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Using IMPrESS to guide policy change in multiple sclerosis

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Title page

Title: Using IMPrESS (International MultiPlE Sclerosis Study) to guide policy change in multiple sclerosis

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Short summary

The IMPrESS (International-MultiPlE-Sclerosis-Study) studied the significant impact of multiple sclerosis (MS) on the health and wellbeing of both people with the disease, and their caregivers, along with its broader socio-economic impact. Results confirmed that there is an urgent need to achieve better outcomes for people with MS. This paper uses results from the IMPRESS to present new international evidence on the socio-economic burden of MS and discuss the merits of a likely paradigm shift in the management of MS towards the use of better (and more accurate) diagnostic follow-up to monitor disease progression and the earlier use of disease-modifying-treatments (DMTs) to achieve better clinical, quality of life and socio-economic results for individuals.

Introduction

Multiple-sclerosis (MS) is the most common cause of disability among central-nervous-system (CNS) diseases. MS is associated with a high cost of illness, both in terms of direct and indirect costs. Given that the onset of MS is in early adult life (average onset at 29 years of age) lasting over an individual's lifetime, there are huge costs relating to productivity losses. There is also a significant impact on the families of people with MS (PWMS).

Treating until no-evidence-of-disease-activity (NEDA) is reached, including no relapses, no increase in disability and no new or active (enhancing) lesions on their MRI scans, is gaining more popularity[1] and magnetic-resonance-imaging (MRI) is increasingly more use to diagnose and monitor disease activity in patients on treatment[2]. Meeting this objective implies regular monitoring of not only clinical relapse and disability progression, but also MRI activity. However, regular use of MRI to monitor disease activity and the effects of treatment is still not universal, though it is increasingly used as an outcome measure for clinical trials.

There are therapies, such as the disease-modifying-treatments (DMTs), which modify the course of the illness. However, considerable neurological damage (some of which may be permanent) can occur if PWMS are not given the appropriate treatment early enough. There is increasing focus on finding ways to identify disease progression as early as possible so that treatments can be adapted to prevent or delay further neurological damage[2]. There is evidence in the recent literature is advocating for an earlier treatments in multiple sclerosis[3]. The IMPrESS (International-MultiPlE-Sclerosis-Study)[4] is the first study that: present the evidence for, and generate debate on, the merits of a policy change in the management of MS, including the use of better (and more accurate) diagnostic follow up to monitor disease progression and the earlier use of DMTs to achieve better outcomes for individuals; and also assess the socio-economic and personal impact of such a policy change compared to the current status.

The IMPrESS (International MultiPlE Sclerosis Study)

The IMPrESS used online surveys with PWMS, their caregivers and clinicians as well as secondary data from the literature and health-technology-assessment (HTA) to produce new international evidence on: the socio-economic burden and health-related-quality-of-life (HRQoL) of people affected by MS; the impact that a paradigm shift in the management of MS could have on health outcomes and resource utilisation; the views of PWMS and treating physicians and to explore the factors which influence these views; the criteria driving value assessments of MS pharmaceutical treatments by analysing HTA recommendations and their impact across different settings. This paper summarises the new findings from the surveys and HTA analysis; more details are presented elsewhere[4]. Data

presented here refers to a larger sample of responses including an additional wave of data collection completed after the publication of the project report[4] (see T 1 and 2).

Primary data collection from PWMS, their caregiver and clinicians

Costs (table 1) **-** The primary analysis of the PWMS and caregiver data sets provided updated international data on the burden of MS they experience as well as their experience of treatment and support when novel DMTs are available in clinical practice. Total average annual PWMS costs were €41,212 (SD € 18,761). Just over half of total average costs (€21,563) were associated with direct medical costs, followed by indirect costs (€17,492) and direct non-medical costs (€2,157). The overall costs (and relative ratio between direct and indirect costs) varied also according to the type of MS and severity of the disease. More severe and disabling cases of secondary-progressive-MS (SPMS) were characterised by increased total costs (€49,070) where indirect costs accounted for the majority (about 65%) compared with relapsing–remitting-MS (RRMS; about €41914) where indirect costs accounted for about 36%. Similar results are available elsewhere[5,6]. Caregiver costs related to productivity losses are about double the cost reported by PWMS (€31,653 vs. €16,318). More data according to type of MS and treatment delays are in appendices 1-4.

