Towards better outcomes in multiple sclerosis by addressing policy change

The International MultiPlE Sclerosis Study (IMPrESS)

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Executive summary

Multiple sclerosis (MS) is a serious and disabling condition, which affects people in early adulthood. It is the second most common cause of disability among central nervous system diseases and epidemiological data suggests that between 3 and 7 people per 100,000 population are newly diagnosed with MS each year. Neurological damage leads to problems with bodily functions, including impairment of muscle coordination, vision and sensation, and also results in cognitive and psychological dysfunction, sleep disorders, fatigue and pain.

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). Based on WHO data at global level in 2012, MS was estimated to cause 1,165,000 disability-adjusted life years (DALYs), of which 387,000 were attributable to the European region and 282,000 to the Americas.

It is becoming common practice to use magnetic resonance imaging (MRI) to diagnose and monitor disease activity in patients on DMTs. Current recommendations of 'treat to target' mean treating until 'no evidence of disease activity' is reached, including no relapses, no increase in disability and no new or active (enhancing) lesions on their MRI scans. 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. A number of senior clinicians from different countries confirmed that MRI is routinely available in their practice, but this does not necessarily mean that it is common practice across clinical settings.

There are therapies, which modify the course of the illness, known as disease modifying treatments (DMTs); that is, their effect is to slow disability and disease progression. 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.

There is an urgent need to achieve better outcomes for PWMS and the evidence suggests that this is possible if policy makers address the following issues.

- **Diagnosis, treatment and management goals should be set to provide the best health outcome for every person with MS.**
  - Early diagnosis and treatment are needed to secure the best outcomes for PWMS, to prevent or avoid irreversible health deterioration and disability progression.
  - Diagnostic imaging is an effective way of capturing disease activity early and should be routinely available in the management of PWMS.
  - Newer and more effective DMTs should be used both earlier and routinely while real world data on their long-term impact is collected.
  - Health systems should involve more actively PWMS in decisions about their disease management.
  - MS specialists should be involved in drawing up a treatment plan for each PWMS.

- **(Further) robust evidence should be generated and used in order to make appropriate decisions about care management in MS strategies.**
  - Robust epidemiological, clinical and disease management data are needed internationally to inform better decisions for priority setting in MS.
  - National registries should be in place and the data from them should be routinely used; the production of such evidence should be adequately resourced.
  - Data should be updated on an ongoing basis and should incorporate dimensions for which little validated information currently exists; for example, registry data should be amended to allow for collection and use of standardised information on MRI use across country settings.
  - Updated and internationally comparable evidence on the use of diagnostic imaging as a means of capturing disease activity should be generated as a priority.
  - Health gain and quality of life data should take account of dimensions that patients say have a significant impact on their daily lives; many of these items are not captured by generic tools often used by HTA agencies internationally (e.g. EuroQol 5 dimensions 5 levels (EQ-5D-5L) questionnaire).
  - Greater consistency is needed in collecting economic data and evaluating the economic impact of MS to ensure that comparisons across settings can be made.
- **Improve the responsiveness of health care systems to new evidence on MS.**
  - Healthcare systems need to be able to respond dynamically as new evidence emerges on the diagnosis, treatment and psychosocial support of MS patients as well as the long-term economic evidence on the impact of MS.
  - Updated guidance on MS management should be developed as new evidence becomes available on the use of imaging and disease modifying therapies and should be implemented promptly.
  - Incentives should support improvement in clinical practice and the incorporation of new evidence on MS management in health care decision-making, especially if such evidence is linked to improvements in quality of care and health outcomes.

1. Multiple sclerosis: Epidemiology, Diagnosis and Clinical Pathways

1.1 Epidemiology

Multiple sclerosis (MS) is an inflammatory disorder of the central nervous system (CNS). In Europe and the US, MS is the leading cause of non-traumatic neurological disability in young adults[1,2]. The distinctive aspects of MS are its manifestation in early adulthood (average age of onset of first symptoms of the disease is 29 years) and its chronic nature. Inflammation can occur in any area of the brain, spinal cord and optic nerve with commonly occurring symptoms including depression and anxiety, limitations in mobility, reduced hand and fine finger control, unclear speech, urinary and faecal incontinence and cognitive impairment, causing memory and concentration difficulties, problems with words, and compromising visuospatial abilities, planning and problem-solving. Depending on the location of inflammation within the CNS, MS can present with a range of symptoms, with variability in severity and disease course.

There are three main types of MS. The most common, affecting about 85% of people with MS, is relapsing-remitting MS (RRMS), where patients experience temporary disability due to acute neurologic symptoms known as relapses, followed by remission periods where symptoms abate and disability may disappear[3,4]. RRMS is usually followed by secondary progressive MS (SPMS), where relapsing-remitting patterns are no longer evident due to a steady increase in disability.

Box 1: Issues in determining MS Epidemiology

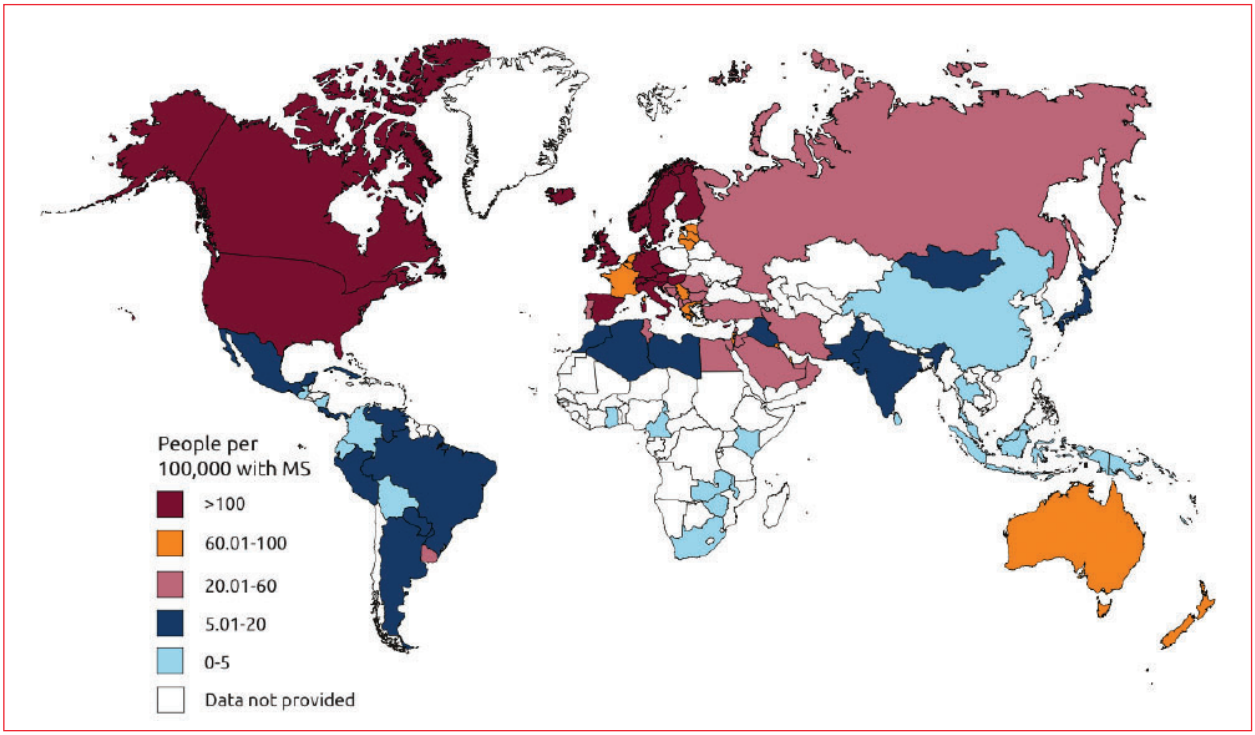
Although there is considerable literature covering prevalence studies, the lack of harmonised data collection across countries may limit the reliability of the available data. Moreover, the absence until 2010 of universal diagnostic criteria (see section 1.2 on diagnosis) means that data from past epidemiological studies may not accurately reflect the true MS population because of variable classification of people with MS across studies (i.e. individuals with definite, possible and/or probable MS)[5]. In addition, the limited availability of country-specific MS registries worldwide[6,7] has resulted in methodological inconsistencies in recruitment. Where nationwide surveys or registries have been employed, prevalence rates have been consistently higher compared to studies where recruitment methods relied on physicians', clinics', or hospitals' records[8]. There is significant fluctuation of figures reported within countries and the epidemiological picture for each country can only be based on approximations. The methodological issues that affect prevalence data apply also to incidence data. In addition, difficulties in capturing the true onset of MS further may also impede accuracy of incidence measurements, resulting in significant scarcity of MS incidence studies[5].

Table 1: Types of MS

	MAIN TYPES OF MS
Relapsing – Remitting MS (RRMS)	• 85% of MS population • Self-limited attacks (≥24hrs) with periods of remission (≥1 month)[9,10] • Acute attacks over days/weeks • Usually accompanied by periods of partial or complete recovery over several weeks
Secondary Progressive MS (SPMS)	• 50% of RRMS cases • Progressive disease, independent of relapses[10] • Ultimately attack rate is reduced with remissions, and plateaus[11] • Steady deterioration in function
Primary Progressive MS (PPMS)	• 10%-15% of MS population • >1year disease progression with occasional plateaus and temporary improvements[12] • Steady decline in function from the beginning without acute attacks[13]
	SUBTYPES OF MS
Rapidly Evolving Severe (RES) RRMS (subtype of RRMS)	• ≥22 disabling relapses in 1 year • ≥22 consecutive magnetic resonance imaging (MRI) scans with increasing lesions
Progressive – Relapsing MS (PRMS) (subtype of SPMS)	• 5% from onset (least common type) • Progressive disease with acute relapses (with or without recovery) • Continuous progression between relapses[11]

Primary progressive MS (PPMS) is described by a more steady increase in disability with the absence of acute relapses. Other less common forms of MS include rapidly evolving relapsing remitting MS (RES) and progressive relapsing MS (PRMS) (Table 1). MS is estimated to affect nearly 2.5 million people (30 per 100,000) at a global level and is believed to be more prevalent in areas further from the equator[8] (Figure 1). MS consistently presents with higher prevalence rates (per 100,000) in Canada (291), North America (140), UK (203.4) and Germany (128)[8,14,15] and lower prevalence rates in Sub-Saharan Africa (2.1), East Asia (2.2), and South East European countries such as Romania (20-30) and Bulgaria (50)[16,17]. France has the lowest rates among other north European countries (94.7)[16]. Incidence estimates mimic prevalence figures, with a global mean annual rate of 2.5 per 100,000[18] and 4.3 per 100,000 in Europe[17] (see also Appendix Figure 1). Methodological issues limit the reliability of prevalence and incidence data (Box 1) and more robust methods leading to more reliable epidemiological data on MS are urgently needed to allow for a complete understanding of its prevalence and incidence, to enable comprehensive and meaningful comparisons across populations.[17]

Figure 1: World prevalence (per 100,000) of MS per country (2013)



Source: MSIF, 2013[19].

