Quality of life and patient preferences: identification of subgroups of multiple sclerosis patients

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Abstract

Purpose. The aim of this study is to estimate preferences related to quality of life attributes in people with multiple sclerosis, by keeping heterogeneity of patient preference in mind, using the Latent Class approach.

Methods. A discrete choice experiment survey was developed using the following attributes: activities of daily living, instrumental activities of daily living, pain/fatigue, anxiety/depression and attention/concentration. Choice sets were presented as pairs of hypothetical health status, based upon a fractional factorial design.

Results. The Latent Class Logit model estimated on 152 patients identified three subpopulations, which respectively attached more importance to: 1) the physical dimension; 2) pain/fatigue and anxiety/depression; 3) instrumental activities of daily living impairments, anxiety/depression and attention/concentration. A posterior analysis suggests that the latent class membership may be related to an individual's age to some extent, or to diagnosis and treatment, while apart from energy dimension, no significant difference exists between latent groups, with regard to Multiple Sclerosis Quality of Life-54 scales.

Conclusions. A quality of life preference-based utility measure for people with multiple sclerosis was developed. These utility values allow identification of a hierarchic priority among different aspects of quality of life and may allow physicians to develop a care program tailored to patient needs.

Introduction

Health-related quality of life (HRQoL) is defined as the impact of an illness or treatment on an individual's physical, social, psychological and general well-being [1]. In the last decades there has been increasing attention on HRQoL and it is now considered an important end-point in clinical studies[2]. Several studies show that quality of life (QoL) assessments in patients with a chronic disease may contribute to improve treatment and could even be of prognostic value [3,4].

Multiple sclerosis (MS) is a chronic disease with a modest impact on life expectancy, but a broad spectrum of physical, social and psychological effects, as well as a significant impact on HRQoL, mainly due to functional and neurological impairment[5]. Moreover MS has an unpredictable course and patients have difficulty maintaining a sense of control over their disease[6]. In the last decades, HRQoL evaluations are receiving particular attention from physicians and health care providers, because their analysis allows them to both achieve a better understanding of patient expectations and make appropriate clinical decisions [7].

Different approaches to the assessment of HRQoL have been proposed [8]. Health profile questionnaires focus on mental and emotional status and physical and social functioning and include a set of items measuring the impairment in each of the HRQoL domains. Overall, physical and emotional QoL indexes are usually derived as a function of specific subscales scores, but these QoL measures do not assess the relative importance or priority of each HRQoL domain.

Preference measures, on the other hand, incorporate weights reflecting the importance that patients attach to any specific dimension [9]. That HRQoL assessment, following the economic decision theory, estimates a ranking of priority for patients, regardless of the measure of physical, emotional and social impairment.

Different econometric techniques may be used to estimate relative importance or utility function, such as Standard Gamble, Time to Trade Off and Discrete Choice Experiments (DCEs). DCEs were originally designed as a method of establishing the relative importance of different attributes (or dimensions) in the provision of a good or service [10], and have been extensively used in health economics to value health-care intervention and policies [11-13] and to understand preferences for QoL attributes [14-17]. The premise about the use of DCEs as a method in health research is that medical conditions and interventions are characterised by a set of attributes and the importance of change in health is a function of these attributes. In DCE, patients are asked to choose between alternative health states. Based on this information, a quantitative rate about the trade-off subjects are willing to make among different health aspects can be obtained. These rates can be regarded as an estimate of the relative importance that subjects place on different health aspects, including HRQoL.

The health measures that incorporate weights about the relative importance of QoL dimensions, usually are calibrated on an healthy general population (see EQ-5D[18]), but a recent study shows that healthy people have difficulty in rating some HRQoL aspects, such as anxiety, depression and pain, since they have little or no experience with them [19]. Another recent study showed that, although generic utility measures include certain items that are important to people with multiple sclerosis (PwMS), others were missing [20]. Previous studies found that demographic, disease and treatment characteristics affect HRQoL [21,22], moreover it can be that heterogeneity preferences may be influenced by patient's characteristics. Particular attention must be paid to methodological aspects, as underline in a recent published checklist for good practice of this methodology [23]. DCEs estimate the mean preferences of the experimental attributes given by respondents, but it is likely that individuals have different preferences that are influenced by health and non-health related personal characteristics. In order to keep the preference heterogeneity in mind, the random utility framework [24] estimates the relative importance of experimental dimensions by separating into the utility function a systematic part (dealing with the experimental attributes) and a random one. The random component captures the residual variability (heterogeneity) present in the data. Preference variation that is unaccounted for in modelling can result in a biased estimate. Random parameter models and latent class models [10, 25] have been proposed, in order to analyse preference heterogeneity. The random parameter model requires definition of a particular pre-specified distribution of random preference variation, but failure to adhere to proper model preference distribution leads to bias in the utility estimate. The latent class models account for preference variation by using the data to identify groups of respondents with similar preferences [26] and may be preferable to the random parameter model because it does not require making distributional assumptions of preferences across respondents.

