# ESTUDIO DEL COSTE DE LA ESCLEROSIS MÚLTIPLE EN EL BAIX LLOBREGAT. ANÁLISIS EN FUNCIÓN DE LA DISCAPACIDAD.

TESIS DOCTORAL

Virginia Casado Ruiz.
Director de tesis: Txomin Arbizu Urdiain

Programa de Doctorado en Investigación de la Fisiopatología de la Enfermedad de la Universidad de Barcelona.

*Barcelona, 21 noviembre 2007.*

# An approach to estimating the intangible costs of multiple sclerosis according to disability in Catalonia, Spain

V. Casado, L. Romero, L. Gubieras, L. Alonso, E. Moral, S. Martinez-Yelamos, A. Martinez-Yelamos, O. Carmona and T. Arbizu

*Mult Scler* 2007; 13; 800 originally published online Mar 15, 2007;
DOI: 10.1177/1352458506073480

*ARTICLE* *Multiple Sclerosis* 2007; **13**: 800–804

# An approach to estimating the intangible costs of multiple sclerosis according to disability in Catalonia, Spain

*V Casado[1], L Romero[1], L Gubieras[1], L Alonso[1], E Moral[1], S Martínez-Yélamos[1], A Martínez-Yélamos[2], O Carmona[3] and T Arbizu[1]*

Multiple sclerosis (MS) is a chronic demyelinating disease, which represents a great economic burden to society. Cost-of-illness studies of MS tend to underestimate the intangible costs related to pain, anxiety and helplessness. The purpose of this study was to estimate the intangible costs of MS, and determine whether these costs increase as disability progresses. We studied 211 consecutive patients with MS who attended our MS unit. Patients mean age was 41.6 (SD: 10.7) years, 69% were female, and their mean Expanded Disability Status Scale (EDSS) score was 2.47 (SD: 2.05). Quality-of-life was measured with the EuroQoL visual analogue scale. Quality-adjusted life year (QALY) was calculated for each patient. Patients were grouped into five disability stages according to their EDSS, and QALY was compared between patients and a group of healthy controls matched by age and sex. A benchmark value was ascribed to each QALY lost, and the intangible costs per patient-year were calculated as €0 (EDSS = 0), €1100 (EDSS = 1–3), €8250 (EDSS = 3.5–5.5), €9900 (EDSS = 6–7) and €11 000 (EDSS > 7.5). Sensitivity analysis showed a similar progression of costs. We conclude that intangible costs are relevant in MS, especially when disability increases. Although the method to calculate the costs remains controversial, we consider that they should be included in cost analysis of MS. *Multiple Sclerosis* 2007; **13**: 800–804. http://msj.sagepub.com

**Key words:** disability evaluation; Expanded Disability Status Scale (EDSS); intangible costs; multiple sclerosis; quality-adjusted life years; quality of life

## Introduction

Multiple sclerosis (MS) is a chronic, demyelinating, inflammatory disease of the central nervous system (CNS). The aetiology of MS is still unknown, and its prognosis is unclear. Although life expectancy is relatively unaffected, MS has considerable morbidity – natural history studies show that 50% of patients need help to walk 10 years after diagnosis [1].

In Spain, the prevalence of MS is approximately 50–60 per 100 000 population [2,3], and MS affects predominantly young adults (onset in third decade of life), and females (female:male = 2:1). Due to these particular features, MS imposes a great economic burden on patients and society; recently, this burden has been estimated in cost-of-illness studies [3,4].