1.2 Diagnosis

It is difficult to identify exactly when MS begins due to the many different symptoms and the variation in early signs and symptoms between individuals. It is not uncommon for a diagnosis to take several months or longer as other possible causes of the symptoms need to be excluded because most people who experience unexplained symptoms do not have MS.

There are a range of tests that neurologists use to confirm whether a person has MS, including magnetic resonance imaging (MRI), evoked potentials and lumbar puncture[20]. MRI is able to confirm a diagnosis in over 90% of people with MS, but it is important to correlate the MRI results with the clinical manifestations. This is captured by the McDonald criteria, which include clinical, laboratory, and MRI tests[21]. According to these criteria, individuals with a single attack of neurological symptoms are considered to have clinically isolated syndrome (CIS). For a diagnosis of clinically definite MS (CDMS) to be made, there must be a second clinical attack, or evidence of dissemination of MRI lesions in time and space.

Use of the McDonald criteria has enabled earlier diagnosis with the possibility to start treatment earlier. They allow a diagnosis of RRMS at the time of a single clinical attack when there is MRI evidence of both new (gadolinium-enhancing T1 lesions) and old (non-gadolinium-enhancing T2 lesions) lesions simultaneously appearing[21].

1.3 Clinical pathways and pharmaceutical care

People do not die directly from MS, but evidence shows that on average life expectancy of people with MS is shorter than that of the general population (76 years compared to 83 years for those without MS).[22] Although it is unclear whether disease-modifying treatments (DMTs) influence life expectancy, their impact on the early stages of the disease (inflammatory component) does reduce the relapse rate. Despite a profound influence on the immune system, a clear effect of these medicines on later stages of disease (preventing or delaying disability) is yet to be confirmed. The degenerative process consists of irreversible brain damage and loss and results in disability progression without relapses.

The main therapeutic goals of DMTs are to act earlier, on the inflammatory component of the disease, and to reduce clinical relapses with the goal of decreasing disability and MRI lesions[13,23]. Current discussion among MS experts[24] suggests that the target of treatment should be those falling under 'no evidence of disease activity' (NEDA).

The most widely used definition of disease activity for NEDA is based on three separate factors: (a) active MRI lesions, (b) relapses and (c) disability progression (NEDA-3)[25].

Brain volume loss (BVL) has been recently proposed as an additional fourth component to be used to detect disease activity (NEDA-4), while a fifth is 'no marker of neuronal inflammation in the cerebrospinal fluid or blood' (NEDA-5). It is anticipated that the definition of NEDA will evolve with technological innovation and clinical practice. A future definition will likely need to include patient relevant outcome measures (PROMS), focal grey matter disease activity, a whole and/or a regional brain atrophy metric and possibly fluid biomarkers[50,51].

Interferon (IFN) and Glatiramer Acetate (GA) are injectable therapies launched in the mid-1990s; they are often referred to as 'platform therapies' since they provide baseline immunomodulatory action and can be administered for an extended period of time. Studies have shown that platform therapies reduce the relapse rate of approximately 30% and the MRI markers of disease activity[8,40,42]. These injectable

Box 2: Clinical Pathways and Pharmaceutical Care – Disease-modifying treatments (DMTs)

Natalizumab (Tysabri, Biogen), an injectable monoclonal antibody introduced in 2004, is an effective medicine but comes with a potentially fatal infection known as progressive multifocal leukoencephalopathy (PML) that occurs in approximately 1 in every 500 people treated[26]. Natalizumab is not the only DMT to have PML as a side effect. Alemtuzumab (Lemtrada, Genzyme) is another injectable monoclonal antibody introduced in the market more recently. However, a few cases of PML have been reported with both fingolimod and gimethyl fumarate.

Three oral DMTs have been approved since 2010 for individuals with RRMS: = fingolimod (Gilenya, Novartis), teriflunomide (Aubagio, Genzyme) and dimethyl fumarate (Tecfidera, Biogen Idec). Based on the results from Phase III trials, these new oral therapies appear to be at least as effective (teriflunomide) or more effective (fingolimod, dimethyl fumarate) than interferon (IFN) and glatiramer acetate (GA) [27,28].

Tolerability is excellent, and the oral route of administration is preferred over injection by many individuals. Safety issues in the 2-year trials have been rare, and open-label Phase IV observation studies to date have not identified new long-term safety problems[6,29]. Less frequently used medicines include mitoxantrone, rituximab, methotrexate, azathioprine and cyclophosphamide.

The efficacy of DMTs in reducing the rate of relapses in patients with relapsing-remitting MS (RRMS) and for slowing the course of MS progression has been shown in several studies. Efficacy is higher when treatment is initiated early[30-33] and early use of a DMT may reduce permanent neurological damage, improving patient prognosis.

Studies indicate that early treatment with DMTs can delay the development of CDMS in patients with CIS[28,34-38]. Brain atrophy, which accompanies axonal damage and loss, can be observed early in the MS disease course, even in patients with CIS[30,39,40] but early treatment with IFN beta-1a has been shown to reduce the rate of atrophy in these patients[40]. Conversely, delays in diagnosis and treatment, even after patients have developed CDMS allows brain damage to accumulate and brain atrophy to progress, leading to the development of severe and irreversible neurological disability[30,41]. In addition to the disability, the delay may result in poorer response to DMTs with an overall negative impact on MS prognosis[3,8,42-47]. For these reasons, early DMT use in MS patients has been recommended in a number of guidelines[9,48,49].

therapies have been used for over 15 years and have manageable side-effect profiles with minimal serious side effects. In the years since their approval, long-term safety of these therapies has been extraordinary strong, with limited side effects (flu-like side effects for IFN and injection site reactions for GA) and few identified serious long-term risks of continued therapy[3,44]. The common side-effects and dislike of injections contribute to injection fatigue, non-adherence[45], and long-term non-persistence with both IFN and GA.

Newer MS therapies (natalizumab, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab) have improved efficacy, offer very good safety and have greater tolerability, and more acceptable routes of administration. A list of DMTs currently available and their recommendations are presented in box 2 and appendix tables 1-2.

The economic benefits of DMTs have been extensively discussed in the literature[9,46-49]. The main limitation reported is the lack of long-term evidence on the effect of DMTs: nearly all studies made use of old natural history data, and comparative efficacy data from head-to-head clinical trials or meta-analyses were not commonly used. Switching to other DMTs following initial treatment discontinuation was not commonly considered and information regarding how well a model was validated was rarely reported. Harmonised wide scale collection of both clinical and economic evidence with the support of national registries would allow more comprehensive analyses and comparisons across populations.

Although the economic impact of early use of DMTs has been addressed in a limited number of studies only, these have indicated that initiation of a DMT in the early stages of disease (after diagnosis of RRMS or even at the stage of CIS) may be cost-effective in the long term[52]. The outcome of reduced relapses, hospitalisation and indirect costs and QALYs gained seemed to outweigh the long term costs of DMTs, although more research is needed to gather evidence of long term benefit.

Different clinical guidelines published across international settings provide advice regarding the care of adults with MS (box 3).

Box 3: Clinical guidelines

Different clinical guidelines published across international settings provide advice regarding the care of adults with MS (Appendix Table 3). The following key aspects were identified as important in the management of MS:

MRI in clinical practice. There is agreement that new MRI lesions are a more sensitive indicator of inflammatory disease activity than clinical relapses. Many clinicians now substitute MRI activity for clinical activity in the classification, diagnosis and management of MS. Annual review conducted by the MS specialist neurologist, with MRI activity routinely assessed over 12-month intervals (at the direction of the neurologist) combined with clinical relapse activity will allow treatment decisions to be tailored to the individual's situation.

Early treatment. Clinicians should consider starting treatment for individuals within 12 months after a first symptom if MRI establishes evidence of MS diagnosis (2010 McDonald criteria) or predicts a high likelihood of recurrent episodes (i.e. development of MS), and perhaps if cerebrospinal fluid examination shows markers of inflammation.

Early treatment with DMTs. Immunotherapies appear particularly helpful when given early to people with active relapsing–remitting disease, before there is fixed disability or secondary progression. Although it seems plausible that reducing relapse rate and MRI lesion accumulation would favourably influence the long-term prognosis, there are as yet no peer-reviewed controlled trial results showing long-term benefit. This may be due to lack of sufficient follow up time, but as there is no consensus on the matter more research is needed.

Treatment target. It is not yet clear whether treatment should aim for a target such as 'no evidence of disease activity'— either clinical or radiological. There is no long-term evidence on which to offer guidance. Therefore, whether a single relapse should trigger an immediate treatment escalation is not known although a number of MS specialists adopt this approach.

2. Aims and objectives of this report

This report addresses the significant impact of MS on the health and wellbeing of both people with the disease, and their caregivers, along with its broader socio-economic impact. Specifically, the report aims to:

- Present the evidence for and generate debate on the merits of a likely paradigm shift 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;
- Assess the socio-economic and personal impact of such a paradigm shift compared to the current status.

In fulfilling these aims, the report objectives are to:

- Provide fresh estimates of the socioeconomic burden and health related quality of life (HRQoL) of people affected by MS;
- Explore the impact that a paradigm shift in the management of MS could have on health outcomes and resource utilisation;
- Identify whether the views of PWMS and treating physicians are aligned on MS management and to explore the factors which influence these views;
- Identify the criteria driving value assessments of MS pharmaceutical treatments by analysing health technology assessment (HTA) recommendations and their impact across different settings.