While several studies applied utility based QoL measures in MS, the use of discrete choice analysis to investigate relative importance has only recently been used [27] on MS treatment choice.

The main aim of the study was to estimate preferences related to QoL attributes in PwMS by keeping patient preference heterogeneity in mind, using a latent class approach. To our knowledge, this is the first attempt to model heterogeneity in QoL preferences by a DCE latent class model in PwMS. Another goal of the study was to explore the relationship between QoL preferences, demographic and clinical data.

Method

Participants

In this prospective observational study, one hundred fifty-five participants were consecutively recruited when they attended a regularly scheduled neurologic visit at the referral regional centre for multiple sclerosis (CReSM), AOU San Luigi, Orbassano, from January 2009 to September 2010. The study was approved by the local ethics committee (n. 07/09, 26/01/2009) and written informed consent was obtained from participants. Potential respondents were first approached by a physician who introduced them to the study. All PwMS were eligible to participate, except for those with new diagnosis or who had a psychiatric disorder.

Procedure

Before performing the experiment, respondents filled out a questionnaire including disease-related and demographic information such as age, gender, education, disease duration and the Multiple Sclerosis Quality of Life-54 (MSQoL54). The MSQoL-54 is a specific health profile questionnaire composed of the Short Form-36-Item Health Survey (SF-36), with an additional set of MS specific questions [28]. Fourteen scales scores and two composite scores (physical and mental) were calculated. Each scales ranges from 0 to 100, higher scores indicate better QoL. Physicians provided clinical information about diagnosis, treatments and Expanded Disability Status Scale (EDSS) scores. EDSS is the most predictive index of disability in MS, it evaluates impairment according to physical functionality and mobility [29]. A member of the research team was available to help in filling out the questionnaire.

Discrete choice experiment

Discrete choice experiments combine the random utility and the experimental theories. The discrete choice experiment specifically devised by the authors of this study, consists of several scenarios in which two health profiles are presented. Each profile is characterised by different levels, on different QoL attributes. Previous studies have investigated which aspects influence QoL in PwMS and found that physical and cognitive impairments, depression and fatigue have the deepest impact on current health state [30]. The presence of anxiety and depression is negatively associated with QoL and with adherence to therapy [31], moreover clinically significant depression is related to increased morbidity and mortality [32,33]. Since there are several aspects that significantly influence QoL in PwMS a review of SM QoL questionnaires was performed to identify a small set of relevant attributes. The selection was guided by 2 main criteria: 1) following the format of the Eq-5d [18] and identifying at maximum 5 dimensions (in order to avoid participants cognitive burden) and 2) having cognition domain since memory and learning capability are some of the most important cognitive impairments [34]. According to the literature [18,28,35,36], the five macro-dimensions identified and included in the analysis were: activities of daily living (ADL), instrumental activities of daily living (IADL), pain and/or fatigue, anxiety

and/or depression and attention and/or concentration difficulties. These attributes allow the evaluation of both physical and mental QoL aspects and take into account some of the MS symptoms (i.e. fatigue, movement, bowel and bladder function), even they are mixed with other components.