The pain, helplessness, anxiety, and other symptoms associated with MS can dramatically affect quality of life in patients and their caregivers, which can be represented by 'intangible costs'. These intangible costs relate to changes in health status brought about by healthcare intervention and the particular disease. Many issues should be included in estimating these costs, such as changes in residence, pain, anxiety, social functioning, ability to perform activities of daily

[1] Multiple Sclerosis Unit, Institute of Biomedical Investigation, University Hospital of Bellvitge, Faculty of Medicine, Campus Bellvitge, University of Barcelona, Spain
[2] Department of Neurology, Hospital de San Lorenzo, Viladecans, Barcelona, Spain
[3] Department of Neurology, Hospital de Figueres, Girona, Spain
**Author for correspondence:** V Casado, Unitat d'Esclerosi Múltiple, Hospital Universitario de Bellvitge (H. Duran i Reynolds), Gran vía s/n, km 2, 7, E-08907 L'Hospitalet de Llobregat, Barcelona. Spain. E-mail: unitatem@csub.scs.es
*Received 7 February 2006; accepted 27 September 2006*

 10.1177/1352458506073480

living (including leisure time), and, in general, changes in the patient's way of life because of the disease. These are not explicitly valued in monetary terms, but they can be measured and valued by health state utility methods.

Other costs are easier to quantify, and are considered 'tangible costs', such as direct medical costs (hospital fees, drugs, equipment, supplies, professional fees), direct non-medical costs (transportation for care, lodging for family, additional home care), and indirect medical costs (earnings lost during illness or treatment, and from disability). The utility value is a standardised quality of life instrument, which describes the current and global health status of a patient. For the purpose of pharmacoeconomic analyses, utility can be used in its strict economic sense: the level or degree of satisfaction or well-being relative to other health states. Utility quantifies the value that an individual places on an aspect of health and well-being. Utility measures are applied increasingly in pharmacoeconomic analyses because many diseases require inclusion of the patient's predilections or preferences for particular outcomes, and these preferences can be assessed through measurement of the patient's quality of life.

Ideally, utility of health states should be derived directly using standard gamble or time-trade off techniques, but there is no gold standard health utility measure. Generic measures of health utility have been used in studies of MS, such as the Euro Quality of Life-5 Dimensions (EQ-5D), HUI Mark III etc. [5,12–15], and visual analogue scale (VAS) scores have also been used to estimate utility [6–9,11].

Cost-utility analysis of different therapies attempts to express health outcomes in terms of the quality-adjusted life year (QALY), where the degree of health utility obtained with a therapy may temper the extension in the length of life. For example, an extra year of life with constant pain from a treatment may be only half as valuable to a patient as a year of perfect health, thereby equating to a QALY of 0.5 and not 1.0.

Utility may be used beyond the cost-utility analysis of drugs or treatments, to assist the practitioner and patient in choosing the optimal treatment. In addition, assessing the utility and quality of life in every state of a particular disease – MS in our case – is relevant as a comprehensive measure of health outcome that includes both mortality and morbidity.

Several studies have shown a significant reduction in quality of life in patients with MS, especially as disability progresses [10–15]. However, the intangible costs are not easy to calculate, and they tend to be underestimated in studies reporting the costs of MS. Only a few of the cost of illness studies on MS have included intangible costs [12–15], and those studies did not consider these costs uniformly.

The aim of this study was to estimate the intangible costs of MS in patients at different disability stages. As it is difficult to express these losses in monetary values, we used quality of life measurements as an approach to estimating the intangible costs of MS.

## Methods

We analysed data from 211 consecutive patients with definite MS, who attended our MS unit, where they were monitored and included in the European Database for Multiple Sclerosis (EDMUS). Their mean age was 41.6 years (SD: 10.7), 69% were female, and their mean Expanded Disability Status Scale (EDSS) score was 2.47 (SD: 2.05). We grouped the patients according to their disability (EDSS score) and compared the quality of life of the patients with that of a group of healthy controls ($n = 58$), matched by age and sex. To include subjects from a similar socio-demographic background as the patients and in the same timeframe, we chose the healthy relatives who accompanied the patients as controls.