3. Methods

Primary and secondary data sources were used in the study to produce quantitative and qualitative evidence. Primary data sources included the collection of resource use and health-related quality of life data from PWMS and their caregivers together with insights about treatment pathways from clinicians. A series of surveys were designed to capture a better understanding of the multiple domains of MS burden on PWMS and their caregivers, and the experience and views of PWMS, caregivers and clinicians about early diagnosis and the drivers for changing to new (including oral) disease modifying treatments. The surveys contributed to the following objectives: to estimate the socioeconomic burden and HRQoL of PWMS; to explore the impact that a paradigm shift in the management of MS could have on health outcomes and resource utilisation; and to identify whether the views of PWMS and treating physicians are aligned on MS management and to explore the factors which influence these views. Secondary data sources included an analysis of health technology assessment (HTA) recommendations and their rationale, across different settings that use this particular tool, with a view to understanding the type of decision-making and the levers and criteria that individual HTA agencies use to enable the coverage of new technologies.

3.1 Primary data collection from PWMS and their caregivers

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 English, French, German, Greek, Italian, Swedish and Romanian. Recruitment was facilitated by national and international MS organisations and MS-centres; 8 of 11 organisations/centres approached (about 73%) supported the dissemination of the online survey in English and/or local languages. The countries approached included: the UK, Sweden, France, Germany, Italy, Greece, Romania, and the USA and covered: different access to MS treatments and services in terms of diagnostic criteria and clinical management of MS (availability of neurologists, MS treatment guidelines and clinical practice); a range of reimbursement policies including eligibility for treatment (restrictive HTA decisions and market access delays); affordability of MS treatments; and availability of registries or databases[7]. The dissemination strategy included blog, website, email, and social media across: USA (two organisations), UK (two), Germany (one), France (one), Romania (one), and pan-European (one).

The surveys captured data on: direct medical costs[a] (medication costs, visits, hospitalisation); direct non-medical costs (help from caregivers); indirect costs (productivity loss); PWMS and their caregiver HRQoL (EQ-5D-5L)[53]; aspects of the health status that are valued by PWMS; their disability (Barthel-Index)[54] [b]; their satisfaction with the treatment received; burden among caregivers[55] [c]; participants' experience of first MS symptoms; diagnosis and treatment with DMTs (orals and injectables); demographic variables, and disease information.

The societal, HRQoL and economic impact of MS management were evaluated for: the overall sample; comparing different country settings and types of MS; and comparing experience of MS management by early diagnosis [<12 months after first symptom] vs. late [>12 months after first symptom]. The 12 month cut off adopted here followed current guidance from the Association of British Neurologists[56] that initiation of DMT within 12 months of a single neurological attack with MRI enhancing lesions should be considered.

3.2 Primary data collection from clinicians

A separate online survey (supplemented by face-to-face/telephone discussions) was designed to collect information from clinicians about their experience of MS treatment. The target group was MS expert physicians across the US and Europe who were approached via personal contacts and patient organisations. A series of MS specialists participating in the first conference of the European Association of Neurologist 2015 were also invited to participate.

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a Types of MS related costs are explained in figure 2.

b The Barthel Index (BI) consists of 10 items that measure a person's daily functioning, particularly the activities of daily living and mobility. Response options range from 0 (severely dependent) to 20 (independent).

c The Zarit Burden Interview, a popular caregiver self-report measure used by many aging agencies, originated as a 29-item questionnaire (Zarit, Reever & Bach-Peterson, 1980). The revised version contains 22 items. Each item on the interview is a statement which the caregiver is asked to endorse using a 5-point scale. Response options range from 0 (Never) to 4 (Nearly Always).

The survey comprised four sections:

- Issues relating to symptoms and diagnosis (the source of information on MS diagnosis, treatment and management; the tools they use more frequently for diagnosis of MS; the age most of their patients experience the first MS symptoms/ receive a diagnosis of MS; the delay between first symptoms and diagnosis of MS in their experience);
- The use of DMTs (how long following the diagnosis of MS they usually start to actively treat a PWMS; which DMTs they use as a 1st or 2nd line treatment; the percentage of their patients for whom they prescribed it; when they escalate from 2nd to 3rd line treatments and the DMT they prescribe; the attributes that are more important when selecting a DMT; whether their patients contribute to the decision making process);
- A series of case studies picturing early treatment as well as switching treatment scenarios;
- Information about themselves (training/practice experience).

3.3 Analysis of secondary data: Impact of HTAs

The review of HTA decisions provided an in-depth understanding of similarities and differences in HTA assessments across different countries. Analysing HTA recommendations and their impact allowed the criteria driving value assessments in MS pharmaceutical treatments to be identified.

A number of country-specific case studies were conducted on 8 different MS treatments (IFNβ 1a IM (Avonex), alemtuzumab (Lemtrada), IFNβ 1a SC (Rebif), glatiramer acetate (Copaxone), teriflunomide (Aubagio), dimethyl fumarate (Tecfidera), fingolimod (Gilenya), natalizumab (Tysabri)). The countries selected (England, Scotland, Sweden, France, Germany and Canada) have notably different approaches to assessing the value of a medicine and the study sought to clarify differences in the evaluation of the evidence and which factors may drive different access to MS treatments across countries. The pharmaceutical products considered in the analysis were all indicated for RRMS, and underwent HTAs prior to June 2015 in at least three of the study countries. For each HTA assessment a series of information points on the decision-making process were identified and analysed as follows:

- Clinical evidence evaluated (type of trials, comparators considered, primary, secondary and HRQoL outcomes);
- Safety profile and adverse events;
- Economic evidence (type of cost-effectiveness analysis and comparator considered);
- Clinical and economic uncertainties (concerns raised around the clinical and economic evidence presented by the manufacturer, see Appendix Tables 5-6);
- Stakeholder input (input from PWMS or clinical experts that influenced the outcome);
- Other factors (specific disease and treatment characteristics that influenced the outcome);
- Time lapse between marketing authorisation and completion of the HTA assessment as indicator of timely access to treatment, see Appendix Table 7.

For each dimension, HTA data were compared across case studies and medicines of interest. The collection and analysis of HTA data were based on a standardised analytical framework developed at LSE[57].

4. Evidence on the socio-economic impact of MS

4.1 MS treatment and monitoring

In MS the central nervous system (CNS) is affected and the neurological damage seems to occur mostly in the early phase of the disease. There is evidence indicating that disability accumulation and health status deterioration are related to the inflammatory attacks to the CNS in the early stages of the disease suggesting an early therapeutic window of opportunity when greatest benefit can be obtained from using the most effective intervention as early as possible[39]. Consequently, early diagnosis and treatment are needed to secure the best outcomes for PWMS, to prevent or avoid irreversible health deterioration and disability progression.

DMTs are able to reduce the inflammation of nerve cells caused by MS and to alter the course of the disease by slowing disability and disease progression. This is in line with the treatment goals of PWMS[58]. All the licensed DMTs for MS reduce relapse rate and MRI lesion accumulation in RRMS with varying levels of efficacy and there is no agreed gold standard treatment. DMTs appear to be most helpful when given early to people with active RRMS, before there is fixed disability or secondary progression. The evidence suggests that newer and more effective disease modifying treatments should be used both earlier and routinely while real world data on their long-term impact is collected.

Despite current treatment paradigms targeting relapse as a proxy for disease progression, it is now evident that MS should be monitored on a more regular basis by alternative diagnostic means, and different measures of disease progression adopted in order to judge whether a change in treatment is indicated[25,51,57,59,60]. This would allow access to more novel therapies earlier in the disease. Evidence from the literature supports the use of new MRI lesions as a more sensitive index of inflammatory disease activity, as opposed to clinical relapses only. MRI is now increasingly used to monitor disease activity in PWMS on DMTs and neuroscience centres with expertise in MS increasingly need ready access to MRI and other diagnostic services in order to monitor PWMS on DMTs. Diagnostic imaging is an effective way of capturing disease activity early and should be routinely available in the management of MS. However, lack of neurologists specialising in MS is one of the main barriers to access in some countries.

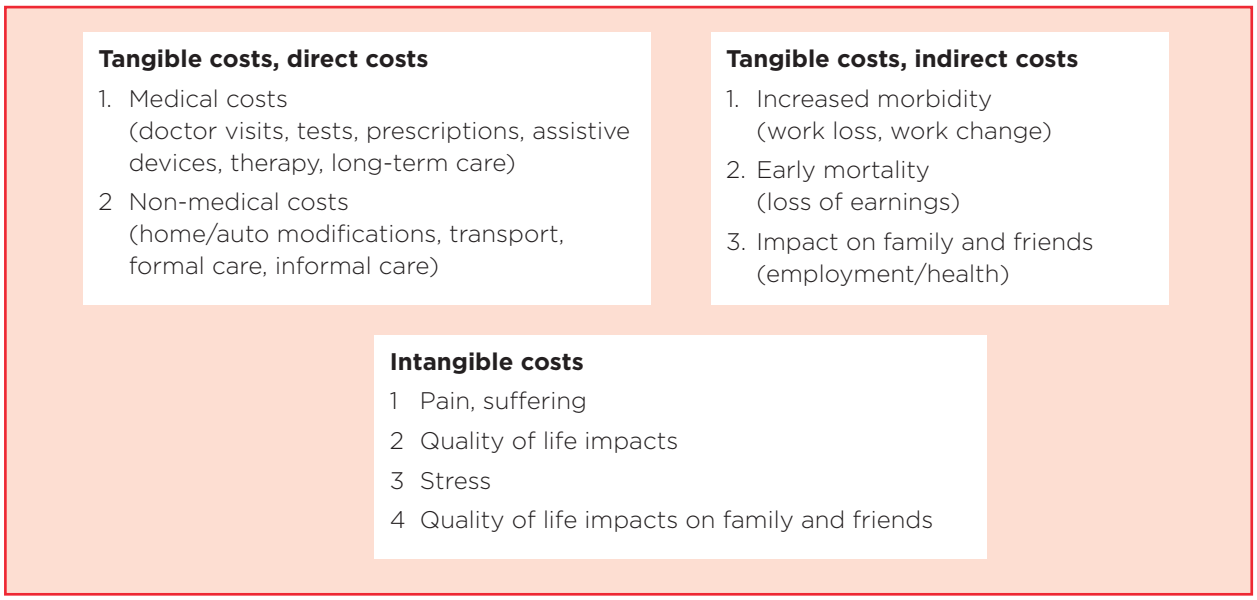
When considering potential DMT options, PWMS and neurologists should discuss together the benefits and potential risks of medicines, as well as monitoring requirements. Other factors that are personally important to a PWMS, such as work and family, should be factored into decisions and individual treatment plans can be agreed based on the type of MS and personal circumstances. PWMS should be given accurate information about what to expect from treatment. In recent years guidelines have been developed at national and/or international level to support the application of current knowledge of best practice in clinical management. Prescribing guidelines should be aligned with the latest accepted diagnostic criteria and treatment options to give PWMS the opportunity to receive the best available treatment and support promptly, once diagnosis is confirmed. Updated guidance on MS management should be developed as new evidence becomes available and the guidelines should be implemented promptly.

