to perform an analysis by disease severity (100-150 by level of severity). However, as patients were not selected according to location, a larger sample was included to ensure a good geographic spread. The target was therefore set to ~1800-2000 evaluable patients. From previous experience within the NARCOMS data base, response rates were expected to be around 50-70%, and a sample of 4000 patients was therefore selected for the mailing.

The sample was selected randomly among the registry patients who had responded to the November 2002 update in order to have the most recent contact details as well as information on drug use. Patients selected had to have indicated treatment with one of the major new MS drugs (Avonex, Betaseron, Copaxone, Rebif).

Thus, the sample does not represent a sample of all MS patients, but a nationwide representative sample of patients treated with recently introduced drugs. This has to be borne in mind for the interpretation of the results.

2.3 Data collection

A specific questionnaire was developed for this study. The original questionnaire used in the 3 European studies was adapted to reflect health care delivery in the USA, and further modified by incorporating parts of the questionnaire used by NARCOMS. The questionnaire asked about symptoms and resource consumption during the preceding 3 months, and current QoL (utility). The questionnaire was preceded by an information note to the patients about the study objectives and the confidentiality of the data, and patients were asked to indicate their agreement with the study conditions by signing the document.

The 4000 questionnaires were bar coded with ID numbers and mailed directly to patients on October 24, 2003. As of December 19, 2003, 1925 survey questionnaires were received by NARCOMS. A reminder postcard was sent to all 4000 patients in January, and

the total of answers received by February was 1989, reaching the target response rate of 50%. Thus, the database was closed at the end of February 2004. Eighty answers had to be excluded because they were returned empty, leaving a total sample of 1909 patients. Data were entered on site into a dedicated database (separate from the NARCOMS database).

2.3.1 Background variables and medical information

Demographic variables were limited age and gender, and no information on patients' private situation, living conditions or health insurance conditions was elicited, as the objectives did not include analysing costs by differences in these parameters.

MS-related questions included

- the year of diagnosis year as well as the age at which patients' recalled to have experienced their first symptoms
- the type of MS (relapsing-remitting, secondary progressive, primary progressive)
- whether they had experienced a relapse during the past 3 months and if so, how many
- use of IV steroids during such a relapse (as an indication of the severity of the relapse)
- the severity level of the disease, using the 9 point scale developed by NARCOMS (Patient Disability Status Scale, PDSS [26]) and used in their database. Details of the scale and conversion to EDSS are in Annex 1.

As patients in this sample were used to answering disease surveys, it was felt that they were well aware of the type of disease they had and what a relapse was. Nevertheless, the types of disease were described, and an extensive explanation of a relapse (exacerbation) was given, and an option "don't know" was included.

2.3.2 Resource consumption

2.3.2.1 Direct resources

With the exception of hospitalisation and major investments, questions regarding resource consumption concerned the 3 months preceding the study. Previous experience had shown that the recall of major events such as admissions or investments is good over a period of 1 year. For example, when comparing mean hospitalisation indicated by a sub-sample of 200 patients in the study in Germany to their hospital charts [28], the difference was 0.25 days (27.15 and 26.90 days). For drug consumption, the recall period generally used is 1 months. However, in order not to include a third time period in the questionnaire, drug use was collected for the past 3 months as well.

Resource consumption collected was

- inpatient and outpatient admissions
- office visits to specialists, general practitioners
- visits to health professionals such as physical or occupational therapists, psychologists, acupuncturist, opticians, alternative medicine specialists, etc
- examinations such as MRI, Cat or T scans, X-rays, electromyogram, electroencephalogram, electrocardiogram, ultrasound, etc

- MS-specific drugs (interferon beta-1a i.m. (Avonex), interferon beta-1b s.c. (Betaseron), Interferon beta 1a (Rebif), glatiramer acetate (Copaxone), azathioprine (Imuran), mitoxantrone (Novantrone), cyclophosphamide (Cytoxan), methotrexate (Reumatrex), gamma globulin (IVIG), IV steroids)
- other prescription drugs
- over the counter medicines
- community and other services such as home care, home help, child care, meals on wheels, etc
- help and care provided by friends and family members
- alterations and items purchased such as adaptation of kitchen or bathroom, stair or bed lifts, rails, ramps, car modifications, walking aids, wheelchair, scooter, glasses, special utensils and devices, etc

All resource use was collected, regardless of who paid for it. It was assumed that the majority of patients with MS had health insurance and was covered for medical care. However, with the exception of hospitalization, patients were asked to indicate for each resource whether they had paid for it themselves or whether insurance had covered it. In addition, for all items likely to be paid by patients themselves, they were asked to indicate the actual cost. This allowed to estimate the cost falling on payers (MCO).

2.3.2.2 Productivity losses

Indirect costs were based on short term work absence, changes in working situation and early retirement, all related to MS only. Patients were asked about

- their current work situation (working, unemployed, early retired, retired, student, homemaker)
- their work schedule (full time, part time, as well as self-employed)
- short term absence from work
- reduction in work time or change in the type of work leading to income loss
- early retirement due to MS.

2.3.3 Utility

Utility scores were collected with a well-validated, generic preference-based instrument, the EQ-5D [29]. Utilities are preferences for given health states on a scale between anchors defined as 1 for full health) and 0 for death. The descriptive part of the EQ-5D consists of five questions concerning five domains of health-related quality of life (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Questions have three levels of answers (1 = no problem, 2 = some problems, 3 = severe problems), leading to 243 possible combinations of answers (where e.g. 11111 represents full health). Based on a number of these combinations, health state descriptions were created and utilities assigned in the general population with the time trade-off method. A health state classification system was then developed from which utility weights for the different combinations can be derived [30, 31]. Within this classification system, states worth than death, i.e. negative utility scores, are possible. There is no firm rule regarding how negative values should be handled, and they can either be used as they are, or set to zero. In this study, 8 negative values have been set to zero. In view of the limited number of questions in the EQ-5D, it is not possible to impute missing values, and patients with incomplete answers are therefore excluded.

The EQ-5D has very recently been adapted and validated in the United States and a specific health states system created [32]. Although the validation has not yet been fully

published, it has been possible to use the system in our current study. Utility scores are thus US-specific.

Patients were asked to complete both the descriptive part of the EQ-5D and the visual analogue scale (VAS) that is also part of the instrument. On the VAS, patients indicate their current health on a scale between 0 (worst possible state) and 100 (best possible state). However, for economic evaluations, only the descriptive part leading to utilities can be used.

2.3.4 Valuation (costing)

The primary descriptive analysis is from the societal perspective, i.e. it takes all costs into consideration, regardless of who pays. In addition, costs borne by patients themselves are included. In view of the objective of the study and the multiplicity of insurance plans, no difference by payer is made.

Costs are calculated as mean annual cost per patient by multiplying the 3-month period by four. This is based on the assumption that in any given quarter, a similar number of patients in a large sample will use a given resource.