Quality of life and how they feel (table 1) **-** The average utility value reported was 0.56 [56% of perfect health] based on EuroQol-5-dimensions-5-levels (EQ-5D-5L), with a loss of 28% compared with the general population. Utilities varied across healthcare systems and types of MS. Comparable estimates were found elsewhere[6-7]. Greater values in utility were accompanied by lower disability and increased satisfaction values with the healthcare service received. Fatigue and weakness, bladder or balance problems were the most frequently reported factors that had a significant impact on PWMS life and they believed a new MS treatment should keep them under control. It can be argued that other health state factors beyond EQ-5D-5L are (more) important to PWMS (appendix 5). Evidence from the literature[7] showed that MS-related complications, including severe urinary tract infections, constipation, fractures and falls (due to increased weakness and fatigue), and pressure sores are major reasons for hospital admissions with significant socioeconomic consequences. This highlights the importance of identifying the most appropriate utility measure to be adopted. Caregivers reported better quality of life compared with PWMS (73% vs. 59% of perfect health), whereas both caregivers and the person they are caring for reported a mild level of discomfort/disability.

Exploring the impact that a paradigm shift in the management of MS could have on health outcomes and resource utilisation - Subgroup analysis compared individuals who received early diagnosis of MS

(≤12 months from first symptoms) with individuals who received diagnosis later than 12 months after the first symptoms[1]. Analysis of the data collected from the PWMS showed that patients treated earlier in the course of the disease showed a trend towards lower total (€39,037vs. €42,996), indirect (€15,733 vs. €18,934) and DMT (€19,364 vs. €20,491) costs and a higher EQ5D score (0.62 vs. 0.56; $p<0.01$) compared to those receiving late treatment. More in appendices 1-4.

Experience of MS - The majority of PWMS had experience of MS treatment with DMTs from the start of their treatment (80%; 685/856); about 38% of the PWMS were currently receiving DMTs (325/856). Results were comparable with USA data[8]. PWMS were aware of the potential side effects of treatments and may prefer to delay possible risks as much as possible; however when they discussed the irreversible effect of MS on brain volume and the attached disabilities with their clinician they may opt for an early intervention. The preferred source of information for PWMS were the internet (MS-specific sites) and clinicians; this is also confirmed in the literature[8]. Although this population was approached online and may be expected to use online resources, only a few of them reported online support groups, social media or online forums as preferred source of information (less than 30% for each type of source).

Both clinicians and patients reported delays between first symptoms and diagnosis (table 2). Patients presented mixed views on the outcomes of being treated before receiving diagnosis (avoiding unnecessary disability vs. receiving wrong treatment). Although early treatment after diagnosis to maintain NEDA is gaining support as appropriate practice, clinical approaches vary across physician-respondents. Similar key factors of effectiveness, tolerability and safety drive treatment more than costs, route of administration and convenience for both groups. They all recognised that there is more to disease activity than just relapse/disability progression. Results from the PWMS survey showed that half of the respondents preferred to make the final decision about their management of care. Whether a PWMS becomes engaged in their care is a choice for the individual, but clinicians recognise that this should be strongly promoted given the derived health benefits to the PWMS and their increased satisfaction[8].

Analysis of HTAs for MS therapies and the factors influencing decision-making in different settings

New comparative evidence from the HTA assessments on 8 different MS treatments[2] conducted

[1] The cut-off of 12 months adopted here followed current guidance recommending that initiation of a DMT within 12 months of a single neurological attack with MRI-enhancing lesions should be considered as a promising, preventative strategy against future accumulation of disability[1-2].