Patients were classified according to their disability (EDSS scores) into five groups, which represented the clinically relevant stages of MS: stage I (EDSS = 0, patient is not disabled but diagnosed with chronic disease; $n = 24$); stage II (EDSS = 1–3, minimally disabled; $n = 124$); stage III (EDSS = 3.5–5.5, rather disabled; $n = 36$); stage IV (EDSS = 6–7, still capable of walking with aid; $n = 14$); and stage V (EDSS = 7.5–9.5, unable to walk at all; $n = 8$).

The intangible costs were calculated per patient per year in each disability stage and in the entire sample.

To estimate the loss of quality of life associated with the occurrence of a relapse, a separate analysis was performed in a subgroup of patients ($n = 14$). Quality of life was assessed in these patients when they first came to our MS unit with new neurological symptoms, when the occurrence of a relapse was confirmed by a neurologist, and at a different time when they were in a stable phase of their disease. Intangible costs due to a relapse were obtained from number of QALY lost because of a relapse, which was calculated as the difference in utility in patients during the relapse and during the stable period, multiplied by the value ascribed to a QALY, and then divided by the mean duration of the relapse.

We obtained the utility derived from the non-descriptive part of the EQ-5D, a generic, validated, preference-based instrument to measure quality of

life, using a VAS. In this scale, patients indicate their current health status on a scale between 0 (worst possible state) and 100 (best possible state), and the measure gives a global approach of their health-related quality of life. Patients and controls provided answers willingly and anonymously. The results of VAS were used to calculate utility and QALY for each group of patients and the controls (general population), according to the formula:

$$(1-u)=(1-v)^{2.29}$$

where $u$ is the utility value and $v$ the result of the VAS [17].

The formula $u=1-(1-v)^q$, describes the previously established relation between VAS scores and utility [6,7,9,17]. We used the value of $q=2.29$, as calculated by Torrance *et al*. [17], where $q$ is derived from a fictitious 'person mean', a person whose responses are all identical to the mean responses of the sample. In this study, the fitted disutility–disvalue relation for the person mean was $u=v^{2.29}$, based on theoretical considerations and risk function estimations. The fitting process used simple straight-line regression through the origin on the natural log transformation. The fitted function is then re-expressed in utility–value terms as $u=1-(1-v)^{2.29}$, which we used in our study.

A benchmark value of €55 000 has been ascribed to each QALY lost [15,16]. The value of the QALYs lost by MS patients, who have a lower QALY than controls, is considered an intangible cost [3,15]. As the value ascribed to a QALY lost is controversial, and has not been specifically established in Spain, we performed a sensitivity analysis that ascribed different values to each QALY lost [15].

Patients and controls gave their written informed consent to participate in the study. The project was approved by the Ethics Committee of Bellvitge University Hospital and Bellvitge Biomedical Investigation Institute, Barcelona, Spain.

## Results

The characteristics of patients ($n=211$) and controls ($n=58$) are described in Table 1. Age and sex did not differ ($P>0.05$) between the two groups.

We obtained intangible costs by multiplying the number of QALY lost because of MS by the value ascribed to a lost QALY, €55 000. These costs were €0 for EDSS group I, €1100 for EDSS group II, €8250 for EDSS group III, €9900 for EDSS group IV, and €11 000 for EDSS group V (Table 2). As €55 000 per QALY lost is a debatable value [15], we used values of €33 000 and €77 000 per QALY lost (or different 'willingness to pay' for a QALY) in the sensitivity analysis, and obtained a similar progression of costs with increasing EDSS scores.

The mean difference in utility due to a relapse in a subgroup of patients ($n=14$) was 0.065. The mean duration of the relapse in these patients was 55.07 days (SD: 32.5), estimated from their clinical charts, giving the intangible cost of €539 per patient and relapse (Table 3). The sensitivity analysis ascribed different values to a QALY lost, and estimated the total intangible cost per patient and relapse as €323.4–754.6 (Table 3).

## Discussion

Intangible costs concern pain, grief, anxiety and social handicap, and are difficult to quantify and translate into monetary values. However, they may be relevant in a chronic disease such as MS, especially in the higher stages of disability.