Unit costs for the resources were obtained from a number of sources:

- Hospital admissions: DRG costs from the Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality. www.ahrq.gov/hcupnet
- Ambulatory care visits:
    - American Medical Association, Current Procedural Terminology CPT™ 2004
    - CMS website: www.cms.hhs.gov
- Prescription drugs:
    - www.drugstore.com
    - www.eckerd.com
- OTC medication: phone survey of local pharmacies in Seattle, Washington area
- Services: as indicated by patients, verified through comparison to rates by the American Health Care Association
- Average hourly salary: Bureau of Labor Statistics, US, 2003. www.bls.gov/oes. Employers' costs are estimated to range between 25-30%, and a rate of 30% was used in this study.
- Informal care: 50% of total wage cost was used as the disposable income (corresponding to 65% of average salary after tax)

All unit costs are for 2004, or were inflated to 2004 using the CPI.

2.3.4.1 Direct cost calculations

Inpatient care

Patients were asked to indicate the hospital department, the reason for admission and the length of stay. Costs were calculated using DRG values corresponding to the department and cause for admission. A small number of admissions clearly not related to MS were excluded. When the cause for admission was not stated, admission for MS was assumed.

Ambulatory care visits and tests:

Patients were given a list of the most relevant specialists and other health care personnel as well as tests and asked to indicate whether they had used the resource, and if so, how often. They were also given an option "other" and asked to indicate the type and the number. From this, the cost of visits to each type of specialist and of each test was

calculated. When a patient answered that a visit or test had taken place but omitted the number of visits or tests, the average usage indicated by the entire sample of the particular resource was imputed.

Drugs:
As for ambulatory care, a list of the most frequently used prescription drugs was provided in the questionnaire and patients asked to indicate the number of days. When the duration of treatment was missing, the mean duration of the sample using the same medication was imputed. When imputation was not possible, e.g. when too few patients took the same treatment to allow calculation of a reliable average, the usage was excluded. Drugs clearly not related to MS were excluded.
The cost was calculated based on the standard daily dose multiplied by the number of days and the daily drug cost. The latter was calculated based on pharmacy prices. When generic drugs were available, it was assumed that at least 90% of patients would use the generic and the cost was weighted accordingly.

The cost of OTC drugs was used as indicated by patients. When the cost was missing, the usage was excluded. In order to verify the cost indicated by patients, the public prices of a small number of frequently used drugs was compared to the costs indicated by patients and found to correspond well. Considering the limited cost of OTC medications, patients' indications were thus used.

Services:
Patients were asked to indicate during how many days, and for how many hours they used services such as home help, child care, etc., as well as their expenses. Costs indicated were verified against average hourly rates of service personnel, when available. However, as it was not possible to verify each cost, and as the variation in cost was considerable, outliers were adjusted. Outliers were defined as lying outside the mean +/- 1 standard deviation. In these cases, as well in cases where the patient indicated using the resource but omitted to indicate the cost, the mean cost of the sample was imputed.

Informal care:
Informal care is considered a direct cost in this study, based on the consideration that if this care is not provided by family or friends, paid help would be required. There are no defined rules on how to value the cost of unpaid labor. The 3 approaches most used are the replacement method where each hour of informal care is assigned the cost of a health care professional (e.g. a community nurse), or productivity loss at the full wage rate, or the loss of leisure time valued as the disposable income, usually around 35-50% of average total salary cost.
The latter approach was applied in this study, using 50% of total wage cost as the disposable income (corresponding to 65% of average salary after tax). These calculations were based on an average of 30% employers' cost and an average income tax rate of 35% (25-40%) income tax.

Investments:
For adaptations of the house or the car, investments (e.g. wheelchair, scooter) and devices, the cost indicated by the patient was used. Outliers and missing values were treated as services (see above).

2.3.4.2 Indirect cost calculations

Short term productivity losses were calculated using the mean wage per hour ($ 17.41 plus 30% salary cost) and patients' indications on the number of missed work hours. No

adjustment for the age of the sample or for gender distribution was made. The cost of early retirement due to MS was calculated as the loss of the average national income ($ 36,210 plus 30% salary cost).

When patients who were not early retired indicated that they had been forced to change the type of work due to MS, with an ensuing loss of earnings, the patient-reported loss of income was included in the calculation of indirect costs. Similarly, when patients had to reduce their working time due to MS, the reduction was included as a cost, provided they had also indicated that they were currently working to some extent. In both cases, outliers and missing values were treated as outlined for services above.

Indirect costs were only calculated for patients who were working or were below 65 in the case of early retirement.

No cost was estimated for the loss of leisure time. Although in the case of MS the loss of leisure time is likely to represent a substantial cost, there are substantial difficulties associated with accurately measuring the loss of leisure time due to illness. We preferred therefore to estimate intangible costs as a loss of quality of life rather than loss of leisure time.

2.3.4.3 Intangible cost calculations

Intangible costs, i.e. costs due to pain, grief, anxiety, social handicap, treatment etc., are usually omitted in cost of illness studies. However, Henriksson et al provided an interesting approach to estimating of these costs in their cost of illness study in Sweden [33], and the same approach was used in the studies in the United Kingdom and Germany [4, 28]. By calculating the difference in utility scores between the study sample and an age- and sex-matched sample of the normal population, and the number of QALYS lost during 1 year by the MS sample compared to the average can be estimated. Assuming a value of a QALY, i.e. a certain willingness-to-pay (WTP) for a QALY, intangible costs are calculated by multiplication of this WTP by the average number of QALY's lost per patient and year.

Unfortunately, gender- and age-specific scores for the general population are not available for the United States, and it is therefore not possible to estimate US specific intangible costs with this method. However, as an indication only, the QALY loss in this sample was calculated using the UK tariff and UK population values. Intangible costs were estimated using an implied WTP for a QALY of $ 60,000-100,000 [34, 35].

2.4 Analysis

Descriptive statistics are presented with mean values and standard deviations (SD), or the proportions of patients falling into a given category.

Resource use is presented as the proportion of patients in the sample using each resource, with the mean quantities and resulting costs calculated for the entire sample as well as for users of that resource only. As mentioned above, when patients indicated that they consumed a given resource, but omitted to complete the quantity, the mean quantity of all users of that resource was imputed. When missing data concerned isolated resources, i.e. when no or only very few other patients used these resources, the patient was excluded from the cost calculations.

3 RESULTS

The target sample size (2,000) and response rate (50%) was reached: 1,989 (49.7%) of the 4,000 patients contacted returned the questionnaire, but 80 of them were returned empty and had to be excluded. This left a sample of 1,909 (47.7%) for analysis.

3.1 Patient demographics

Table 3-1 presents the demographics of the sample.