4.2 Costs and Quality of Life

MS is a ‘hidden disease’ and the extent of its impact is not always visible to others. A number of symptoms limit the ability of PWMS to work; these include depression and anxiety, limitations in mobility, reduced dexterity, slurred speech, urinary and faecal frequency and urgency, and cognitive impairment causing memory and concentration difficulties. The disease is associated with a variety of direct and indirect costs and due to its nature there are also intangible costs, which may include additional dimensions of burden related to pain and impact on quality of life for PWMS and their family/caregivers (Figure 2).

MS is estimated to cause 1,165,000 disability-adjusted life years (DALYs) globally, of which 387,000 are attributable to Europe, and 282,000 in the Americas[61]. Disease progression leads to disability, which affects individuals’ and their informal caregivers’ social functioning, quality of life and reduced productivity, resulting in increased burden on health systems and society and significant productivity losses. The proportion of total costs attributable to medical costs (e.g. medical costs, inpatient care), non-medical costs (e.g. formal and informal care by family or friends) and other cost categories (indirect costs related to productivity losses) varies across studies.[62] Despite applying different methodologies and reporting on different types of costs, all economic studies in MS clearly highlight the high societal cost of this disease. They also clearly illustrate how different health-care systems provide different levels of services for PWMS.

Figure 2: Economic impact of MS: Conceptual model and cost categories



4.2.1 Costs

The proportion of total costs attributable to direct medical costs (e.g. prescriptions, hospitalisations), direct non-medical costs (e.g. formal and informal care by family or friends) and other cost categories (e.g. indirect costs related, among others, to productivity losses; or intangible costs related to the impact on quality of life, pain or suffering) vary across settings[8,62-65].

Available evidence suggests that the average PWMS is 47 years old, with an average annual cost of US$41,133 (€54,844[d]). Direct costs accounted for approximately 70% of total costs, of which the main component was medication costs. Only 40% of PWMS are active in the labour market[65]. Additional evidence found that in the USA, the total healthcare costs range between US$8,528 to US$54,244 (€11,371 to €72,325[e]) per person per year, with direct costs accounting, on average, for 77% and indirect costs for the remaining 23% of the total[64]. Total costs increase with progressive disease. Intangible costs were estimated at around €13,000 per person (in 2005)[63]. Evidence from Europe highlighted that the total mean annual costs per PWMS were €18,000 for mild disease (Expanded Disability Status Scale[f] (EDSS) <4.0[g]), €36,500 for moderate disease (EDSS 4.0 – 6.5[h]) and €62,000 for severe disease (EDSS >7.0[i])[63]. Appendix Table 4 provides a summary of cost of illness studies.

Pharmaceutical costs generally decreased from moderate to severe MS due to the lack of MS-specific treatments for severe disease. Indirect costs tended to be more of a contributing factor as individual disability increased e.g. higher Expanded Disability Status Scale (EDSS) scores. The highest cost is seen among individuals with an EDSS score of 8[j] – 9[k].

The use of health care resources and services is not only influenced by severity and disease activity (relapses), but also by the organization and availability of care and the ease of access. The amount of informal care is generally a function of the extent of services offered by individual healthcare systems. Limited healthcare services available to PWMS usually lead to a greater use of informal care. Although a significant proportion of total costs relate to informal caring arrangements, this cost element is most often not reimbursed by health care systems, impacting both family income and caregiver quality of life.

d At 2013 exchange rates.

e At 2013 exchange rates.

f Expanded Disability Status Scale (EDSS) score is a measure of disease activity weighted towards the physical, especially mobility, aspects of the disease and is used to monitor changes in the level of disability over time (from 0= no disability to 10=death)

g EDSS of 4 = Able to walk without aid 500 meters.

h EDSS of 6.5 = Constant bilateral support (cane, crutch or braces) required to walk 20 meters without resting.

i EDSS of 7 = Unable to walk beyond 5 meters even with aid, essentially restricted to wheelchair, wheels self, transfers alone; active in wheelchair about 12 hours a day.

j EDSS of 8 = Essentially restricted to bed, chair, or wheelchair, but may be out of bed much of day; retains self-care functions, generally effective use of arms.

k EDSS of 9 = Helpless bed patient, can communicate and eat.

4.2.2 Impact on quality of Life of PWMS and their caregivers

There is a clear deterioration in health outcomes of PWMS compared with the healthy population, and the deterioration may increase with the severity of the disease. A decrease in individual's preferences for specific health outcomes (utility loss) in PWMS compared with the general population varied between the case studies of interest[62,63]. European evidence showed that quality of life scores among PWMS were similar across countries at around 0.70 (70% of perfect health) for a person with an EDSS of 2.0 (with minimal disability in one functional system) and around 0.45 (45% of perfect health) for a person with an EDSS of 6.5 (with constant bilateral support with cane, crutch or braces required to walk 20 metres without resting). People with SPMS reported a higher symptom burden than individuals with RRMS, highlighting the need to prevent progression from RRMS to SPMS[66].

The stress and physical burden of caring for a person with MS may have an adverse effect on the psychological and physical health of caregivers and increase their health care use[8]. The burden on caregivers is substantial, and its amount varies by the PWMS' level of disability. Caregivers experience a high socioeconomic burden as a result of their role, with caregivers for individuals with SPMS experiencing a more significant burden than those of individuals with RRMS, reflected in their decreased ability to be employed full-time and the effect of their role as a caregiver on their work[67].

EuroQol 5 dimensions 5 levels (EQ-5D-5L)[/] is one of the most widely used utility measures in MS and it is currently used to evaluate the cost-effectiveness of different interventions. However, the challenge of using such a measure in people with a specific health condition, such as MS, is that it may not capture all of the domains that are impacted upon by the health condition. If important domains are missing from the generic measures, the value derived will be higher than the real impact creating invalid comparisons across interventions and country settings. Several disease-specific HRQoL instruments have been validated for use in MS patients. These include: the PRIMUS (Patient Reported Outcome Indices for Multiple Sclerosis)l, a set of outcome measures including assessments of HRQoL and activity limitations; the MSQLI (Multiple Sclerosis Quality of Life Inventory), a series of instruments consisting of 10 individual scales providing a quality of life measure that is both generic and MS-specific; or the 12-item Multiple Sclerosis Walking Scale (MSWS-12). In clinical practice, MS-specific questionnaires appeared to be more appropriate than generic instruments due to a better ability to capture HRQoL differences in MS patients. In economic evaluations more methodological work is still needed to support the use of utility scores derived from disease specific instruments into decision modelling[68].

4.2.3 Access to Disease Modifying Treatments

Although DMTs can reduce relapse rates and evidence of disease activity can be identified using magnetic resonance imaging (MRI)[69], access to treatments and services can vary significantly across countries. WHO[19] found that only half of the treatment-eligible population among all countries worldwide that contributed to the Atlas of MS 2013, actually did receive a DMT; with patient choice (61.1%), reimbursement policy (57.7%), clinical practice (29.6%) and access to MS healthcare professionals (27.8%) being the main reasons for not receiving a DMT despite being eligible. When used, DMT high prices may increase the impact of direct costs on the total MS related annual costs, although treatment costs are likely to be offset in the long-term by increased productivity at work.

/ EuroQol 5 Dimension 5 level (EQ-5D-5L) is a standardised instrument for use as a measure of health outcome. It consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which can take one of five responses. The responses record five levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D-5L dimension. Utility values vary between 0 (dead)—1 (full health).

5. An analysis of patient, caregiver and clinician primary data on costs, HRQOL and clinical practices

5.1 Primary data analysis: People with MS

In conducting primary research across settings, the objectives were to estimate and compare the costs, HRQoL, and impact on daily living reported by PWMS and their caregivers across international settings. This would allow to: (i) address the lack of data on the multiple domains of MS burden on affected people as well as their HRQoL and experience of care; (ii) explore the potential impact that a paradigm shift in the management of MS could have on health outcomes and resource utilisation; (iii) compare the views of PWMS with the views of clinicians on early diagnosis and preferences related to a possible move towards early diagnosis and treatment with new (including oral) disease modifying treatments.

5.1.1 PWMS: responses and sociodemographic data

Valid responses suitable for analysis were received from 246 individuals. The majority of responses came from France (n=97, 39%) followed by USA (n=70, 28%), Romania (n=44, 18%), UK (n=25, 10%) and Germany (n=10, 4%). The majority of individuals were females (203, 83%), with an average age of 43.7 years. The reported mean age at first symptoms and diagnosis were 30.4 and 35.2 respectively. The majority of the individuals were diagnosed with RRMS (175, 66%), followed by SPMS (30,11.32%) and PPMS (26, 9.8%). For 34 individuals (12.8%) the type of MS was unknown. About half of the individuals reported an early MS diagnosis[m] (118 or 48%). Further detail is provided in Appendix table 8.

5.1.2 PWMS: their treatment for MS

About 82% (203/246) of PWMS started on DMTs and slightly more than half were currently receiving DMTs (135, 54.9%) at the time of completing the survey; of those taking DMTs, 58 (58/135; 42.9%) were treated with oral DMTs. Further detail on the use of DMTs according to type of MS is reported in Table 2. Evidence from the PWMS survey confirmed the choice of first and second line treatments reported in the literature (appendix tables 1 and 2). More details are available upon request.