These attributes are scaled on three levels: severe, moderate and no impairment (table 1). A full factorial design included all possible combinations of attributes and levels for making health profiles or choice sets. As a result, the effect of each attribute level upon the responses can be isolated, but with five attributes measured on a three-level scale, a full factorial design, combining each attribute by level, involved 243 potential health profiles (i.e., 3^5: three levels of difficulty for each of the five attributes). To reduce this set of combination to a manageable number, an orthogonal fraction of the full factorial design was derived by maximizing efficiency [37]. The orthogonal factorial design made provisions for orthogonality (attributes are statistically independent of one another) and level balance (levels of any given attribute appear the same number of times). The 'ChoicEff' SAS macro [37], based on a relative efficiency of design (precision of parameter estimates), searches for a choice design that maximizes the D-efficiency for the nonlinear logit model and reduced the set of experimental design in 18 paired health profiles (here called scenarios). Each scenario was subsequently checked by a psychologist and a neurologist, in order to avoid implausible combinations of level attributes and, at the same time, ensure a balance between the natural progression of the disease and a spread of realistic options. Finally, three scenarios were deleted because they included implausible combinations of attribute levels. A fourth scenario was not used in the utility analysis and treated as a control scenario to test internal validity. In the control scenario, the attribute levels of one alternative were all better ('*no limitation'*) than the attribute levels of the other alternative.

For each scenario, respondents were asked which hypothetical person was, in their opinion, in the worst health state (figure 1). In order to prevent a potential bias based on order presentation, the scenarios were randomized. Moreover, a face-to-face pre-test interview describing the task was conducted, and each respondent received the attribute list along with the level of measurement (table1).

DCE sample size was defined following Orme's [38] 'rule of thumb', for which sample size (n) should be greater than (500c)/(ta), where t is the number of tasks, a is the number of choices per task and c is the maximum number of levels for any one attribute for a main effects model or the largest product of the levels of any two attributes for all first-order interactions. With 14 tasks (t=14), five-attributes scaled by three-levels (c=3), and two-choice alternatives (a=2), this means a sample size of 54 for a main effects model and of 161 for a model containing all first-order interactions. The sample size of n=155 seemed to be more than sufficient to isolate the main effects, while the interaction effects were not estimated in this preliminary analysis.

Statistical methods

Using a finite mixture logit model, the share of preferences in the data was converted into utilities (see Appendix 1). QoL attributes were put in the analysis as dummy variables, contrasting the severe and moderate attribute levels with those with any limitation (i.e., for ADL attributes, the utility coefficients estimate the impact of *''severe limitation"* and *"moderate limitations",* up to *"no limitation*s" on the worst stated health). The experimental task asked participants to choose which health status profile (*"person A"* or *"person B"*), in each scenario, was the worst. Since the labels of the two alternatives did not convey information, data were analysed by an unlabelled DCE [10]. The overall model and latent class models with 2, 3 and 4 classes, respectively, were applied on 2128 matched observations (152 respondents for 14 scenarios). To account for the within subject correlation on the 14 scenarios a sandwich estimator was applied [39]. The selection of the model was made according to goodness of fit statistics, i.e. the Likelihood-Ratio test (that compares likelihood function of nested models), Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and McFadden R^2. The information criteria indexes are computed from the log likelihood and the number of parameters estimated, the McFadden R^2 and the adjusted R^2 compare the log likelihood between the current model and the overall one. A posterior descriptive analysis was applied in order to evaluate the effect of covariates (gender, age, QoL scales, education, EDSS, disease duration and treatments) on the estimated classes of utility coefficients. The Kruskal Wallis one-way analysis of variance and the exact Fisher test were applied to compare the three latent classes. Latent class models were estimated using NLOGIT V4.0 statistical software package [40], other analyses were performed with SAS [41].

Results

Due to incomplete data or an incoherent response to the control scenario, three respondents were excluded from the analyses. Table 2 reports individual characteristics from the prospective outpatient cohort. Patients were young (mean age 39.6 yrs.), mainly female (71% of sample) and with an EDSS mean (and median) equal to 2, which means half of sample had a fairly good moving capability. Only 15.8% of the sample reported mobility impairment (EDSS> 5). Disease duration (min=1, max=29) showed a skewed distribution, almost half of the sample had a history of disease shorter than 5 years, and 29.6% of patients had received their diagnosis of MS more than 11 years prior.