Table 3-1 – Sample demographics and disease information (N=1,909)

Variable	Proportion (%) or Mean
Age	
Mean (SD)	49.2 (9.5)
- <30	2.0%
- 30-39	14.5%
- 40-64	78.5%
- >= 65	5.0%
Gender	
Proportion female	76.4%
Proportion male	23.6%
Time since diagnosis	
Mean (SD)	13.1 (8.1)
Age at first symptom of MS	
Mean years(SD)	30.2 (10.2)
Type of MS	
Primary progressive MS	10.5%
Relapsing-remitting MS	47.6%
Secondary progressive MS	33.3%
Don't know	7.6%
No answer	0.9%
Relapses	
Relapses during past 3 months	
Yes	28.8%
No	57.7%
Unsure	12.8%
No answer	0.7%
Treated with IV steroids during relapses	10.6%

The mean age was 49 years and three quarters were women. Their age at first symptoms was 30 years, and time since diagnosis was 13 years.

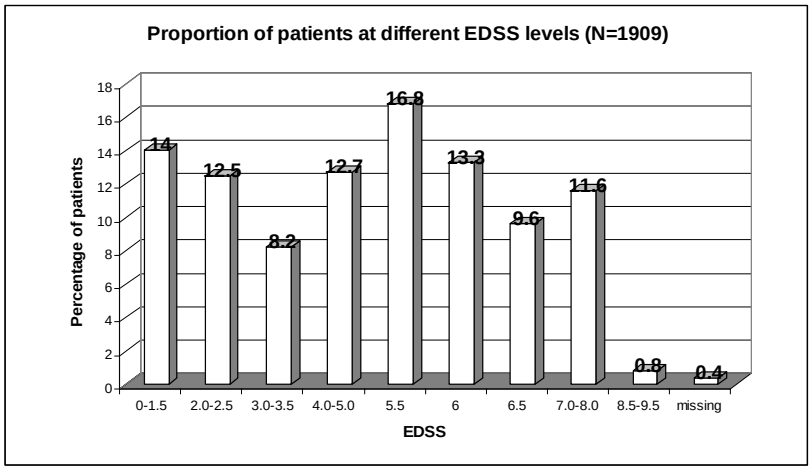
The proportions of patients with the different types of MS are as expected and representative of the prevalence, with 10.5% of patients with primary progressive, 47.6% with relapsing-remitting and 33.3% with secondary progressive disease. Less than 1% of patients did not answer the question, but 7.6% were unsure. This distribution is in line with published data [13].

Slightly less than a third of patients (28.8%) indicated to have experienced a relapse during the past 3 months, with over a third of these needing IV steroid treatment indicating severe relapses. In addition, 12.8% were unsure about their answer.

Around one third (34.8%) had mild disease defined as a PDSS of 0 to 2 (EDSS 0-3.5), 42.7% had moderate MS defined as a PDSS of 3 to 5 (EDSS 4.0-6.0) and 22.1% had severe disease with a PDSS of 6-8 (EDSS 6.5-9.5). Only 0.4% did not answer. The distribution into the EDSS levels is shown in Figure 3-1. The natural history cohort in Ontario, Canada, showed a similar bi-modal distribution[36], although the second "peak" is found around EDSS 6 rather than at 5.5 as in our sample. The relatively high proportion of patients at EDSS 4-5.5 is likely due to the selection of patients on treatment. In fact, the approved indication for DMDs (RRMS) would bias a sample towards milder patients than the general prevalence. This is illustrated by the fact that bed-ridden patients (EDSS 8.5 and above) are underrepresented in our sample. These patients would likely have needed proxies to complete the mailing and therefore chose not to return the questionnaire. The group therefore only represented 0.8% of the sample, compared to 2.5%, 3.7% and 5.0% in the studies in Germany, the UK and Sweden respectively [4, 8, 9]. In the Canadian sample, DSS 9 and 10 represented 3% [36]. In a sensitivity analysis, costs for a sample with a higher proportion (4%) of very severely ill patients is presented.

There appeared to be no major bias in the sample that returned the questionnaire compared to the sample that was contacted (4000). The gender distribution was similar (24.8% males and 75.2% females in the mailing). As the overall sample was rather young, there was no difference in the rate of return of the questionnaires by age groups, the mailing included 6.7% of patients aged 65 and over, and this groups represents 5% in the study sample.

Figure 3-1 - Distribution of patients by EDSS scores



Note: for ease of understanding and comparison, PDDS scores in the survey have been transformed into EDSS scores according to the original translation:
0/1 = 1-1.5 / 2 = 2.0-2.5 / 3 = 3.0-3.5 / 4 = 4.0-4.5 / 5 = 5.0-5.5 / 6 = 6.0 / 7= 6.5 / 8= 7.0-7.5 / 9 =8.5-9.5

Slightly under one third of patients (31.4%) had been forced to take early retirement due to MS. The mean age of these patients was 53 (SD 8.1). However, 42.3% answered that they had stopped working due to MS. The most likely explanation of this discrepancy might be that some of these patients are not receiving an invalidity pension, and therefore did not indicate that they were on early retirement benefits. Thus, productivity losses occur at least for 31.4% of patients, but may be as high as 42.3%. The higher value is therefore also calculated.

A further 21.4 % of patients indicated that they had been forced to either change the type of work, or to reduce their working time. Changes in the type or duration of work leading to a reduction of earnings were included in the calculation of indirect costs. Details are presented in Table 3-2.

The proportion of patients working full time is very similar to data found in Norway and Sweden (23%) [37, 38]. Both these studies found that amongst these patients, about one fifth are likely to lose their job within 2-3 years.

Table 3-2 - Employment situation

	Proportion (%)
Employment	
Employed during last 3 months	40.9%
- *Full time*	*25.7%*
- *Self employed*	*3.9%*
- *Reduced time*	*11.3%*
No answer	59.1%
Changed work situation	
No change	31.5%
Changed work	12.3%
Reduced hours	9.1%
Stopped working	42.3%
No answer	4.8%
Early retirement	
Early retired (mean age 53 years)	34.3%
Early retired due to MS	31.4%

3.2 Resource consumption and costs

3.2.1 Inpatient care

Hospitalisation was infrequent with only 6.2% of patients using any type of inpatient care. Of these, one quarter were admitted to a Neurology department for a mean duration of 10.4 days, while 6.9% were admitted to a nursing home for an average of 184.5 days.

The mean annualized length of inpatient stay (LOS) for the entire sample was 2 days, leading to a cost of $ 1,245. The mean annualized cost for patients that were hospitalised was $ 23,309.