Table 2: Use of Disease Modifying Treatments (DMTs) according to type of MS

ALL SAMPLE (N=246, 100%)	Started on DMT (N=203, 100%)	Changed between first and current DMT (N=75, 100%)	Currently on DMT (N=135, 100%)
RRMS (n=164, 67%)	148 (72.9%)	48 (64%)	106 (78.5%)
SPMS (n=28, 11%)	24 (11.8%)	12(16%)	8 (5.9%)
PPMS (n=21, 9%)	9 (4.4%)	4 (5.3%)	4 (2.9%)
Unknown (n=33, 13%)	24 (11.8%)	11 (14.6%)	17(12.6%)

Primary progressive multiple sclerosis (PPMS); Secondary progressive multiple sclerosis (SPMS); Relapsing remitting multiple sclerosis (RRMS).

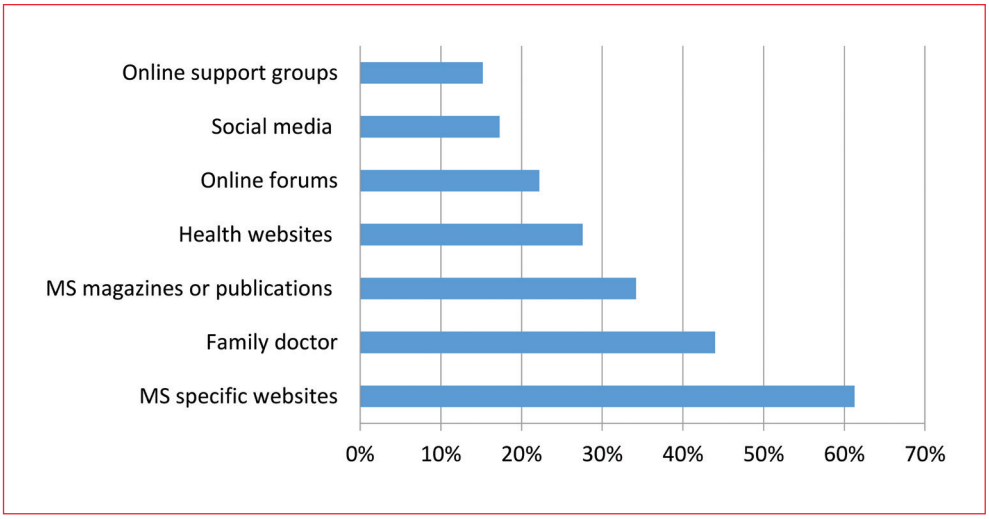
5.1.3 PWMS: Views on MS management

When treatment should be started. Respondents had varied views. 67.5% reported that treatment should be started at clinical diagnosis whereas 31.3 % thought it should be at first symptoms. The former group was aware of the potential side effects of treatments and preferred to delay possible risks as much as possible. The latter group was knowledgeable about the irreversible effect of MS on brain volume and the associated disabilities.

The preferred sources of information for MS management are listed in Figure 3. This is a young population that may be expected to use online resources, whereas 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). Only 31 respondents (12.8%) discussed with family and friends their experience of MS and 27 (11.1%) respondents attended support or self-help group meetings.

m Early MS diagnosis/treatment was defined as diagnosis/treatment made within the first 12 months from the first symptom of MS.

Figure 3: The preferred source of information for PWMS



When making decisions about their treatment: 50% preferred to make final decision (I prefer to make the final decision alone, 21%; I prefer to make the final decision after seriously considering my doctor's opinion, 29%); 27% preferred to share responsibility with the doctor; and 23% of respondents preferred the doctors to decide on their behalf.

5.1.4 PWMS: Tangible/intangible costs and satisfaction with the healthcare service received

Tangible costs – direct medical costs, informal care costs and loss of productivity at work. Total average annual costs were €40,313 (SD[n]= €18,352). The majority of costs were associated with direct medical costs €21,093 (medicines, consultations with a specialist, hospitalisations), followed by indirect costs €17,110 (productivity loss) and direct non-medical costs (€2,110, caregivers cost). The proportion of indirect costs became more significant as the level of disability increased (see subgroup of individuals with SPMS and PPMS characterised by steady deterioration in function vs. RRMS usually accompanied by periods of partial or complete recovery over several weeks). People with SPMS had the most substantial burden due to incurring both high medical and non-medical costs and greater disability compared with peoples with RRMS. More details are presented in Figures 4 and 5 (excluding Romanian data, where unit costs were not available).

Figure 4: Tangible costs: Average annual costs per person by country (€, 2014-15)
(All sample and country case studies)

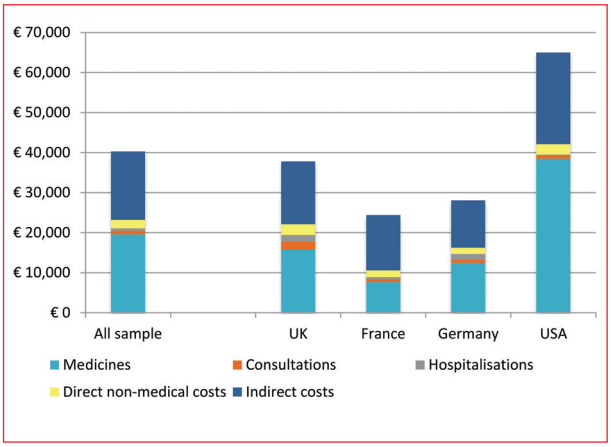
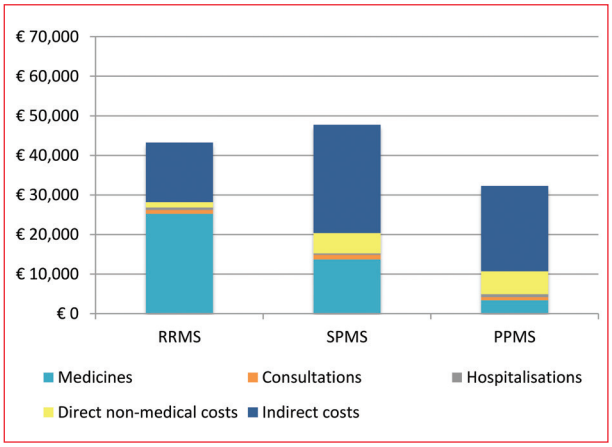


Figure 5: Tangible costs: Average annual costs per person with MS (€, 2014-15)
(By type of MS)



Relapsing remitting multiple sclerosis (RRMS); Secondary progressive multiple sclerosis (SPMS); Primary progressive multiple sclerosis (PPMS). Differences across countries were statistically significant at 0.05 level except "Direct non-medical costs" and "Consultations". All differences in the total, direct medical/non-medical and indirect costs were statistically significant across MS types.

n Standard deviation.

Intangible costs – Quality of life, wellbeing and disability. The average utility score (based on EQ-5D-5L) was 0.60 (60% of perfect health), with a loss of 0.25 (25%) compared with the general population. Utility varied across countries: Germany reported the highest mean utility (0.77; 77% of perfect health) and lowest utility loss compared with the general population (9%); France, Romania and the UK presented the lowest values for utility (49%, 51%, and 54% of perfect health, respectively) and the highest utility loss compared with the general population (34%, 35% and 32%, respectively). The majority of the individuals reported that they were independent (did not need help with daily living), 36.8%, or mildly dependent, 48.5%. Disability levels varied across country case studies: Germany reported the lowest levels of disability (only 10% moderately dependent; 0% severely dependent); the UK presented the highest levels of disability (26% were moderately dependent or severely dependent). The subgroups of individuals with PPMS and SPMS reported more severe disability and greater loss in utility compared with the RRMS group. Overall, the utility scores for PWMS were lower than those obtained for the general population in each country. More details on the specific case studies and MS types are presented in Figures 6-9**.**

Figure 6: Intangible costs – Utility (EQ-5D-5L measure) and disability (Barthel index) in PWMS by country
(All sample and individual countries)

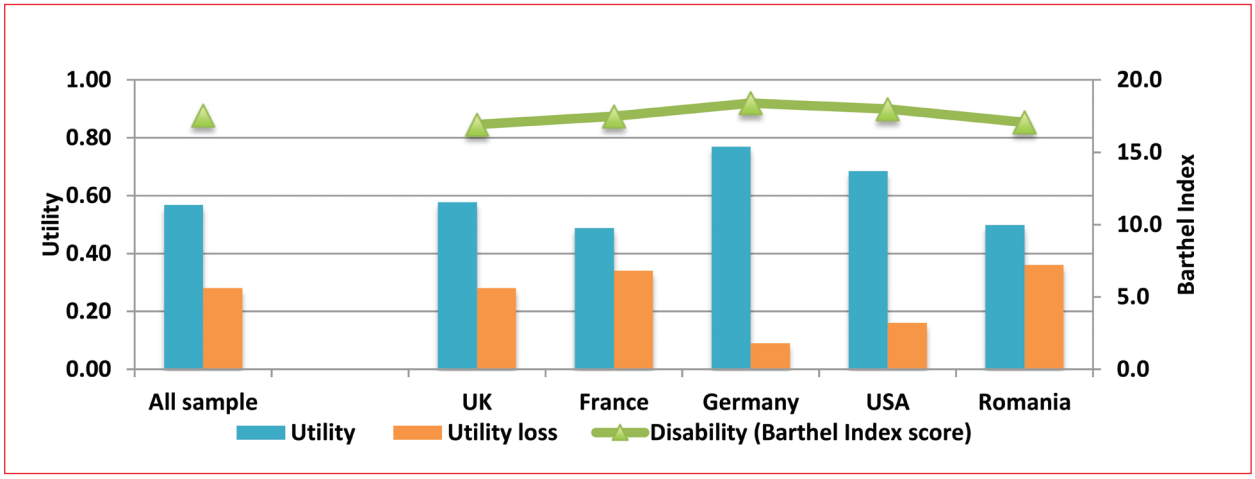
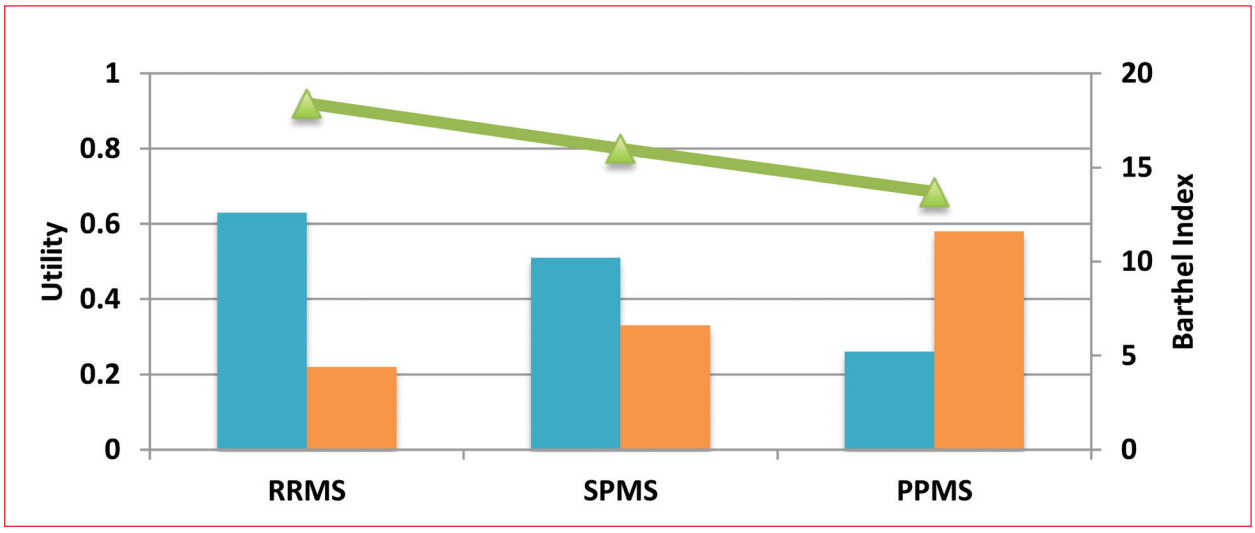