The physical and mental QoL composite scores showed high values (64.5±21.8 and 65.0±20.1 respectively). The same pattern was found in almost single sub-scales, with the exception of health perception

and energy, which reported lower values (47.7±19.9 and 50.7±20.9). The percentage of missing data on MSQoL54 items was low (0.66% -1.97%), except for items regarding sexual function and satisfaction with sexual function scales (9.21% - 14.47%). The prevalent diagnosis (85%) was relapsing remitting. One hundred twenty-nine participants were receiving treatment, 13.1% of whom received only symptomatic remediation, while 24% received both disease modifying and symptomatic treatments (data not shown). As reported in table 2, immunomodulatory treatment was the most frequent (46.7%), while one-third of samples used another or symptomatic treatment.

An overall logit model and two, three and four latent class models were estimated on 2128 matched observations (152 respondents for 14 scenarios). Table 3 shows the goodness of fit statistics of different models. According to the LR statistic test (α=0.01), the adjusted R^2 and AIC/BIC indexes, the three latent classes model was optimal. In fact, there was a trend of increase in the goodness of fit indexes only up to the three latent classes model.

Table 4 shows the utility coefficients for QoL attributes, estimated by the 3-class utility model. As can be seen from the table, attribute coefficients have the expected positive sign except for anxiety level 2 in class 2 and pain level2 in class 3, moreover in class 3 ADL several limitations coefficient is smaller than one limitation, but these unexpected estimates are all not statistically significant. Increasing limitations on QoL attributes are associated with a worsening health state, since the experimental task asked participants to choose which person's situation was the worst (figure 1). In the first class, coefficients for almost all attributes were significant, but if magnitude of the coefficients is taken into consideration, we can characterise the first class as composed by people highly worried about physical impairments, i.e. several limitation on ADL (β =2.26, *SE* = 0.16) and on IADL (β=2.24, *SE*=0.20). The second class depicts higher relative importance in defining the worst health state to pain/fatigue (β=6.98, *SE*=2.45) and anxiety/depression attributes (β=3.78, *SE*=1.58), respectively. Due to the reduced sample size of this class (approximately 24 patients, 16% of the sample), the other attributes did not reach statistical significance, even if the size effect for cognition and IADL attributes was relatively high. The third class was characterised by high coefficients associated with IADL, anxiety/depression and cognitive attributes. The analysis identified three subpopulations of PwMS, who attach more importance to physical dimension (class 1) and to emotional dimension (class 2 and class 3). The last two classes are different for the importance attached to the pain and/or fatigue dimension that is the main worry for the second class.

In order to examine the association between the three latent class memberships and demographic, clinical (gender, age, EDSS, disease duration and treatments) and MSQoL54 scores, the Kruskal Wallis one-way

analysis of variance and the exact Fisher test were applied (table 5). No significant differences were found overall between patient covariates, except in the age, type of diagnosis/treatment and energy MSQoL-54 sub-scale. In particular, the second class was characterised by older patients with a lower proportion of relapsing remitting diagnosis and immunomudulatory treatment and with lower energy MSQoL54 scores. The three groups reported almost overlapping MSQoL-54 measures, even if group two seemed to have overall lower scores than other groups.

Discussion

The aim of this study was to identify a priority ranking of QoL dimensions among PwMS, using the DCE approach. In order to account for heterogeneity of individual preferences the latent class approach was used, and four models with respectively 1, 2, 3 and 4 latent classes were estimated. The analyses suggested that three classes of PwMS exist in the sample, the first mainly worried about physical impairments, the second about pain/fatigue and emotional dimensions, while attention/concentration, physical functional limitations (IADL) and anxiety/depression are the attributes of great importance to the third class.

A posterior analysis suggested that latent class membership may be related to some extent to the individual's age and to the nature of MS (diagnosis and treatment), while the only statistically significant MSQoL-54 sub-scale was energy. The few significant differences may be due to the reduced number of participants recruited for DCE, however.

Both the second and third latent classes assign great importance to the emotional dimension, but the second class which gives great importance to pain/fatigue include older people with more compromised health and an higher proportion of primary or secondary relapsing diagnoses.