Table 3-3 - Mean cost of inpatient care (N=1909)

Inpatient care	Proportion using the resource	Mean number of inpatient days per patient and year		Mean cost per patient and year ($, 2004)	
		Entire sample	Patients using the resource	Entire sample	Patients using the resource
Total inpatient care	**6.2%**	**2.0**	**n/a**	**1245**	**23309**
- Neurology	25.5%	0.2	10.4	273	13351
- Nursing home	6.9%	1.3	184.5	314	46135

3.2.2 Ambulatory Care

3.2.2.1 Consultations

Table 3-4 - Ambulatory care visits (N=1909)

Ambulatory care	Proportion using the resource	Mean number of visits per patient and year		Mean cost per patient and year ($, 2004)	
		Entire sample	Patients using the resource	Entire sample	Patients using the resource
Total	**80.9%**	**24.8**	**n/a**	**1582**	**1949**
-Outpatient admission	19.6%	0.2	7.6	165	886
-Acupuncturist	1.5%	0.4	24.1	10	687
-Alternative medicine specialist	1.6%	0.3	17.1	8	486
-Cardiologist	0.5%	0.0	7.1	2	448
-Chiropractor	6.4%	1.6	24.7	54	833
-Emergency medicine	0.1%	0.0	6.0	0	378
-General practitioner	15.1%	1.3	8.4	80	529
-Internist	8.7%	0.7	8.2	45	515
-Massage therapist	7.1%	1.5	21.0	33	467
-Neurologist	64.7%	3.7	5.7	230	356
-Neuropsychologist	1.5%	0.2	13.7	13	864
-Nurse	9.5%	2.8	29.0	95	999
-Occupation therapist	2.2%	0.9	41.7	58	2620
-Ophthalmologist	9.9%	0.6	5.8	36	367
-Optician	5.4%	0.3	6.0	29	535
-Other specialist	6.4%	0.5	8.1	30	467
-Physical therapist	10.1%	5.2	51.0	324	3202
-Psychiatrist	6.7%	0.7	10.0	136	2042
-Psychologist	5.0%	1.1	22.8	126	2507
-Rehab specialist	3.1%	0.8	25.4	45	1454
-Social worker	3.2%	0.7	21.2	21	671
-Speech therapist	0.6%	0.2	27.6	10	1735
-Unknown	0.6%	0.1	9.0	0	0
-Urologist	9.6%	0.6	5.9	35	369

Almost all patients had one or several consultations and visits to different physicians or other health care specialists during the study period (80.9%). The mean annualized number of consultations was 24.8 per patient. 65% of patients had 5-6 visits on average to a neurologist. Ten percent needed physiotherapy with an average annualized number of 51 sessions, while 11-12% of patients saw a psychiatrist or psychologist.

Costs for the 80.9% of patients with consultations resulted in $ 1,949 per year, and for the entire sample in $ 1,582 per year.

3.2.2.2 Tests

Half of the patients in the sample required tests, most frequently blood tests. However, 27% underwent MRIs, which represented close to 70% of all test costs.

Table 3-5 – Mean cost of tests

Tests	Proportion using the resource	Mean number of tests per patient and year		Mean cost per patient and year ($, 2004)	
		Entire sample	Patients using the resource	Entire sample	Patients using the resource
Total tests	**52.8%**	**6.9**	**n/a**	**857**	**1626**
Blood test	39.9%	4.3	10.7	70	175
Bone density test	0.4%	0.0	4.0	1	144
CT scan	2.7%	0.1	5.3	58	2113
ECG	3.9%	0.2	5.3	40	1026
EEG	1.3%	0.1	4.3	10	780
EMG	1.1%	0.1	5.9	9	784
Evoked potential	0.1%	0.0	4.0	1	494
Hearing exam	0.1%	0.0	12.0	0	459
MRI	0.2%	0.0	4.0	9	4427
MRI (Brain)	18.3%	0.8	4.5	414	2258
MRI (Spine)	8.4%	0.4	4.6	180	2149
Myelogram	0.1%	0.0	4.0	1	1240
Other	0.9%	0.0	3.5	5	585
Spinal tap	0.3%	0.0	4.0	2	643
Ultrasound	4.6%	0.2	5.1	28	615
Unknown	0.8%	0.0	8.9	0	0
Urine analysis	0.9%	0.1	7.6	0	23
Urodynamics	0.3%	0.0	4.7	4	1391
VEP	0.1%	0.0	4.0	0	270
Visual field exam	0.4%	0.0	4.6	1	227
X-ray	6.3%	0.5	7.7	23	368

3.2.2.3

Drugs

Almost all patients in the sample were treated with one of the recent disease modifying drugs (94%) as this had been one of the selection criteria in the data base. The 6% of patients not using them had stopped since the last assessment in NARCOMS, but were included nevertheless. The majority (78%) also used other prescription drugs and 58% OTC medication. The most used drug category was drugs for depression and anxiety, followed by treatments of spasticity and fatigue. Interestingly, while the use of antispastic drugs was increasing with disease severity, treatments for depression and fatigue were used to a similar extend by patients with moderate and severe disease.

Table 3-6 - Mean cost of drugs

Drugs	**Proportion using resource (%)**	**Mean cost per patient and year ($, 2004)**	
		Entire sample	**Patients using the resource**
All drugs	**98.1%**	**18628**	**18925**
- Interferons	59.5%	10757	18085
- Glatiramer	33.6%	5293	15763
- Novantrone	4.5%	243	5396
- Other prescribed drugs	77.6%	2213	2756
- OTC drugs	58.1%	122	243
-			

Table 3-7– Type of prescription drugs used

Drug category	**Proportion of patients (%)**
Depression/psychiatric disorders	52.7%
Spasticity	48.5%
Fatigue	38.4%
Neurogenic pain	12.8%
Genitourinary dysfunction	11.7%
Hypertension/Dyslipidemia	9.8%
Inflammation	7.5%
Other	3.4%

Table 3-8– Drug use by disease severity

Disease severity	**Proportion of patients using drugs for**		
	Spasticity	Depression	Fatigue
Mild	13.4%	19.1%	22.9%
Moderate	45.5%	37.6%	39.5%
Severe	65.6%	35.4%	32.1%

Table 3-9 – Most commonly used prescriptions

Drug	Proportion of patients (%)
BACLOFEN	23.6%
PROVIGIL	21.5%
NEURONTIN	16.7%
ZANAFLEX	14.4%
SYMMETREL	11.9%
PROZAC	10.6%
VALIUM	8.8%
KLONOPIN	7.0%
ELAVIL	6.4%
METHYLPREDNISOLONE	6.3%
LIPITOR	4.8%
ZOLOFT	4.6%
ZOCOR	3.9%
RITALIN	3.2%
TEGRETOL	3.1%
OXYBUTYNIN	3.0%
DETROL	2.9%
WELLBUTRIN	2.8%
CELEXA	2.7%
XANAX	2.4%
DETROL LA	2.2%
DITROPAN XL	1.9%
EFFEXOR	1.7%
BACLOFEN PUMP	1.7%
CYLERT	1.7%
DITROPAN	1.7%
HYDROCODONE	1.6%
AMBIEN	1.3%
LEXAPRO	1.3%
IBUPROFEN	1.2%
NORTRIPTYLINE	1.2%
PRAVACHOL	1.2%
PREDNISONE	1.2%
4AP	1.0%
TRAZODONE	1.0%

3.2.3 Services

Twenty-two percent of the sample required services, most frequently home help and home care. Few patients needed help with child care.