[2] IFNβ 1a IM (Avonex), alemtuzumab (Lemtrada), IFNβ 1a SC (Rebif), glatiramer acetate (Copaxone), teriflunomide (Aubagio), dimethyl fumarate (Tecfidera), fingolimod (Gilenya), natalizumab (Tysabri).

across country settings (England, Scotland, Sweden, France, Germany and Canada – see appendix 6 and [4]) showed that there is a need for a standardized approach in HTA decision making when including PWMS' views and a wide range of evidence and outcomes must be considered. Greater homogeneity across HTA bodies is needed when taking into account HRQoL data and they should include dimensions that patients say have a significant impact on their daily lives but they are not captured by the generic tools (such as EQ-5D-5L) usually adopted by HTA agencies. The lack of real world data on the clinical and economic benefits of the technology is a key issue commonly reported by HTA bodies[9]. The collection of long-term benefit of DMTs using real world evidence is a necessary step forward (and currently underway), but should not cause delays to HTA decision-making. Crucially, discussion on an earlier use of DMTs to reduce accumulation of irreversible long term damage and decrease socioeconomic burden is currently missing from HTA assessment.

Conclusion

The IMPRESS findings demonstrate the need for a comprehensive policy discussion to tackle the problem of improving health outcomes for people with MS.[10] The evidence suggests that this is possible if policy makers address a series of issues to secure the following three main goals: (1) improve the quality of care and health outcomes for every person with MS; (2) generate further robust evidence to inform decision making; (3) increase responsiveness of health care systems to new evidence on MS.

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Declaration of Conflicting Interests

The Authors declare that there is no conflict of interest.

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Table 1: The primary analysis of the PWMS and caregiver data sets (costs, quality of life, and how they feel)

	Caregivers (n= 265) Mean (SD)	**PWMS (n= 856) Mean (SD)**
Total annual direct medical costs	n/a	€21,093 (€13,317)
Total annual direct non-medical costs	n/a	€2,110 (€587)
Total annual indirect costs	€31,653 (33,475)	€16,318 (4910)
EQ-5D-5L utility	0.73 (0.20)	0.59 (0.28)
How they feel/level of disability	The majority of the caregivers felt no or mild burden because of their status as caregiver (Zarit score=5.98)	The majority of PWMS reported low levels of disability (Barthel index=16.95)

Note: An observational study of adults with MS (at all levels of self-reported disease severity) and their caregivers was administered through anonymous online surveys available in 21 different countries. Recruitment was facilitated by national and international MS organisations and MS-centres; about 40 organisations/centres approached (about 73%) supported the dissemination of the online survey in English and/or local languages. The organisation/centres approached included 21 different countries (Australia, Canada, Czech republic, Croatia, Estonia, France, Germany, Greece, Italy, Poland, Portugal, Romania, Russia, Serbia, Slovenia, Spain, Sweden, the Netherlands, UK, USA) and responses were collected from individuals resident in 34 different nations. The majority of responses were collected from Australia, Croatia, France, Greece, Italy, Poland, Romania, Serbia, Slovenia, Spain, UK, USA (>2% from each individual country). The notal number of PWMS questionniares returned was 1152 (856 were considered suitable for analysis). The surveys captured data on: direct medical costs (medication costs, visits, hospitalisation); direct non-medical costs (help from caregivers); indirect costs (productivity loss); PWMS and their caregiver health-related quality of life HRQoL (EuroQol-5-dimensions-5-levels, EQ-5D-5L); PWMS disability (Barthel-Index); their satisfaction with the treatment received (Likert scale from 0-not satisfied - to 10 – very satisfied); burden among caregivers (Zarit Burden Interview). Additional information on the PWMS data (Access to medicines and hospitalization, Access to informal care, Quality of life and disability, and Productivity lost) according to type of MS and treatment delays are available from electronic appendices (1-5).