The main finding of this study was the absence of homogeneity in the mean preference attached to HRQoL attributes among mildly impaired PwMS. To our knowledge, only one previous study reported sub-groups with different priorities and was conducted in patients with Glaucoma [42]. Other studies reported small differences in preference ranking of health conditions [43] or posit that differences in preferences between social, geographic or ethnic groups are small, as reported by Kaplan, [44]. Two remarkable reasons for this low consideration for heterogeneity may be as follows: most of the studies used statistical methods that do not allow the researcher to directly test for the presence of heterogeneity and, secondly, preference heterogeneity could be influenced by individual characteristics other than (or combined with) socio-demographic or health related

conditions, such as values and beliefs. Preferences may be "more a function of how [people] value their life than of how they value their health" [45]. In our study, the differences in relative importance attached to physical and emotional health domains in the different groups may be related to their systems of belief and adjustment to MS. A recent study [46] on a large cohort of PwMS found a moderately positive correlation between health status and self-rated health state that may be due to adaptation and coping strategies that patients with a chronic condition develop to realign their expectations and experience. Independently from the current health status, people can be mostly worried about physical or mental problems because of their personality characteristics, values' priority, and self-confidence about the ability to cope with physical or mental difficulties. In addition, individuals' time perspective (i.e. the individual tendency to emphasize a particular temporal frame when encoding, storing and recalling experiences and in forming expectations and goals, [47]) can play a role in orienting health priorities. Time perspective has been found to be associated to well-being [48] and it could be that future oriented people are more worried about physical impairments (since this is a typical future scenario for PwMS) than past or present oriented people. Further studies including psychological constructs like those mentioned above are needed to better understand these findings.

The second major result is the weak relationship between the latent classes' membership and the health status evaluated by MSQoL54 scales. This result is in agreement with the literature [45, 49] and is not surprising because, unlike health preference evaluations, health profiles are based on the respondent's feelings about their QoL. HRQoL measures assessed with health profile questionnaires provide important information on the patient's health status, but this information does suggest to the clinician how patients feel about these dimensions. Conversely, through the decision utility approach, clinicians can obtain an indirect measure of the desirability of the health (disease) state [50]. In practical terms, the utility value associated with a specific QoL aspect indicates what patients desire about their ability to perform daily activities.

Finally, it worth discussing the relatively low importance attached to the cognitive dimension in this study. This result is surprising, since memory and learning performance are some of the most important aspects of cognitive impairment in relapsing remitting PwMS, as Prakash et al, found in their meta-analysis [34]. Since cognitive impairment is a common and disabling part of the ageing process, and given the younger age of respondents in this study, this particular QoL dimension seemed to be less important, moreover the magnitude of cognitive impairment is usually underestimated, probably due to an adaptive illness behaviour or unawareness of cognitive decline in PwMS [30,34,51].

The primary limitation of our study was the decision of not including a social dimension among the experimental QoL attributes, a choice made to avoid participants' burden. In order to derive priority weights of QoL aspects, future work must also involve people with severe MS and social and cost attributes must be included in the experimental design. Another limitation of the study was the reduced sample size, defined according to the DCE. This enabled us, however, to statistically characterise latent groups according to clinical and demographic information. Moreover, further research should explore the presence of variance heterogeneity, not only mean heterogeneity as in this study [14], as well as collect information about values, personality and beliefs, in order to better characterize the differences of preference.

A major strength of this study was the identification of the priorities attached to the QoL attributes in PwMS. Considering that one of the goals of physicians is to maintain or to improve both QoL and length of life, these results may help in planning psychological interventions for improving QoL for these patients.

An advantage of using a DCE to obtain subjective weights related to different QoL attributes is that this method requires respondents to make trade-offs between impairments of the given dimensions, as well as to estimate indirectly the relative importance of QoL attributes. Furthermore, if a cost attribute or a proxy is included in the experiment, the mean willingness to pay for the attributes can be estimated. Finally, preference based measures may be used in clinical practice [52] as well as in health economic analysis, in addition to functional QoL measures that are based on the ability to carry out specific tasks.

Acknowledgements

This study was supported by the Piedmont Region –Regional Health Authority, and Fondazione Ricerca Biomedica Onlus.