Figure 7: Intangible costs – Utility (EQ-5D-5L measure) and disability (Barthel index) in PWMS by type of MS
(Types of MS)



Primary progressive multiple sclerosis (PPMS); Secondary progressive multiple sclerosis (SPMS); Relapsing remitting multiple sclerosis (RRMS). Utility (mean) – All differences were statistically significant across countries and MS types. Disability (Mean) – Differences were not statistically significant across countries; Differences across MS types were statistically significant at 0.05 level. Utility values vary between 0 (dead)—1 (full health). Barthel index values vary between 0 (severely dependent) to 20 (independent).

Satisfaction with the healthcare service received. Overall 69% of the individuals were satisfied/very satisfied with the healthcare service received. The majority of individuals who reported to be satisfied/very satisfied were from USA (76%) and France (75%); in the UK, Germany and Romania only about half of the respondents reported to be satisfied/very satisfied with the service received (52%, 56% and 57% respectively). Individuals with PPMS were likely to be less satisfied with the service received compared with people with RRMS and SPMS. More details on the specific case studies and MS types are presented in Figures 8 and 9.

Figure 8: Intangible costs: Utility (EQ-5D-5L) and satisfaction with the healthcare received by country
(All sample and individual countries)

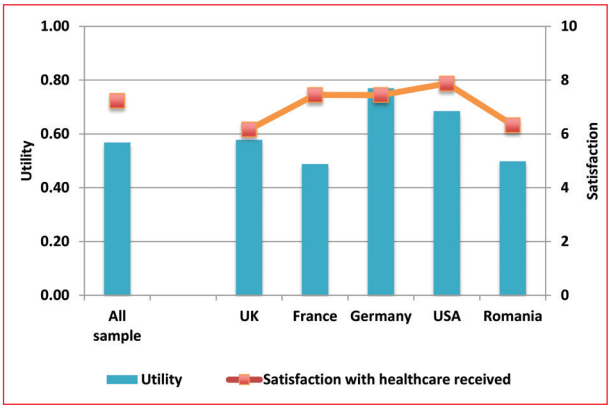
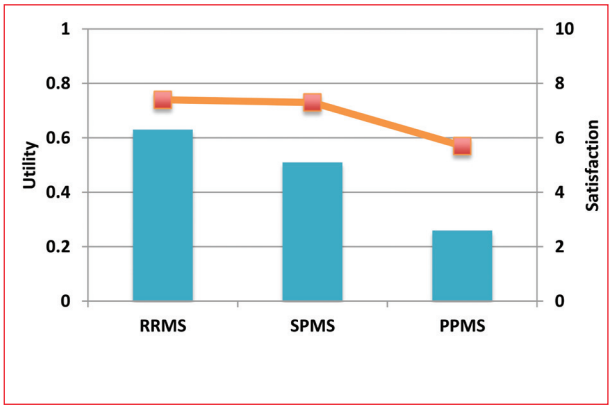


Figure 9: Intangible costs: Utility (EQ-5D-5L) and satisfaction with the healthcare received by type of MS
(Types of MS)

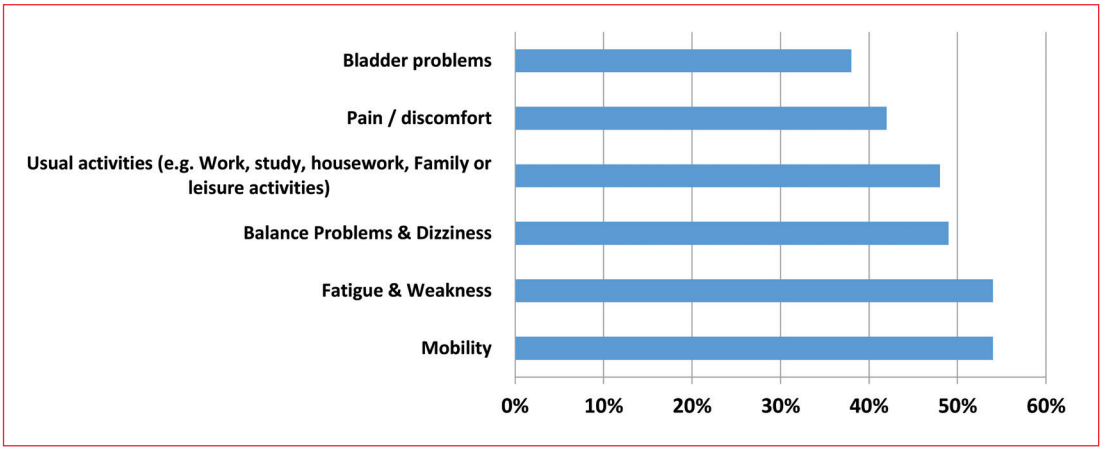


Note: Satisfaction with the healthcare service was ranked on a scale from 0 to 10. The following categories were considered for analysis: not satisfied/indifferent (0-6); satisfied (7-8); very satisfied (9-10). Differences were statistically significant across countries and types of MS.

5.1.5 Health status aspects valued by PWMS

The health status aspects that are particularly important to PWMS are reported in Figure 10. A series of aspects, including mobility, usual activities or pain/discomfort, are commonly valued when using generic utility measure (such as EQ-5D-5L), whereas fatigue and weakness, balance and dizziness, or bladder problems are specific aspects that respondents raised as they felt these were not adequately addressed by EQ-5D-5L. The six aspects reported above also represent the most recurrent factors that changed over the course of the illness. Respondents also stated that their change had a significant impact on the quality of their life. MS-related complications, such as bladder infections, fractures and falls (due to balance problems, reduced mobility, weakness and fatigue, as well as joint pain) are major reasons for concerns and respondents believed a new MS treatment should keep them under control.

Figure 10: Health status aspects valued by PWMS



5.1.6 Access to MS treatment

Primary data from PWMS showed easier access to MS treatments in European countries compared to North America. More precisely, in North America the main factors impeding access to MS treatments were low reimbursement rate for DMTs (14%) and lack of prompt disease diagnosis (29%). In Europe, reimbursement rates for DMTs were higher than 90% (among all countries), apart from Romania (81%). Early diagnosis was a barrier in all case studies. Germany reported the lowest rate of early diagnosis (24%) whereas Romania reported the highest (61%). Availability of MS neurologists appeared to be a potentially impeding factor in the UK and Romania, which both had the lowest rate of MS neurologists (64%) compared to all other countries. Overall, Germany ranked first in our "easy access to MS treatment" country ranking scale; it accumulated the highest percentages (>70%) among the majority (4 out of 6) of factors affecting access to MS treatment. Following are France, UK, Romania and USA. Other studies in the literature attempted to value access to MS treatment across EU country settings and used similar factors to the ones considered in our study (Table 3). Our results were consistent with findings from previous studies that equally ranked France and Germany as best performers compared with the UK and Romania.[6,7]

Table 3: Access to MS treatments in selected countries

Factors affecting access to MS specific treatments	USA	UK	France	Germany	Romania	Source
Clinical management of MS Diagnosis (received early diagnosis)	29%	56%	53%	24%	61%	Primary data analysis from this study
Availability of MS treatment guidelines (clinician utilization)	AAN	ABN NICE	HAS	EMSP	EMSP	Primary data analysis from this study [6]
Availability of MS specific neurologists (annual PWMS utilization)	87%	64%	70%	90%	64%	Primary data analysis from this study
Reimbursement (reimbursed by NHS)	14%	92%	95%	92%	81%	Primary data analysis from this study
Affordability of DMTs (utilisation of DMTs among treatment-eligible PWMS)	66%	56%	53%	70%	41%	Primary data analysis from this study
Availability of MS registries or databases	n/a	n/a	n/a	93.5%	n/a	[6]
Country rankings for access to MS	**5**	**3**	**2**	**1**	**4**	The authors of the report based on primary data analysis from this study
	n/a	**4**	**2**	**1**	**3**	[6]
	n/a	**3**	**1**	**2**	**4**	[7]

Note: Affordability is measured as utilisation of DMTs from treatment eligible PWMS. **AAN** = American Association of Neurology; **ABN**= Association of British Neurologists; **NICE**= National Institute for Health and Care Excellence; **HAS** = Haute Autorité de Santé; **EMSP**= European Multiple Sclerosis Platform.