Table 2: Clinician and PWMS experience of MS

	What clinicians said (n=49)	What PWMS said (n=856)
Diagnosis and treatment		
When their patients/they themselves experienced the first MS symptom	70% -the majority of their patients experienced the first MS symptom aged 20-30 years	30.02 years old (mean)
Age at diagnosis of most patients	25% - 31-40 years old 75% - 20-30 years old	34.5 years old (mean)
Delay between first symptoms and MS diagnosis	37.5% - 1 year or more	5.1 years (mean)
Delay between diagnosis and treatment with DMTs	86.7% - Within 6 months	1.9 years (mean)
Treatment with DMTs		
Choosing DMTs: the most important three attributes are…	Effectiveness Safety Tolerability	Convenience (25%) Doctor's advice (19%) Other* (19%) Tolerability (17%) Effectiveness (14%)
Treating PWMS with oral DMTs	75% were treating their patients with oral DMTs	54.9% were treated with DMTs
Switching DMTs	For 57% of respondents the waiting time before switching the patients to another first- or second-line DMT may vary according to the clinical situation of the PWMS	31% switched from one DMT to another

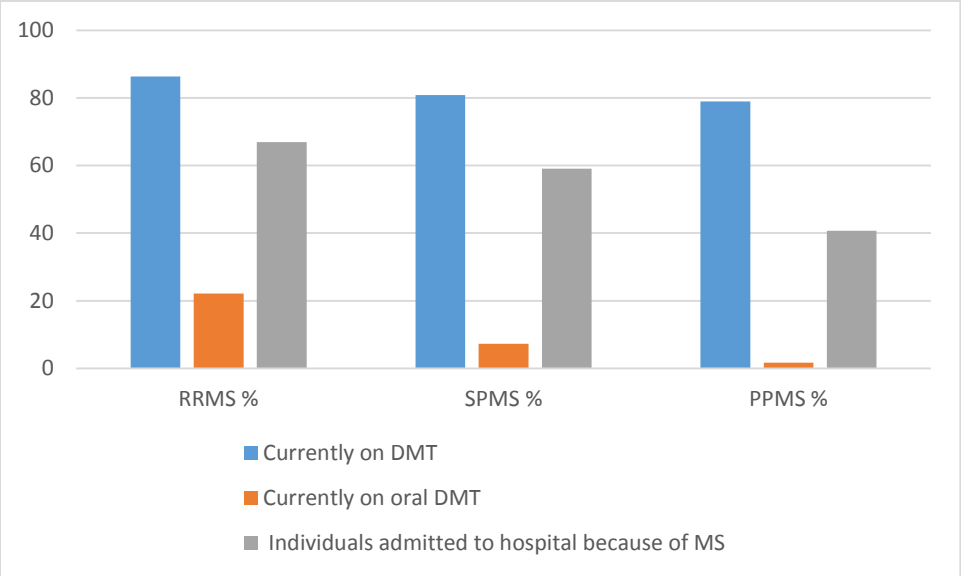
Note: A separate online survey (supplemented by face-to-face/telephone discussions) from the PWMS (see table 1) was designed to collect information from clinicians about their experience of MS treatment and support. The target group was MS expert physicians across the participating countries who were approached via personal contacts and patient organisations. A series of MS specialists participating in the conference of the European Association of Neurologist 2015 were also invited to participate. Clinicians' countries of practice included: Croatia, Denmark, France, Germany and Greece, Italy, Poland, Russia, Spain, Switzerland, the Netherlands, UK, USA (the total number of questionnaires returned was 94; 49 were suitable for analysis); the PWMS survey was disseminated in Australia, Canada, Czech republic, Croatia, Estonia, France, Germany, Greece, Italy, Poland, Portugal, Romania, Russia, Serbia, Slovenia, Spain, Sweden, the Netherlands, UK, USA (1152 questionnaires returned; 856 were suitable for analysis).

Supplementary material (Electronic appendices)