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Figure 1 An example of a five-attribute conjoint analysis paired comparison task used in the present study

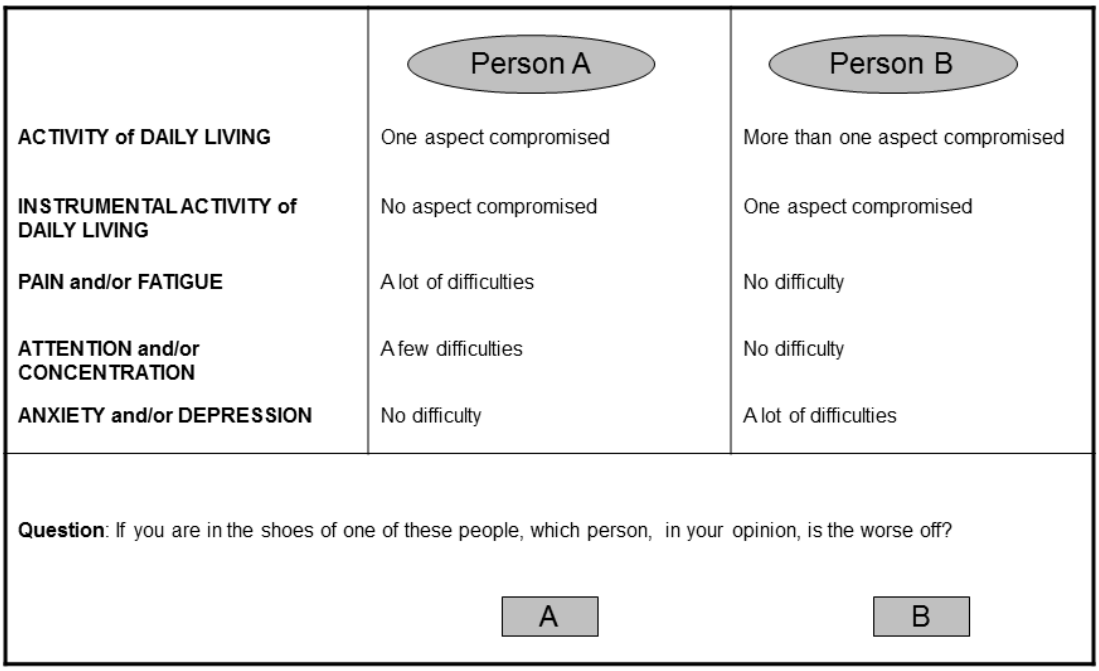

Table 1**.** Summary of the attributes and levels used in the choice experiment task

Attributes	**Level**
Activity of Daily Living (ADL) (Personal hygiene, dressing and undressing, self feeding, functional transfers, bowel and bladder management and ambulation)	✓ No aspect compromised ✓ One aspect compromised ✓ Two or more aspect compromised
Instrumental Activity of Daily Living (IADL) (Housework, taking medications as prescribed, managing money, shopping for groceries or clothing, use of telephone or other form of communication, transportation within the community)	✓ No aspect compromised ✓ One aspect compromised ✓ Two or more aspect compromised
Pain and/or Fatigue	✓ No difficulty ✓ A few difficulties ✓ A lot of difficulty
Anxiety and/or depression	✓ No difficulty ✓ A few difficulties ✓ A lot of difficulty
Attention and/or concentration (Cognitive impairment)	✓ No difficulty ✓ A few difficulties ✓ A lot of difficulty

Table 2. Descriptive data of 152 patients with Multiple Sclerosis

	N (%)
Gender	
Female	108 (71.1%)
Age[§] [18; 66] (yrs)	39.6 (10.3)
Education	
Secondary or degree	103 (67.8%)
Disease duration[§] [1; 29] (yrs)	7.8 (6.3)
1	16 (10.5%)
2-5	56 (36.8%)
3-10	35 (23.0%)
≥11	45 (29.6%)
EDSS[§] [0; 8.5]	2.6 (2.1)
0	14 (9.2%)
1-1.5	59 (38.8%)
2-4	55 (36.2%)
≥5	24 (15.8%)
MSQOL54 scales[§] [6.4; 99.2]	
Physical function	67.0 (32.3)
Role limitations - physical	63.3 (39.4)
Role limitations-emotional	61.6 (41.9)
Pain	73.9 (26.9)
Emotional well-being	61.9 (21.5)
Energy	50.7 (20.9)
Health perceptions	47.7 (19.9)
Social function	74.0 (23.0)
Cognitive function	72.5 (23.0)
Health distress	70.3 (23.9)
Overall quality of life	63.8 (18.7)
Sexual function	73.5 (30.6)
Physical health composite	64.5 (21.8)
Mental health composite	65.0 (20.1)
Diagnosis	
Relapsing Remitting	129 (84.2%)
Others^	23 (15.8%)
Disease modifiing treatment	
Immunomodulatory[#]	71 (46.1%)
Others[##]	43 (28.3%)
Symptomatic Treatment	48 (31.5%)