Table 3-10 – Mean cost of services

Service	Proportion of patients (%)	Mean cost per patient and year ($ 2004)	
		Entire sample	Patients using the resource
Total	**22.0%**	**822**	**4004**
Home care	9.8%	392	4008
Home help	13.6%	316	2328
Child care	0.9%	24	2508
Day care center	0.4%	10	2572
Meals on wheels	1.4%	10	680
Other	4.0%	72	1764

3.2.4 Adaptations, investments, special devices

Half of the patients in the sample had purchased special items or made adaptations to their living environment during the past year. The most costly items were as expected wheelchairs, scooters, car modification and stair lifts or elevators.

Table 3-11 – Cost of adaptations, investments and devices

Adaptations/items	Proportion of patients (%)	Mean cost per patient and year ($ 2004)	
		Entire sample	Patients using the resource
Total	**51.5%**	**1885**	**3702**
-Adaptation of kitchen	2.5%	34	1255
-Adaptation of bathroom	12.9%	110	848
-Adaptation (other) of house	3.7%	129	2866
-Bed lift	0.9%	18	1459
-Stair lift/Elevator	1.2%	66	3964
-Stair rail	3.6%	18	511
-Ramps	4.2%	48	922
-Alarm	0.6%	19	1607
-Adaptations at work	2.8%	4	258
-Car modifications	4.4%	301	6532
-Walking stick/aid	21.7%	15	68
-Wheelchair	7.9%	207	2000
-Electric scooter	7.9%	208	2405
-Glasses	12.7%	40	273
-Special kitchen utensils	4.1%	2	52
-Special hygiene devices	5.8%	9	143
-Special writing devices	2.5%	1	62
-Other	9.1%	636	5540

3.2.5

Informal care

37.8% of respondents received care from family members or friends, for an average of 29 hours per week. Using 35% of national average wage cost for adults, as was done in the earlier studies in Sweden, Germany and the United Kingdom, the yearly cost per patient using informal care would be $8,570. Using the higher estimate of post-tax disposable income for the US, 50%, the cost is $ 12,199.

The mean annual cost per patient in the entire cohort is $3,228 and $ 4,614 respectively, for a mean of 11 hours per week.

3.2.6 Indirect costs

3.2.6.1 Short term absence

40.9% of respondents were employed or self-employed during the 3 months preceding the survey. The mean number of sickness absence days per year was 2.8 amongst all patients, 7.2 amongst those employed, and 25.6 amongst those taking short-term sick leave. This corresponded to 22.4, 57.6 and 204.8 hours of absence per patient group and year, respectively. Lost working time was calculated taking into consideration part time employment, and the cost per employed patient was estimated at $ 1,305 per year, while the cost per patient with work absence was $4,628 per year. Applied to the entire sample, the cost was $ 533 per patient.

3.2.6.2 Lost working time and income

19.0% of employed patients had reduced their working time, at a cost of $ 16,812 per patient concerned, at $2,886 per employed patient and at $ 1,180 per patient and year in the entire sample. 12.6% of employed patients indicated that they had suffered a loss of income through being forced to change their work because of MS. The mean cost per patient concerned, based on patients' indications, was estimated at $20,030, compared to $4,875 per employed patient. For the full sample, the cost was estimated at $ 2,182 per patient and year.

3.2.6.3 Early retirement

599 patients had retired early due to MS (31.4% of total sample). For patients aged 65 or less, the average national annual income of $36,210 (gross $ 47,073) was counted as productivity loss. The average cost of early retirement per patient across the whole sample was thus $13,685.

Using the higher number of patients who had stopped working because of MS (see 3.1. patient demographics), 42.3%, the cost of early retirement would be $ 18,436.

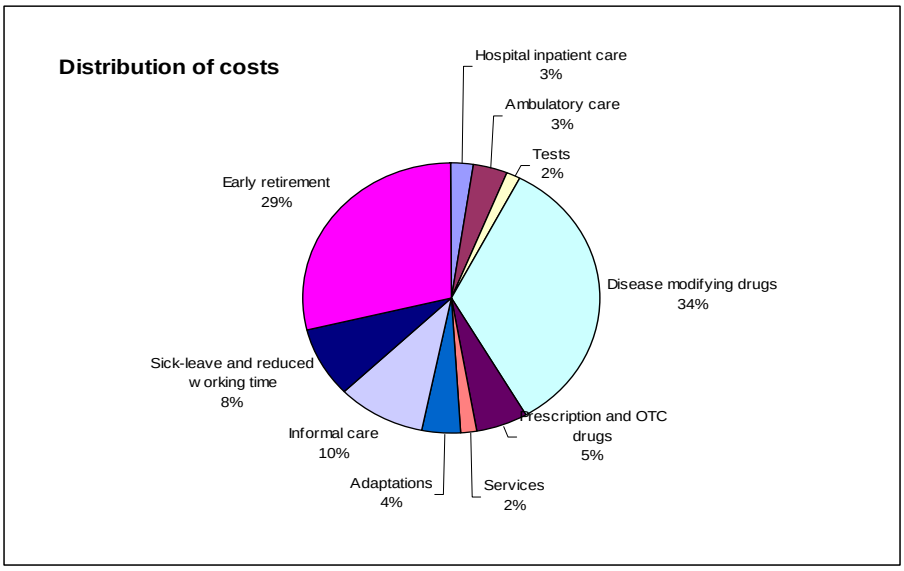
3.3 Total costs per patient

Total costs per patient and year are estimated at $ 47,215. The largest proportions of costs are due to drugs (39.5%) and indirect costs (37.2%).