Appendix 1 socio-demographic and clinical sample characteristics

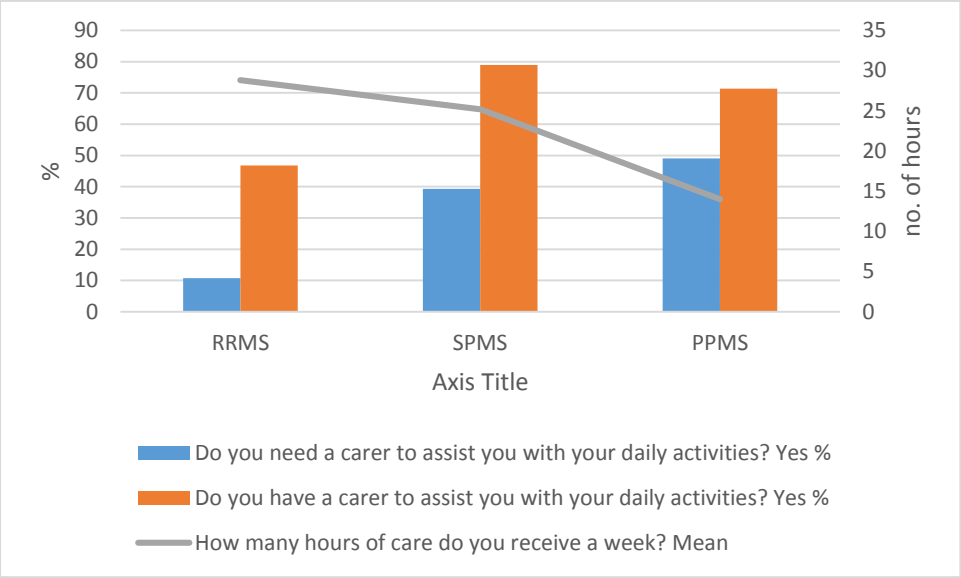
		Frequency	Percent
Age	mean (sd)	45.49	69.082
Gender	Male	199	23.2
Type of MS	Relapsing remitting MS (RRMS)	542	65.6
	Secondary Progressive MS (SPMS)	110	13.3
	Primary Progressive MS (PPMS)	61	7.4
	I'm not sure	113	13.7
Marital status	Single	221	26.1
	Married or cohabiting	514	60.6
	Divorced	71	8.4
	Separated	31	3.7
	Widow	11	1.3
Level of education	Primary	29	3.5
	Secondary School Certificate	110	13.1
	A levels	208	24.8
	University	407	48.5
	others	53	6.3
	none	33	3.9
At what age did you first experience MS symptoms? (years)	mean (sd)	30.0	69.0
At what age were you diagnosed with MS? (years)	mean (sd)	34.5	68.7
Delay between first symptoms and diagnosis (years)	mean (sd)	5.1	8.2
When do you think the treatment should be started?	When you first experience symptoms that are likely to be due to MS (that is, before you are formally diagnosed with MS)	270.0	32.9
	After being diagnosed with MS	550.0	67.1
Utility	EQ-5D5L score	0.6	0.3
Severity	Barthel score	17	4.1
	Severe dependence (Barthel score<=15)	168	23.8
	Moderate dependence (Barthel score 16-17)	122	17.3
	Slight dependence (Barthel score 18-19)	165	23.3
	Independent (Barthel score 20)	252	35.6