[§] min and max [], mean, standard deviation ();

^Secondary Progressive, Primary Progressive;

[#]Interferon Glatiramer Acetate;
[##]Tysabri, Azatioprina, Methotrexate

	Overall model	Two-classes model	Three-classes model	Four-classes model
Log Likelihood (logL)	-1245.78	-1167.17	-1107.41	-1096.98
AIC*	1.18	1.12	1.07	1.07
BIC^	1.21	1.17	1.16	1.19
Mc Fadden $R^{2\,\$}$	0.16	0.21	0.25	0.26
Num of parameters (k)	10	21	32	43
Adjusted $R^{2\,\$\$}$	0.15	0.20	0.24	0.24
LR test§	--	157.23#	119.51#	20.87
DF°	--	11	11	11
Number of respondents 152 Number of observations (n) 2128 logL (null model)= -1475.02				

Table 3. Goodness of fit statistics of overall to three classes nested models

*Aikaike Information Criterion: -2(logL – k)/n

^ Bayesian Information Criterion: (-2logL +klog(n))/n

§ Likelihood-Ratio test: -2[logL(previous model)-logL(model)]

LR chi squared test statistically significant, α=0.01

° Degree of freedom of LR test

$ Mc Fadden R^2= 1 - logL(model)/logL(null model)

$$ Adjusted R^2= 1-[n/(n-k)]*(1-R^2)

Tables 4. Utility parameters and average class probability in 3-latent class logit model. Number of respondent: 152, number of observations: 2,128

	First class			Second class			Third c
Attributes	b	se	p	b	se	p	b
ACTIVITIES of DAILY LIVING							
- No limitation	(Ref)			(Ref)			(Ref)
- One limitation	0.65	0.12	<.001	0.31	0.47	.517	0.18
- Several limitations	2.26	0.16	<.001	1.34	0.97	.167	0.01
INSTRUMENTAL ACTIVITIES of DAILY LIVING							
- No limitation	(Ref)			(Ref)			(Ref)
- One limitation	0.94	0.15	<.001	2.25	1.22	.065	1.96
- Several limitations	2.24	0.20	<.001	3.60	2.01	.073	2.03
PAIN and/or FATIGUE							
- No difficulties	(Ref)			(Ref)			(Ref)
- Some difficulties	0.22	0.15	.15	3.15	1.17	.007	-0.86
- A lot of difficulty	1.23	0.13	<.001	6.98	2.45	.004	0.90
ANXIETY and/or DEPRESSION							
- No difficulties	(Ref)			(Ref)			(Ref)
- Some difficulties	0.68	0.18	.001	-0.77	0.67	.250	2.46
- A lot of difficulty	1.17	0.14	<.001	3.78	1.58	.017	3.61
ATTENTION and/or CONCENTRATION							
- No difficulties	(Ref)			(Ref)			(Ref)
- Some difficulties	0.59	0.13	.001	1.01	0.96	.295	0.96
- A lot of difficulty	1.18	0.18	<.001	2.47	1.41	.079	2.01
Average class probability	0.62	.05	<.001	0.16	.04	.001	0.22

Table 5. Posterior analysis of patient characteristics and sub-group identify by latent class model