5.2 Primary data analysis: Caregivers

5.2.1 Caregivers: Responses and sociodemographic data

Fifty four responses were received, 22% (12/54) of which were suitable for analysis[o]. The majority of individuals were females (67%, 8), with an average age of 51 yrs. About 75% of individuals were the spouse of a person with MS, and had cared for a person with MS for an average of 8 years. About 67% of respondents were employed and for about 50% of caregivers in employment, caring for the person with MS meant some work-related problem in the previous 12 months. Given the limited sample size and poor completion rates of the questions, the analysis covered the few socio economic aspects reported below.

5.2.2 Caregivers: Costs and quality of life

The average indirect costs to informal caregivers in the previous year were €31,155 (only productivity loss data were reported; 50% (n=4) (Table 4). The average time spent by a non-professional caregiver in caring for a person with MS was 22.4 hours per week. Respondents reported an average utility of 0.70 (utility loss of 0.15 compared with the general population; EQ-5D-5L score). The majority of the caregivers felt no (83%) or mild burden (17%) because of their status as a caregiver. Caregiver costs, quality of life, and how they feel are compared with data from the PWMS survey. Caregiver costs related to productivity losses are about double the cost reported by PWMS, whereas they reported better quality of life compared with PWMS (70% vs. 60% of perfect health). Both caregivers and the person they are caring for reported a mild level of discomfort / disability.

Table 4: Caregiver costs, quality of life, and how they feel (compared with people with MS [PWMS])

	Caregivers	PWMS
Total annual indirect costs related to productivity loss: **Mean (standard deviation)**	**€31,155** (€32,945)	**€16,061** (€4,833)
EQ-5D-5L utility: **Mean (standard deviation) [explanation]**	**0.70** (0.19) [70% of perfect health]	**0.60** (0.12) [60% of perfect health]
How they feel/level of disability	The majority of caregivers felt no (83%) or mild burden (17%) because of their status as caregiver	The majority of PWMS reported low levels of disability (independent, 37%; mildly dependent 12%)

5.3 Primary data analysis: Clinicians

5.3.1 Responses and sociodemographic data

Thirty seven clinicians were contacted; 43% of them (16/37) returned the online survey (87%, 14/16) or were interviewed (12%, 2/16). Overall, 12 experts returned data suitable for analysis (32%, 12/37). The majority of the respondents were male (71%; 5/7) with an average age of 43 years.[p] The countries of practice included: Italy (2), Spain (2), UK (2), USA (2), France (1), Denmark (1), Germany (1) and Greece (1). Seven respondents reported on the training they had received as follows: two in general neurology; five received MS specialist training. The average number of years in practice after completing all medical training was 16, and the practice settings included: community hospital (one case), university hospital (5 cases), and private hospital (one case).

5.3.2 Diagnosis and treatment

The majority of their patients experienced the first MS symptom when they were 20-30 years old (67%) and received a diagnosis of MS between 20-30 years old (42%; 5/12), or later (31-40 years old, 58%; 7/12). The majority of clinicians reported a gap between diagnosis and treatment of less than 2 months (67%, 8/12). Table 5 compares clinician and PWMS views on diagnosis and treatment.

o Blank/partially completed questionnaires were not considered for analysis.

p Please note that only 7 individuals reported their demographic data.

Table 5: Diagnosis and treatment: Clinician and PWMS views

	What clinicians said	What PWMS said
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	Average of 30.4 years old
Age at diagnosis of most patients	58% – 31-40 years old 42% – 20-30 years old	Average of 35.2 years old
Delay between first symptoms and MS diagnosis	58% – 1 year or more	Average of 4.8 years
Delay between diagnosis and treatment with DMTs	67% – Within 2 months	Average 1.9 years*

Note: * PWMS were not asked explicitly about their delay between diagnosis and treatment. The age they started treatment (calculated as difference between their current age and the number of years on DMTs) was then subtracted from the age of their diagnosis.

5.3.3 Treatment recommendations for MS

Choosing DMTs. Effectiveness, tolerability, safety and PWMS' preferences are the most important attributes for clinicians when choosing among DMTs. The clinicians reported that their patients had similar reasons for choosing a DMT (Table 6). PWMS put greater value on aspects such as convenience, doctor's advice and safety compared with clinicians.

Table 6: Treatment with DMTs: Clinician views compared with those of PWMS

	What the clinicians said	What the clinicians said drove PWMS' decisions	What the PWMS said
Choosing DMTs: the most important three attributes are…	Effectiveness Safety Tolerability	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	n/a	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	n/a	30% switched from one DMT to another

Note: *Other factors reported: side effects (i.e. safety), do not currently take/want to take any medications.

When would clinicians use DMTs? The majority of clinicians treated SPMS with DMTs only in the presence of relapses (88%, 7/8; Table 7). About 92% (11) of clinicians did not consider starting treatment with DMTs when a person has a normal MRI, as they considered it unnecessary at this stage. They would consider starting treatment with DMTs only in the presence of brain lesions, optic neuritis or severe initial relapse. They would consider reviewing the person every: 4-6 months (clinical review), 3-6 months (blood analysis); 12 months (MRI).

Table 7: When would clinicians use DMTs?

People with ...	Yes	Comments
... secondary progressing multiple sclerosis (SPMS)	88%	Depending on the presence of relapses
... a normal MRI	8% (unnecessary at this stage)	Only in the presence of brain lesions, optic neuritis or severe initial relapse
... an MRI reporting 1 or more non-enhancing lesions	77%	Either with injectable (100%) or orals (80%) (multiple choice)

Treating PWMS with oral DMTs. 75% of clinicians were treating PWMS with oral DMTs (9/12) whereas about 55% of the PWMS reported that they were treated with DMTs. One clinician who did not treat PWMS with DMTs reported that oral DMTs are: less convenient, less efficacious, and more expensive than injectable DMTs.

Switching DMTs. Just over half of the clinicians (57%) reported that they may vary the waiting time before switching a patient to another DMT according to the individual clinical situation.

Discontinuation of DMT. More than half of clinicians (57%) reported that between 10-30% of individuals discontinue the use of their DMT within 6 years. However, it was not possible to clarify the precise reason(s) for discontinuation (e.g. treatment stops working).

Treating a person when they have an MRI reporting 1 or more non-enhancing lesions. About 77% of clinicians would consider starting the treatment with DMTs (44% definitely yes; 33% maybe) either with injectable medicines (100%, 5/5) or orals (80%; 4/5). The presence of a series of risk factors (number and site of MRI lesions, oligoclonal bands on CSF, clinical presentation) was reported as the main reason to start treatment with DMTs. About 50% (2/4) would consider reviewing the person every 1-3 months (as first visit), then every six months; the other half would consider an annual review.

6. An analysis of HTAs for MS therapies and the factors influencing decision-making in different settings

6.1 Coverage decisions for MS therapies across countries

Despite their systematic nature, HTA decision-making processes and evidence differ significantly across countries and this may lead to different coverage recommendations for MS medicines. This is further confirmed by our database (Table 8) in which none of the nine study medicines received homogenous recommendations in the HTA settings studied in this report.

All the medicines shown in Table 8 had homogenous indication for the treatment of relapsing – remitting multiple sclerosis (RRMS) across the countries considered. The recommendations were divided into three categories: a) listed (L), b) listed with restrictions of the medicine to a subgroup of the population or under certain conditions (LWC), and c) do not list [reject] (DNL).

6.2 Main criteria leading to HTA recommendations across countries

A number of criteria drive value assessments in MS treatments across countries. These are outlined and compared in this section and help explain some of the disagreements in the recommendations shown in Table 8.

6.2.1 Clinical trials and comparators

About 51% of all clinical studies considered across all six agencies (n=113) were phase III trials (designed to assess the effectiveness of the new intervention and, thereby, its value in clinical practice in comparison with the current best alternative treatment), followed by indirect comparisons (31%) designed to compare interventions using data from separate studies; and other types of trials (18%) such as extension of the primary trials (n=9 across the entire sample) phase II trials (n=7 across the entire sample) and marketing surveillance studies (n=4). The comparators most commonly used for the trials were: beta-interferons or other DMTs (57%) or placebo (43%) (see Appendix Figure 2).

6.2.2 Clinical endpoints used in the trials

Substantial differences were seen in the number of primary and secondary endpoints (or measures) extrapolated by the studied agencies. The disparities seen may be explained by differences in trials reported, a different level of detail in reporting the same clinical trials, as well as a different number of subgroups and interim analyses considered (see Appendix Figure 3). For instance, in the case of alemtuzumab, NICE reported 22 primary endpoints whereas SMC, TLV and CADTH reported only seven, four and two primary endpoints, respectively. By contrast, in the case of teriflunomide, NICE, TLV and CADTH included a mixed treatment comparison that compared the study medicine with each of the treatments in the decision problem (beta interferons, glatiramer acetate, natalizumab and fingolimod). This was not considered by the other agencies and therefore led to a difference in the total number of endpoints across the agencies for teriflunomide.

6.2.3 Safety

The proportion of cases with adverse events (AEs) reported was higher in the cases of SMC and HAS compared with NICE. The rate of treatment discontinuations was more commonly reported by HAS and CADTH compared to SMC, IQWIG and NICE (Appendix Figure 4).

Table 8: 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).

6.2.4 HRQoL

HRQoL evidence was reported and considered differently across the various agencies and the number of quality of life endpoints varied across agencies. Only in two cases were multiple sclerosis-specific measures used: for fingolimod, the PRIMUS (Patient Reported Outcome Indices for Multiple Sclerosis); and for natalizumab the MSQLI (Multiple Sclerosis Quality of Life Inventory). The most widely used generic measures (total n=36) were: EQ-5D-5L utility measure (50%; n=18) and the 36-Item Short Form Health Survey (SF-36; 17%; n=6). In the remaining cases (33%; n=12) the measure used was not specified. Interestingly, and in the case of teriflumide only, the HRQoL data was considered by all study agencies and measured using the same tool (SF-36 and EQ-5).