Imprecision is assumed when estimating intangible costs because of the subjectivity involved in estimating parameters, such as quality of life or utility, and the lack of validated published studies in Spain that assign monetary values to quality-of-life measurements. We consider that the inherent imprecision when estimating quality of life is a limitation of our study. We used the VAS, which

**Table 1** Baseline characteristics of patients and controls, matched by age and sex, where quality of life was analysed

| | Patients ($n=211$) | Controls ($n=58$) | P |
|---|---|---|---|
| Mean age (years) | 41.6 (SD: 10.7) | 41.02 (SD: 15.07) | 0.7 |
| Sex (% females) | 69 | 64 | 0.4 |
| EDSS mean (SD) | 2.47 (2.05) | | |
| EDSS median | 2 | | |
| Mean age years at disease onset (SD) | 29 (10) | | |
| Disease duration, years mean (SD) | 13 (9) | | |
| Clinical form (% of patients) | | | |
| Relapsing-remitting | 94.6 | | |
| Primary progressive | 2.4 | | |
| Secondary progressive | 3 | | |

SD, standard deviation; EDSS, Expanded Disability Status Scale.

**Table 2** Intangible costs in euros per patient/year according to disability (EDSS stages)

| EDSS | 0 | 1.0–3.0 | 3.5–5.5 | 6.0–7.0 | 7.5–9.5 | Mean | Controls |
|---|---|---|---|---|---|---|---|
| No. of patients | 24 | 124 | 36 | 14 | 8 | 211 | 58 |
| VAS mean score | 75.5 | 71.7 | 52.1 | 52.9 | 49.4 | 67.3 | 75.5 |
| QALYs (mean number) | 0.92 | 0.9 | 0.77 | 0.74 | 0.72 | 0.84 | 0.92 |
| Cost (if a QALY lost = €55 000) | 0 | 1100 | 8250 | 9900 | 11000 | 4400 | |
| Cost (if a QALY lost = €33 000) | 0 | 660 | 4950 | 5940 | 6600 | 2640 | |
| Cost (if a QALY lost = €77 000 | 0 | 1540 | 11550 | 13860 | 15400 | 6160 | |

EDSS, Expanded Disability Status Scale; VAS, Visual Analogue Scale; QALY, equality-adjusted life years. Costs were calculated for the five groups based on the EDSS stages and in the entire sample. A sensitivity analysis was also performed, which ascribed different values to each QALY lost.

has a strong 'floor effect', and tends to overestimate quality of life perception in patients. However, it also has the advantage of being easily applicable.

There are many significant controversies relating to utility measurement [5]. We used the VAS to obtain utility in an indirect way because the VAS alone does not measure health utility. Many examples of this method have been reported, and have shown that utility measurements and VAS scores are highly correlated [6–9,17]. Based on previous studies and the presumed controversy about utility measurement, we considered it reasonable to obtain the predicted utility derived from the VAS scores of patients and controls, which provided an easier method to estimate utility. The VAS is a simple instrument to measure health preferences, and it is easily applicable, inexpensive and quick to administer. It may imply less variability in utility obtained than other complex methods (choice-based, by time-trade off, multiattribute, etc.), and provide information that is more precise. Predicted utility appears to be a reasonable alternative for use in decision analysis in the absence of directly derived data.

**Table 3** Measure of quality of life and estimate of intangible costs in MS patients having a relapse

| $n = 14$ | During relapse | During stabilisation period |
|---|---|---|
| Age (years) | 38.2 (SD: 9.9) | |
| Female (%) | 57% | |
| EDSS (mean/median/SD) | 4.2/4/1.9 | 3.1/3/2.4 |
| VAS mean score (SD) | 49.7 (25.8) | 57.3 (26) |
| QALY mean (SD) | 0.71 (0.2) | 0.77 (0.3) |
| Difference in QALY-mean | 0.065 (0.15) | |
| Mean (SD) duration of a relapse days | 55.07 (32.5) | |
| Intangible costs per patient and relapse | | |
| If one QALY = €55 000 | €539 | |
| If one QALY = €33 000 | €323.4 | |
| If one QALY = €77 000 | €754.6 | |

VAS, visual analogue scale; QALY, quality of the adjusted life years; EDSS, Expanded Disability Status Scale; SD, standard deviation.