Appendix PWMS - Access to medicines and hospitalisation



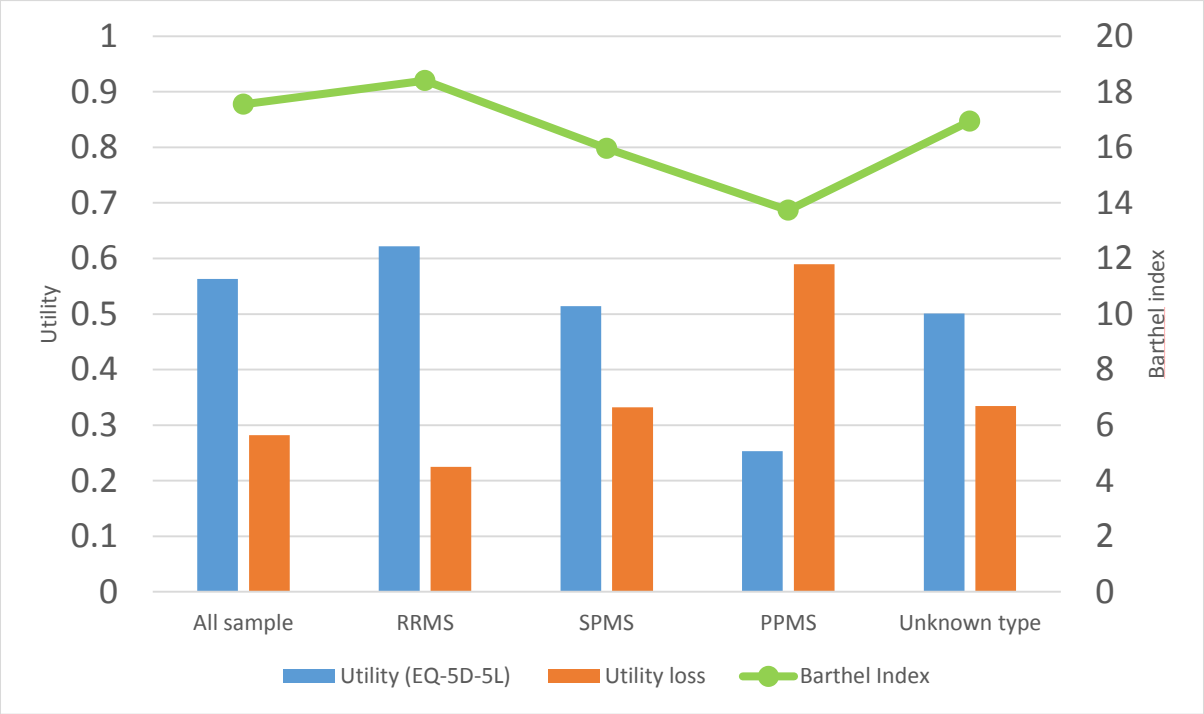
PWMS treated earlier (starting treatment within 12 months after a first symptom if MRI establishes evidence of MS diagnosis (compared with more than 12 months) showed a trend towards being on oral DMT (20% vs 14%; $P<0.05$). Patients treated earlier showed no change in hospital admissions. More severe PWMS were less likely to access DMTs but were more likely to be hospitalised ($P<0.05$).

Appendix 2 PWMS - Access to informal care



PWMS treated earlier showed no change in access to informal care (compared with individuals starting treatment more than 12 months after diagnosis). Levels of access to informal care was correlated to the severity of the disease ($p<0.05$).

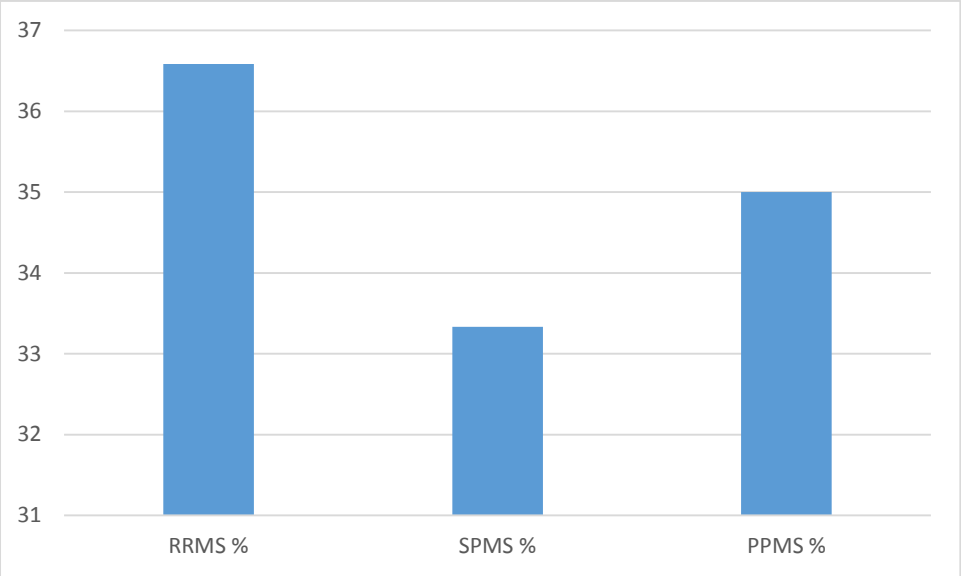
Appendix 3 - PWMS - Quality of life and disability



Note: Utility loss (compared with general population)