	First LC N=94	Second LC N=24	Third LC N=34	p
Gender[*]				
Female (%)	70.2	83.3	70.6	0.43
Age[§] (yrs)	37.8 (9.5)	44.0 (11.3)	41.5 (10.5)	**0.02**
Education[*] (%)				
Secondary or degree	71.3	54.2	67.7	0.29
Disease duration[§] (yrs)	8.1 (6.2)	8.8 (8.1)	6.3 (4.8)	0.43
EDSS[§]	2.3 (1.8)	3.6 (2.9)	2.5 (2.2)	0.33
Symptomatic Treatment[*] (%)	29.8	41.7	35.3	0.49
Diagnosis[*] (%)				
Relapsing Remitting^	92.5	58.3	82.4	**<.001**
Disease modifying treatment[*] (%)				
Immunomodulatory[#]	48.9	20.3	55.9	**0.02**
MSQOL54 scales[§]				
Physical function	71.2 (28.8)	54.2 (40.0)	64. 6 (33.6)	0.12
Health perceptions	47.6 (21.1)	45.2 (18.3)	49.6 (17.9)	0.69
Energy	50.9 (20.6)	42.2 (17.8)	56.0 (22.6)	**0.03**
Role limitations - physical	66 (37.7)	53.1 (46.8)	63.2 (38.5)	0.49
Pain	75.6 (25.1)	65.7 (33.1)	74.7 (27.9)	0.39
Sexual function	76.9 (28.9)	66.7 (36.3)	68.7 (30.8)	0.30
Social function	75.5 (21.5)	79.8 (27.7)	72.7 (23.6)	0.69
Health distress	71.4 (24.3)	64.6 (25.6)	71.3 (21.9)	0.44
Overall quality of life	65.2 (16.8)	55.8 (26.2)	65.7 (16.4)	0.29
Emotional well-being	60.7 (20.0)	63.5 (24.1)	64.3 (24.1)	0.38
Role limitations-emotional	60.6 (40.5)	66.7 (44.7)	68.6 (44.1)	0.37
Cognitive function	72.1 (23.2)	68.1 (24.8)	76.8 (21.1)	0.35
Physical health composite	66.6 (18.9)	56.3 (23.2)	64.6 (20.5)	0.20
Mental health composite	64.7 (21.0)	61.1 (24.0)	68.5 (22.4)	0.40

[°] Latent Class

[§] mean, (standard deviation), p for Kruskall Wallis test;

[*] p for exact Fisher test

^ Vs Secondary Progressive or Primary Progressive diagnosis;

[#] Immunomodulatory treatments (Interferon Glatiramer Acetate) vs other treatments (Tysabri, Azatioprina, Methotrexate)

Appendix 1

Latent Class model (finite mixture logit model) in discrete choice experiments

Following the random utility framework, the utility that individual *n* assign to alternative *j* can be written as $U_{jn} = V_{jn} + \varepsilon_{jn}$, where $V_{jn} = \sum_{k=1}^{K} \beta_k x_{jkn}$ is the deterministic part of utility (in which K is the number of attributes used in the experiment, k=1,2,…,K, x_{nk} is an observed variable related to attribute k and β_k is the attribute coefficient, homogeneous across the population), while ε_{jn} is the stochastic part, also capturing the unobserved heterogeneity Given two alternatives *i* and *j*, an individual will choose alternative *j* if $U_{jn} > U_{in}$.

Let $P_{nt}(j|\beta)$ give the probability of respondent n choising alternative j on an occasion (called here scenario) *t*, conditional on a vector of attributes coefficients (β), in a fixed logit model we have:

$$P_{nt}(j \mid \beta) = \frac{\exp(x_{jnt}\beta)}{\sum_{j=1}^{J} \exp(x_{jnt}\beta)}$$

Preference variation among individuals that is unaccounted for in modelling can result in a biased estimate. Two types of approaches allow to take into account differences in preferences: the random coefficient and the latent class models.

In the random utility model (continuous mixture model), the vector β followes a random distribution with parameters Ω and the choice probabilities are given by:

$$P_{nt}(j \mid \Omega) = \int_{\beta} P_{nt}(j \mid \beta) f(\beta \mid \Omega) d\beta$$

where $P_{nt}(j \mid \beta)$ is the logit choice probability and $f(\beta \mid \Omega)$ is the density function for the vector of attributes coefficients β.

In a latent class model (finite mixture model) preference variation is accommodated by identifying C groups of respondents with different values for the vector of attributes coefficients (β_c). In this model $f(\beta)$ is a discrete distribution and the choice probability is the weighted sum of the choice probabilities across the C classes, with the class allocation probability π_{nc} been used as weight:

$$P_{nt}(j \mid \beta_c) = \sum_{c=1}^{C} \pi_{nc} P_{nt}(j \mid \beta_c)$$

This specification is useful if there are C segments in the population, each of which has its own choice preferences. The share of population in class c is π_{nc} ($\sum_{c=1}^{C} \pi_{nc} = 1$) and it is estimated along with the β's for each segment.