To estimate the intangible costs in our cohort, we considered the method of Henriksson appropriate [15], and applied it to the utility values of patients monitored in our MS unit. We obtained the utility values from the VAS, therefore, they are less accurate than those obtained from generic instruments to directly measure health-utility, such as the EQ-5D or HUI Mark 3, which have a multiattribute, preference-based system. We consider that our estimates of intangible costs constitute an interesting approach to these costs when estimating the minimum intangible costs to assign to MS, and that they are simpler to obtain using our method.

The value ascribed to a QALY in our study is based on the reference value calculated in 1996 in the US, and in 1998 in the UK [16], and it has already been applied to MS in a Swedish study [15]. When population-specific QALY values are not available, we believe that using reference values together with a sensitivity analysis [15] may be appropriate as an approach to estimate intangible costs in MS patients. Attaching a common value to a QALY lost implies that individual preferences are over-ridden, and that the over-riding variations appear at different times when quality of life is evaluated. Nevertheless, QALY constitute one of the best instruments available to measure quantity and quality of life, although the best method to translate QALY into monetary values remains controversial. A recent paper by Gyrd-Hansen [18] on this issue concluded that although a unique monetary value cannot be theoretically established for the QALY, a pragmatic perspective should be applied to obtain QALY values which could be used to improve efficiency in healthcare.

Another limitation of our study is the small sample, especially in higher stages of disability. Regardless of the small sample size, we included patients distributed across the entire spectrum of MS, and our results may approximate what occurs in the general MS population. In the case of patients having a relapse, although the sample we used to estimate utility was very small ($n = 14$), the value obtained for the difference in QALY due to a relapse (0.065) is similar to that obtained by

Henriksson *et al.* (0.063) [15], which may indicate the reliability of our results.

Intangible costs have been included in some studies of the cost of MS [12–15]. The results obtained with our approach show a similar progression of costs with the progression of disability as those reported previously and when a relapse of MS occurs, although our values are lower than the published values in all EDSS stages. This difference might be explained by a more positive perception of MS in our patients, but it may also be a consequence of overestimating quality of life by the VAS and methodological differences. Thus, we believe that our results are a minimum approach to estimate the intangible costs due to MS to take into account when assessing the total costs of the disease.

According to our estimates, the intangible costs of MS reach between €1100 and €11 000 per patient per year, depending on the extent of disability. The occurrence of a relapse implies an intangible cost of €539.

Our work is intended to highlight the relevance of estimating intangible costs in a chronic disease such as MS. We believe these costs are important contributors to the global costs of the disease, and that they increase with the progression of disability and relapses. However, the relevance of intangible costs involves more than their monetary value because the global conception of cost implies the inclusion of a measure of other costs of MS, including quantity and quality of life. This would allow comparisons with the costs of other diseases. Intangible costs may be comparable among different MS populations because the patients' quality of life would not be affected by parameters such as unit costs, resource consumption or healthcare systems, which affects direct and indirect costs when calculated between different countries; this is a major problem in assessing costs in multicentric studies.

Intangible costs are easy to obtain with our approach. Even if the method to calculate these costs is controversial (due to subjectivity of quality of life parameters, suitability of quality of life scales, utilities measurement, QALY monetary values, and, in general, to the lack of a standardised methodology), we consider that intangible costs should be included in costs analysis of MS.

## Acknowledgements

We thank Dr Kobelt for her suggestions and for reviewing the manuscript, and our own institutions for funding this project.