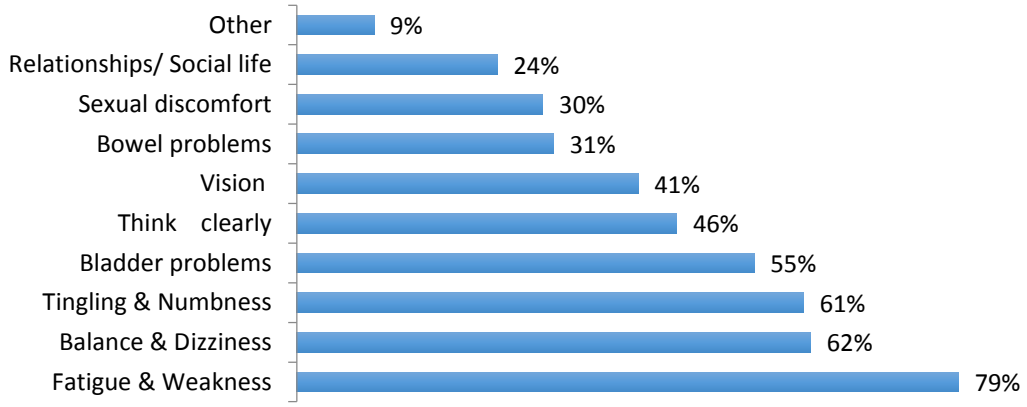
PWMS treated earlier in the course of the disease showed a trend towards higher EQ5D utility score. PWMS. EQ5D utility score was inversely correlated to the severity of the disease ($p<0.05$).

Appendix 4 PWMS - Productivity lost



Note: Frequencies reported here refer to positive responses to the question “The fact that you are affected by the disease led to any work-related problems in the last 6 months?”. PWMS treated earlier in the course of the disease reported less work-related issues compared with individuals starting treatment more than 12 months after diagnosis (30% vs 42%; $p<0.05$). Productivity loss was correlated to the severity of the disease ($p<0.05$).

Appendix 5 PWMS - Most commonly quality of life aspects, not captured by the EQ-5D



Appendix 6 – HTA - Treatment recommendations for MS

Molecule name (branded name)	Indication considered	Evidence from HTA agencies					
		NICE (UK)	**TLV** (Sweden)	**HAS** (France)	**SMC** (Scotland)	**IQWIG** (Germany)	**CADTH** (Canada)
IFNβ 1a IM (Avonex)	RRMS	DNL	DNL	LWC	LWC	N/A	N/A
Alemtuzumab (Lemtrada)	Active relapsing–remitting multiple sclerosis	L	L	N/A	L	N/A	DNL
IFNβ 1a SC (Rebif)	RRMS	DNL	L	LWC	DNL	N/A	DNL
IFNβ 1b SC (Betaferon, Extavia)	RRMS	N/A	L	LWC	N/A	N/A	N/A
Glatiramer acetate (Copaxone)	RRMS	DNL	N/A	L	N/A	N/A	N/A
Teriflunomide (Aubagio)	RRMS	LWC	L	L	LWC	A	DNL
Dimethyl fumarate (Tecfidera)	Active relapsing-remitting multiple sclerosis	LWC	LWC	LWC	L	A	N/A
Fingolimod (Gylenia)	Highly active relapsing–remitting multiple sclerosis	LWC	L	LWC	LWC	A	LWC
Natalizumab (Tysabri)	Rapidly evolving severe relapsing–remitting multiple sclerosis (RES).	L	L	LWC	DNL	N/A	LWC

Notes: **RRMS**=relapsing remitting multiple sclerosis; **L**= Listed (accepted); **LWC**= Listed with criteria (restricted); **DNL**= Do not list (rejected); **A**= assessed without decision. **N/A** = not appraised for the indication; **NICE**=National Institute for Health and Care Excellence (England); **TLV**=Dental and Pharmaceutical Benefits Board (Sweden); **HAS**=Haute Autorité de Santé (France); **SMC**=Scottish Medicines Consortium (Scotland); **IQWiG**=Institute for Quality and Efficiency in Healthcare (Germany); **CADTH**=Canadian Agency for Drugs and Technologies in Health (Canada).