Table 3-12 – Total mean cost per patient and year (N=1909)

Costs	Cost per person and year ($, 2004)	Share of total cost (%)
Total costs (SD)	**47215 (35292)**	**100.0%**
Total direct costs (SD)	**29634 (17553)**	**62.8%**
Hospital inpatient care	1245	2.6%
Ambulatory care	1582	3.4%
- day stays	165	0.3%
- physicians	565	1.2%
- nurses/physiotherapists	419	0.9%
- paramedical	436	0.9%
Tests	857	1.8%
Drugs	18628	39.5%
- Disease modifying drugs (DMD)	16050	34.0%
Services	822	1.7%
Adaptations	1885	4.0%
Informal care	4614	9.8%
Total indirect costs (SD)	**17581 (23640)**	**37.2%**
Short-term absence	533	1.1%
Reduced working time/income	3362	7.1%
Early retirement	13685	29.0%

Figure 3-2 – Distribution by type of cost



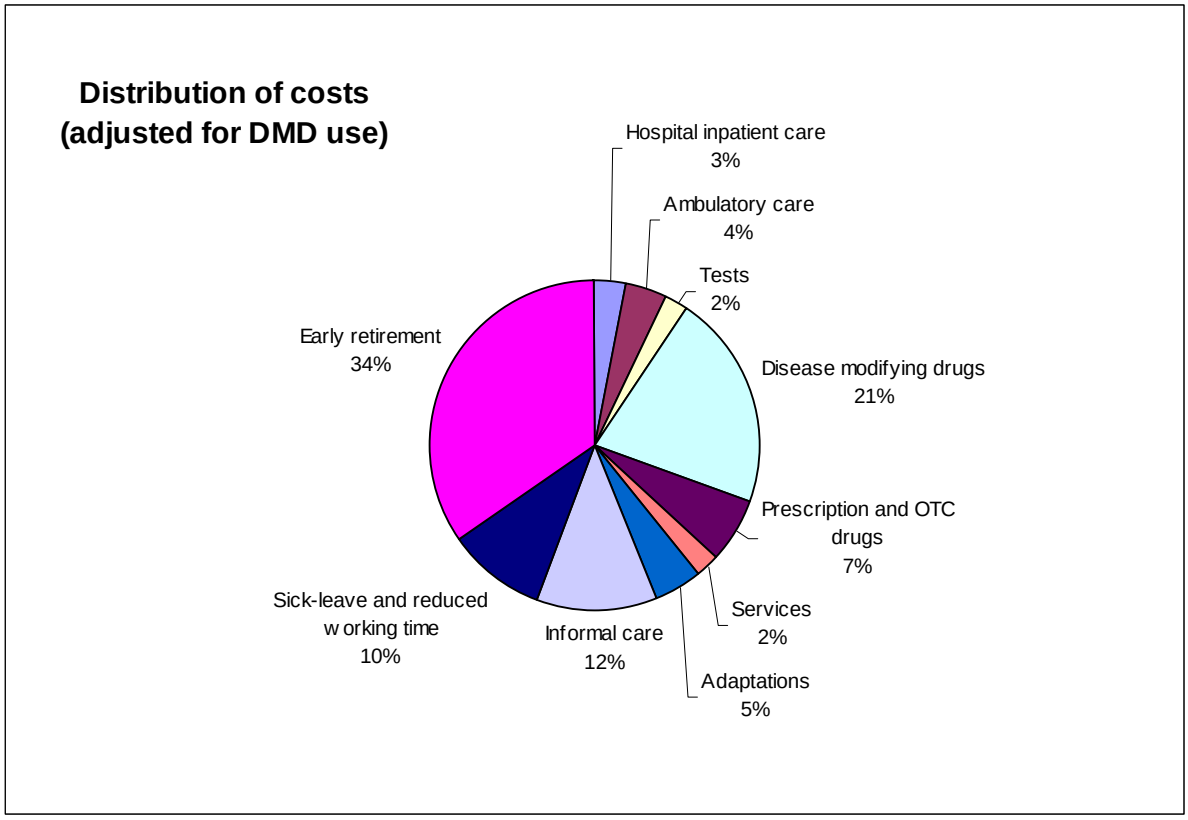
3.3.1 Total costs per patient, adjusted for national use of disease modifying drugs

All patients in this sample were treated at the last follow-up with one of the disease-modifying drugs (DMD), and 94% were on treatment at the time of the survey. It is therefore not possible to directly extrapolate the costs to an estimate of the cost of MS in the United States. However, as EDSS has been shown to be by far the strongest predictor of total costs (in the absence of a relapse), a rough estimate can be made by simply adjusting DMD use to the estimated national usage. The current estimate of the number of patients treated with DM drugs is 52% (Schering AG, data on file).

Thus, after adjustment, total costs would be reduced by € ~7,700 leading to total costs of approximately € 39500, of which 55.5% will be direct costs, and 21% MS treatments as shown below.

This estimate may be both, either an over- or an underestimate. There has been anecdotal evidence that patients treated with DMDs are more intensively managed and will therefore have overall higher costs. On the other hand, the relapse rate will be lower and costs caused by relapses therefore also lower. However, the estimated average costs or effects will only marginally be affecte.

Figure 3-3 – Total costs per patient adjusted for current national use of DMDs



3.4 Utilities

Thirty-one (1.6%) EQ-5D questionnaires had to be excluded due to missing values, leaving 1,878 answers for analysis. The mean utility in the sample was 0.698 (SD 0.206), with women having higher scores than men. Utilities were lower by 0.094 for patients who experienced a relapse during the preceding 3 months. Thus, the QALY loss for a relapse of 1 month can be estimated at 0.03.

Table 3-13 - Mean utility scores

	N	Mean values (SD)	Range
EQ-5D			
All patients	1878	0.698 (0.206)	0, 1
Male	445	0.667 (0.231)	0, 1
Female	1433	0.709 (0.196)	0, 1
Relapses during the past 3 months			
patients with	544	0.648 (0.219)	0, 1
patients without	1087	0.742 (0.185)	0, 1
Visual Analogue Scale			
All patients	1832	66.13 (20.06)	0-100

The difference in utilities by gender seems to be explained by age, with the mean age for men being 51.4 years, compared to 48.5 years for women.

3.5 Intangible costs

Intangible costs are indicative only. In the absence of standardized population values by age and gender for the United States, values for the United Kingdom are used. The QALY loss estimated in this sample would be 0.255 QALY per patient. Using a willingness to pay for a QALY of $ 60,000, intangible costs are estimated at $ 15,315 per patient.

Utility values in the US are consistently higher than for the UK as shown in Table 3-14. Thus, it could be hypothesized that this is a general trend, rather than specific to MS, i.e. population values are also higher. Thus intangible costs might not be fundamentally different.