## References

1. **Weinshenker BG, Bass B, Rice GPA.** The natural history of multiple sclerosis: a geographically based study. *Brain* 1989; **112**: 133–46.
2. **Bufill E, Blesa R, Galan I, Dean G.** Prevalence of multiple sclerosis in the region of Osona, Catalonia, Northern Spain. *J Neurol Neurosurg Psychiatry* 1995; **58**: 577–81.
3. **Kobelt G, Pugliatti M.** Cost of multiple sclerosis in Europe. *Eur J Neurol* 2005; **12**: 63–67.
4. **Patwardhan MD, Matchar DB, Samsa GP, McCoy DC, Williams RG, Li TT.** Costs of multiple sclerosis by level of disability: a review of literature. *Mult Scler* 2005; **11**: 232–39.
5. **Fisk JD, Brown MG, Sketris IS, Metz LM, Murray TJ, Stadnyk KJ.** A comparison of health utility measures for the evaluation of multiple sclerosis treatments. *J Neurol Neurosurg Psychiatry* 2005; **76**: 58–63.
6. **Havranek E, Simon TA, L'Italien G, Smitten A, Hamber AB, Chen R** *et al*. The relationship between health perception and utility in heart failure patients in a clinical trial: results from an OVERTURE substudy. *J Card Fail* 2004; **10**: 339–43.
7. **Mrus JM, Yi MS, Freedburg KA, Wu AW, Zachin R, Gorshi H** *et al*. Utilities derived from visual analog scale in patients with HIV/AIDS. *Med Decis Making* 2003; **23**: 414–21.
8. **Naglie G, Tomlinson G, Tansey C, Irvine J, Ritvo P, Black SE** *et al*. Utility-based quality of life measures in Alzheimer disease. *Qual Life Res* 2006; **15**: 631–43.
9. **Torrance GW, Feeny D, Furlong W.** Visual analog scales: do they have a role in the measurement of preferences for health states? *Med Decis Making* 2001; **21**: 239–34.
10. **The Canadian Burden of Illness Study Group.** Burden of multiple sclerosis: part II: quality of life. *Can J Neurol Sci* 1998; **25**: 31–38.
11. **Grima DT, Torrance GW, Francis G, Rice G, Rosner AJ, Lafortune L.** Cost and health related quality of life consequences of multiple sclerosis. *Mult Scler* 2000; **6**: 91–98.
12. **Kobelt G, Lindgren P, Parhin D, Francis D, Johnson M, Bates D** *et al*. *Costs and quality of life in multiple sclerosis. A cross-sectional study in the United Kingdom*. EFI Research Report No. 398, 2000.
13. **Kobelt G, Lindgren P, Smala A, Jönson B.** Costs and quality of life in multiple sclerosis. An observational study in Germany. *HEPAC* 2001; **2**: 60–68.
14. **Kobelt G, Berg J, Atherley D, Hadjimichael O, Jönson B.** *Costs an quality of life in multiple sclerosis, a cross-sectional study in the USA*. SSE/EFI Working Paper Series in Economics and Finance No. 594, December 2004: 2–34.
15. **Henriksson F, Fredrikson S, Masterman T, Jönson B.** Costs, quality of life and disease severity in multiple sclerosis: a cross-sectional study in Sweden. *Eur J Neurol* 2001; **8**: 27–35.
16. **Newhouse JP.** US and UK health economics: two disciplines separated by a common language? *Health Econ* 1998; **7**: S79–92.
17. **Torrance GW, Feeny DH, Furlong WJ, Barr RD, Zhang Y, Wang Q.** Multiattribute utility function for a comprehensive health status classification system. Health Utility Mark 2. *Med Care* 1996; **34**: 702–22.
18. **Gyrd-Hansen.** Willingness to pay for a QALY, theoretical and methodological issues. *Pharmacoeconomics* 2005; **23**: 423–32.