Table 3-14 – Comparison of utilities calculated with US and UK tariff

	US tariff	UK tariff
EQ-5D		
All patients	0.698	0.594
Male	0.667	0.552
Female	0.709	0.608
Relapses during the past 3 months		
patients with	0.648	0.518
patients without	0.742	0.659
Mild disease	0.824	0.770
Moderate disease	0.679	0.563
Severe disease	0.533	0.368

3.6 Effect of functional status on utilities and cost

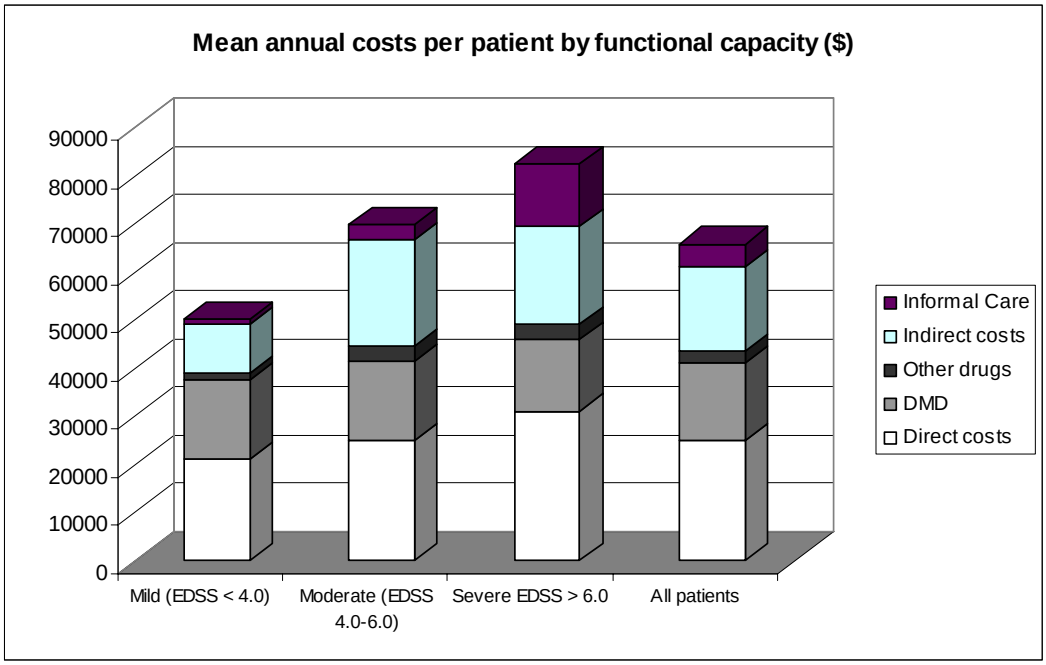
As in previous study, functional status (PDSS or EDSS) is highly predictive of utilities and costs, although more severe disability is also associated with higher age. As a consequence, indirect costs represent a higher proportion of costs at the moderate disease level, as more patients are at working age.

Table 3-15 - Mean costs and utilities by disability

Disability level	Proportion of patients	Utilities	Costs ($, 2004)					
		EQ-5D	Direct costs	*DM drugs**	*Other drugs*	Indirect costs	Informal care costs	Total costs
Mild (EDSS 0-3.5)	34.8%	0.824	21121	*16396*	*1500*	10254	923	32297
Moderate (EDSS 4.0-6.0)	42.7%	0.679	24984	*16369*	*3167*	22080	3230	50293
Severe (EDSS 6.5+)	22.1%	0.533	31154	*14905*	*3127*	20194	13144	64492
Total		**0.698**	**25020**	***16050***	***2578***	**17581**	**4614**	**47215**

* DM = disease-modifying

Figure 3-4 - Costs by functional capacity



3.7 Analysis by perspective

The previous analyses present costs from a societal perspective, regardless of who pays for it. Table 3-16 presents an estimate of direct costs that would likely be paid by a health plan, or fall on patients themselves. Costs were estimated as follows:

- For a number of resources (services, devices, adaptations and investments) patients had been asked to indicate whether they had paid out of pocket or whether insurance had covered them, and these indications were used for each item.
    - On average 22.8% of the cost of services was covered: However, 37.5% of patients did not answer this question, and we assumed that patients paid themselves.
    - For adaptations and investments, an average of 20.2% of costs were covered, and 15.2% provided no answer. The highest coverage was for wheelchairs, scooters and glasses
- Patients were also asked whether they had prescription drug coverage, and almost all patients did. OTC drugs were considered not covered.
- For the remainder of the resources (hospitalisation, visits to physicians and other health professionals, procedures and tests), we used the following assumptions:
    - Inpatient care and physician services were covered, while paramedical services were covered partly (excluding acupuncturist, alternative medicine, massage, chiropractor, optician).

Table 3-16 – Cost estimate by payer

Costs	Total costs (societal perspective)	Costs covered by a typical MCO plan	Patients' out of pocket costs
Total direct costs (SD)	**29634**	**22585**	**7049**
Hospital inpatient care	1245	1245	0
Ambulatory care	1582	1448	134
- day stays	*165*	*165*	*0*
- physicians	*565*	*565*	*0*
- nurses/physiotherapists	*419*	*419*	*0*
- paramedical	*436*	*302*	*134*
Tests	857	857	0
Drugs	18628	18506	122
- Disease modifying drugs	*16050*	*16050*	*0*
- Other prescription drugs	*2213*	*2213*	*0*
- OTC drugs	*122*	*0*	*122*
Services	822	197	625
Adaptations	1885	331	1554
Informal care	4614	0	4614

4 DISCUSSION

This is to our knowledge the first complete study that investigates the cost of illness o MS after the introduction of the interferons and glatiramer acetate, collecting exhaustive information directly from a large sample of patients with all types of MS.

An earlier study had used the top down method to investigate the direct cost of patients with relapsing-remitting MS treated with immunomodulating drugs using managed care claims data for a cohort of 8457 patients [7]. The study found that DMDs represented 70/75% of total direct costs. Similar proportions (75%) were found in a retrospective chart review of 630 patients with relapsing-remitting MS study in Italy [39], as well as in a systematic claims review performed by the French national health insurance[40]. This latter study also included indemnities for sick leave and invalidity pensions paid, and the proportion of total charges for the insurance represented by DMDs was reduced to 56%. In our study, DMDs represent 54% of direct costs and 34% of total costs. The difference is explained by the fact that top down studies using claims databases, or retrospective analysis of claims, will not only ignore indirect costs, but also miss a considerable proportion of costs not paid for by health plans or other third party payers. We found that indirect costs represented 37% of total costs, and costs borne by patients at least 15%.

There are shortcomings in the bottom-up method as well. Firstly, it is difficult to ensure that the sample of patients included is truly representative of the patient population. It will crucially depend on the study centers chosen and on the selection of patients within these centers. Second, it is difficult to assert that the information received from patients is totally accurate. The guarantee of total anonymity of the information will often prevent a comparison between patients' answers and e.g. their medical charts. Also, the choice of the recall period might influence the answers. Third, the information received is sometimes difficult to interpret, as patients will use their own language for certain resource items, or it will contain a large number of items that are consumed only by one or a few patients, leading to a cumbersome analysis.

We have attempted to minimize all of these issues:

1) The sample was carefully chosen from a very large national MS registry, ensuring that the mailing addressed a sample that represents the actual prevalence of the types of MS. In addition, the sample size was chosen to ensure that all degrees of disease severity, particularly the very severe patients, would be represented in sufficient numbers to allow analysis. However, despite of this, it is probable that patients at the very severe EDSS levels (8 and above) are underrepresented.
2) Patients participating in the NARCOMS registry are used to complete questionnaires, as they provide bi-annual data since several years.
3) The questionnaire provided lists of resources used most frequently by MS patients, with tick boxes, in order to minimize the need for interpretation and the time required to complete the questionnaire. Despite of this, a large number of "other" items were added by patients, requiring some interpretation and cumbersome analysis. However, this appears a "necessary evil" if the objective is to collect comprehensive information.
4) The recall period was limited to 3 months, except for major events such as inpatient admission or purchases of major items such as a wheelchair or scooter. Although for drugs a recall period of 1 month is generally advocated, it was felt that this particular type of patients were well aware of their treatments, and that it was therefore better use the same recall period for the majority of items rather than add a third period.

5) The study was done in complete anonymity and no control regarding the answers was planned. This was based on previous experience in Europe where a comparison between hospitalization indicated by patients and collected from medical charts showed a difference of less than half a day (on average hospitalization of 27 days).

The results confirm the overall findings of our earlier studies in this series, using the same methodology [4, 28, 33]. Costs are clearly correlated with functional disability, as expected most pronounced for informal care and indirect costs, and utility decreases with increasing disability.

When using the UK tariff to assess utilities, the scores are very similar to those found in our earlier studies in Europe, except for the group with severe disability (EDSS >6.0). The reason for this is most likely that in the European studies between 2.5 and 5% of patients were at EDSS levels above 8.0, while this was the case only for 0.8% of patients in our sample. If the proportion of patients with EDSS 8.5-9.5 is increased to 4%, using mean utility values of the patients who answered the survey (discounting outliers according to the method used for costs of services etc.), the utility score of the severe group becomes comparable to the values found in Europe.

However, when using the new US tariff, scores are overall higher by around 0.1. There can be several reasons for this. It is likely that the US population values certain domains of QoL differently from the UK population. It is also possible that values have improved in general since the time when the UK tariff was estimated. However, the absolute values are not important when e.g. evaluating the effect of a disease, or disease severity, on patients' utility. Such evaluations are driven by the difference in utility between different levels of severity, and it appears that these are not dissimilar from the European values (~0.15 between mild and moderate, ~0.3 between moderate and severe).

Costs are higher in the USA than in European studies from the late 90s. One reason for this – apart from the use of immunodulating drugs - is the difference in timing between the studies. Indeed, the way patients are managed has changed and patients are followed much more closely. Any comparison should therefore be considered with caution.

The biggest difference in costs is however clearly the cost of drugs. While in the studies in Germany and Sweden around 40% of patients were treated with the new drugs (as a consequence of selecting patients in university centers), and in the United Kingdom 2.5%, patients in the US study were selected based on DMD use in the previous regular 6-month survey of the NARCOMS study. Thus, total drug costs represent 39.5% of total costs, compared to 16%, 11.6% and 3.7% in Germany, Sweden and the UK, respectively, and an average of less than 3% in the earlier societal study in the USA [6]. DMDs represent 34% in this sample, but by adjusting their use to the currently estimated penetration among the US patient population (~52%), the cost of DMDs represents 21%. This estimate is however indicative only, as it assumes that treated and untreated patients are similar, and that resource use outside the DMDs remains the same. Although this was shown in the study in Germany, there is no data to assert that this would be the case five years later in the United States as well.

Costs for patients with severe disease (EDSS levels above 6.0) are lower in the US than in Europe, most probably due to an under-representation of very severe patents at EDSS levels above 8.0. However, even if the proportion of patients with most severe disease (EDSS 8.5 and above) is adjusted to the levels found in the earlier European studies (4%), the costs in the severe group of patients increase only by $681 to $65,173. Utility on the other hand changes from o.533 to 0.479. Thus, in this study, the impact of a disease severity above 8 appears stronger on patients' utility than on costs.

However, cost comparisons between countries are difficult to make and indicative at best. Thus, despite the fact that our four studies used the same methods both for data collection and for analysis, there are substantial differences that do not permit direct comparison:

- differences in the sample (type of patients, usage of new treatments)
- differences in the timing and therefore general treatment patterns
- differences in health care provision
- differences in social support.

5 CONCLUSIONS

The objective of this study was to investigate the overall costs for patients treated with the new immunomodulating therapies, and cost distribution among different resources after the introduction of the new MS treatments. In view of the cost of these treatments, our results are not surprising, with MS drugs representing 34% of total costs. When the use of disease modifying drugs is adjusted to the estimated national average (52%), the share of costs represented by these drugs is 21%.

This study does not investigate the value of the investment into these treatments. Rather it provides the necessary input into a disease model where costs and utility are linked to disease progression, with or without treatment, or with different treatments.

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8 Annex 1 – PDSS and conversion of PDSS to EDSS

"Patient Disability Status Scale" definitions and corresponding scores on the Kurtzke "Expanded Disability Status Scale".

The Patient Determined Disease Steps (PDDS) [26] is a scale based on disease steps, which has a correlation of 0.958 with the EDSS and evaluates disease progression over time.

= 0 Normal: I may have some mild symptoms, mostly sensory due to MS but they do not limit my activity. If I do have an attack, I return to normal when the attack has passed.
EDSS =0-1.5

= 1 Mild Disability: I have some noticeable symptoms from my MS but they are minor and have only a small effect on my lifestyle.
EDSS=2.0-2.5

= 2 Moderate Disability: I don't have any limitations in my walking ability. However, I do have significant problems due to MS that limit daily activities in other ways.
EDSS=3.0-3.5

= 3 Gait Disability: MS does interfere with my activities, especially my walking. I can work a full day, but athletic or physically demanding activities are more difficult than they used to be. I usually don't need a cane or other assistance to walk, but I might need some assistance during an attack.
EDSS=4.0-5.0

= 4 Early Cane: I use a cane or a single crutch or some other form of support (such as touching a wall or leaning on someone's arm) for walking all the time or part of the time, especially when walking outside. I think I can walk 25 feet in 20 seconds without a cane or crutch. I always need some assistance (cane or crutch) if I want to walk as far as 3 blocks.
EDSS=5.5

= 5 Late Cane: To be able to walk 25 feet, I have to have a cane, crutch or someone to hold onto. I can get around the house or other buildings by holding onto furniture or touching the walls for support. I may use a scooter or wheelchair if I want to go greater distances.
EDSS=6.0

= 6 Bilateral Support: To be able to walk as far as 25 feet I must have 2 canes or crutches or a walker. I may use a scooter or wheelchair for longer distances.
EDSS=6.5

= 7 Wheelchair / Scooter: My main form of mobility is a wheelchair. I may be able to stand and/or take one or two steps, but I can't walk 25 feet, even with crutches or a walker.
EDSS=7.0-8.0

= 8 Bedridden: Unable to sit in a wheelchair for more than one hour.
EDSS=8.5-9.5