6.2.5 Economic evidence

Only NICE, SMC, TLV and CADTH assessed the cost-effectiveness of each study medicine. Across all the agencies a total of 21 economic evaluation studies were reported: 76% (n= 16) of the studies were cost-utility analyses; 19% (n=4) were cost-minimisation analyses; and one study was a cost-effectiveness analysis. In the case of NICE only cost-utility models were reported. An interesting case is teriflunomide where SMC and TLV considered a cost-minimization analysis, whereas NICE and CADTH considered a similar cost-utility model. Between TLV and SMC there was a different comparator considered in the cost-minimization analysis, as SMC considered beta-interferon or glatiramer acetate whereas TLV considered only interferon 1-b. These assessments were associated with differing outcomes (listed with restriction by NICE, TLV and SMC, but rejected by CADTH).

Uncertainties

Each agency raised a number of concerns about the clinical and economic evidence presented by the manufacturer. Using an iterative approach, we collected all types of uncertainty across the entire sample by agency.

- Uncertainties around the reliability of the treatment's clinical benefit were raised most often by NICE (n=12 total number of uncertainties across nine appraisals), CADTH (n=6 uncertainties across five appraisals) and TLV (n=3 total number of uncertainties across eight appraisals). These were followed by uncertainties surrounding study design, which were mostly raised by SMC (n=8 total number of uncertainties across seven appraisals), IQWiG (n=5 total number of uncertainties across three appraisals) as well as NICE (n= 6 total number of uncertainties across nine appraisals). SMC also placed a lot of emphasis on issues around the study population (n=6) whereas safety and data issues were commonly raised by CADTH (n=5), SMC (n=3 total number of uncertainties across nine appraisals) and HAS (n=3).
- Uncertainties related to the economic evidence were divided in two broad categories: first, uncertainties around the economic model were most commonly raised by NICE (n=52 uncertainties across nine appraisals); CADTH (n=21 uncertainties across five appraisals); SMC (n=24 total number of uncertainties across seven appraisals) and TLV (n= 9 uncertainties across eight appraisals). The uncertainties most frequently raised across all the agencies related to the clinical assumptions in the evidence. Other types of uncertainties included, for example, the type of modelling, type of costs, type of effects, and possible variation in the ICER. (Appendix Figure 5). Second, uncertainties raised around the clinical evidence used for the economic evaluation were more frequently raised by NICE, TLV and CADTH. The three agencies included uncertainties around the estimates of clinical benefit (e.g. if the benefits of oral treatment were captured by the dimethyl fumarate model) followed by concerns around the study comparators or other factors such as the comparator used, the conduct and design of the trial, etc**.** (Appendix Figure 6).

6.2.6 Stakeholder input

Input from external stakeholders played an important role in shaping the HTA assessments across HTA bodies. In particular, when looking at both the interpretation of the evidence (see "clinical uncertainties") and the "other considerations " criteria, their input was reported 183 times (across all the appraisals examined in the 6 countries). With the exception of HAS and IQWIG where there is no clear presence of any external stakeholder opinion, the stakeholder input was considered across agencies in England, Scotland, Sweden and Canada. In 67% of cases (n=123) the HTA assessments considered input from clinical experts, in 20% (n=37) from PWMS, and 13% (n=24) from non-specified experts.

6.2.7 Time lag between regulatory approval and HTA completion

The time between a medicine receiving regulatory approval and the completion of an assessment was similar for HTA assessments conducted by TLV, HAS and SMC (the lag times are 61.5 months, 54 months, and 58 months, respectively). The median lag time for NICE was 21 months[q] whereas for IQWIG it was 6.6 months (Appendix Table 7).

6.2.8 Other considerations

A series of additional elements (considerations) were identified and considered across HTA assessments, beyond the clinical, safety and economic evidence. Their impact on the final decision was reviewed and they were classified into two main categories: first, elements related to the disease and second, elements related to the treatment. Overall 142 "other considerations" were identified across a total of 26 health technology assessments; 51% of other considerations (n= 72) related to disease characteristics, whereas 49% (n=70) covered treatment characteristics. The most common considerations related to the disease raised by all agencies included: the nature of the disease affecting the individual (77% of the HTA assessments); and the financial and emotional burden created by the disease on the family and their caregivers (65%). NICE and CADTH raised particular concerns on the ability to work (64% and 58%, respectively) and the financial burden created by the disease (61% and 60%, respectively). Other considerations related to the treatment characteristics included: adverse events of the treatment alternatives and the possible advantages from new oral medicines.

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q Please note that time lapse between marketing authorisation and completion of the HTA appraisal was longer for interferons (2002), whereas for the other DMTs (from 2006 onwards) the appraisal system changed and the time lags decreased. More details are in appendix 12.

7. Using primary and secondary evidence to inform policy change in MS

7.1 What the PWMS and caregiver surveys suggest about policy change in MS

7.1.1 Estimating and comparing the costs, HRQoL and experience reported by PWMS and caregivers across settings

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 HRQoL/experience of care when novel DMTs are available in clinical practice. The evidence collected covered the following key issues:

Experience of MS treatment with DMTs

The majority of PWMS had experience of MS treatment with DMTs from the start of their treatment; slightly more than half of the PWMS were currently receiving DMTs. Results were comparable with a similar survey conducted in the USA[70].

Starting treatment early at the point of clinical diagnosis

PWMS are aware of the potential side effects of treatments and may prefer to delay possible risks as much as possible; however when they discuss the irreversible effect of MS on brain volume and the attached disabilities with their clinician they may opt for an early intervention.

Sharing information with the PWMS

It is important from the outset to give patients accurate information on what to expect from treatment, including the evidence that DMT efficacy can be only partial, moderate and non-curative (Association of British Neurologists 2015)[56]. Patients should also discuss the potential risk as well as expected benefit of treatment; monitoring requirements; possible future disabilities; and work, family and other factors that are personally important. Clinicians should take account of their views when recommending a personalised treatment selection. More research is needed to further investigate stakeholder views on changing MS management practices to include early intervention.

Experiences of MS-management

The primary care data analysis of the clinician survey gave the opportunity to compare PWMS and clinician experiences of MS-management, to identify whether their views on MS management are aligned with patients' and to explore the factors that influence these views. 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 and other stakeholders recognise that this should be strongly promoted given the derived health benefits to the PWMS and their increased satisfaction[71].

The preferred source of information for PWMS

The preferred source of information for PWMS is the internet (MS-specific sites as well as social media or support group sites) and clinicians; this is also confirmed in the literature[58,70]. Whether a person is newly-diagnosed or has had MS for a long time, information available from the media (particularly social media) can be overwhelming, and many PWMS may be unsure of where to look for the information they need. While the Internet can be a vast source of information about MS, it can also be a source of inaccurate, biased, or confusing information. It is important that people can filter the content as needed and patient organisations have an important role to play in providing information to support shared decision making, including conveying the importance of early treatment[1].

Economic burden of the disease (tangible costs)

Total average annual PWMS costs were €40,313. Just over half of total average costs (€20,631) were associated with direct medical costs (medicines, consultations with a specialist, hospitalisations), followed by indirect costs such as loss of productivity (€16,061) and direct non-medical costs (€2,127), which reflect caregiver costs. The proportion of indirect costs became more significant as the level of disability increased. Results from similar surveys with PWMS conducted in Europe and elsewhere[63,72] reported comparable total costs across countries, although medication costs contributed a smaller

proportion compared with the results presented here. Crucially, previous surveys did not account for expensive pharmacological developments in MS management such as dimethyl fumarate, fingolomid and alemtuzumab.

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 SPMS were characterised by increased total costs (€48,000) where indirect costs accounted for the majority (about 65%) compared with RRMS (about €41,000) where indirect costs accounted for about 36%. Results were similar to international evidence in the literature[62,73].

Socio economic burden of the disease on PWMS (intangible costs)

The average utility value reported was 0.60 (60% of perfect health) based on EQ-5D-5L, with a loss of 25% compared with the general population. Utilities varied across healthcare systems (USA as well as Germany reported greater levels compared with other countries) and types of MS. Comparable estimates were found elsewhere[8,72].

Greater values in utility were accompanied by lower disability and increased satisfaction values with the healthcare service received. However in a few country settings (e.g. France and Romania) lower levels of disability and increased satisfaction with the healthcare service were accompanied by a noticeable decrease in utility compared with the general population. It can be argued that other health state factors beyond EQ-5D-5L[63] are (more) important to PWMS. If their improvement is missed by EQ-5D-5L this can be showcased by other indicators (increased satisfaction with the service and decreased disability).

Valuing health outcomes beyond EQ-5D-5L

If the clinical focus for MS has relied heavily on the measurement of disability, more recently the importance of MS outcome assessment from the perspective of the individual with MS has been recognized[74]. Patient relevant outcome measures (PROMs) include information provided by the individual that reflects their functioning health and well-being from their perspective, including how the disease and medical interventions impact on their quality of life. The diverse subjective symptoms associated with loss of quality of life are difficult to quantify, hence discrepancies arise between the perceptions of PWMS and their physicians concerning which domains of health are the most important.

The challenge of using generic measures of quality of life in people with a specific health condition such as MS is recognised as they may not capture all of the domains that are impacted by the condition. If important domains are missing from the generic measures, the value derived will be higher than the real impact creating invalid comparisons across interventions and populations. Integrating PROMs into clinical practice has the potential to capture those benefits and understand them better. Results from the survey reported fatigue and weakness, bladder or balance problems as the most frequently reported factors that changed over the course of their illness. Respondents stated also that their change had a significant impact on their life and believed a new MS treatment should keep them under control. Evidence from the literature[75] showed that MS-related complications, typically severe urinary tract infections, constipation, fractures and falls (due to increased weakness and fatigue), and pressure sores are major reasons for hospital admissions with important socioeconomic consequences. This highlights the importance of identifying the most appropriate utility measure to be adopted.

Socio economic burden of MS on caregivers

While sampling issues prevented the production of robust results on caregiving, the findings may provide a preliminary understanding of the differences in socioeconomic burden between PWMS and their caregivers. The total annual indirect costs related to productivity loss for caregivers were about €31,000, almost double those reported by PWMS (€16,000).

7.1.2 Exploring the impact that a paradigm shift in the management of MS could have on health outcomes and resource utilisation

The primary analysis of the PWMS allowed an exploration of the economic impact of introducing earlier interventions in the disease pathway. 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. 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[52,56,76,77]. 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 (€38,185 vs. €42,058), indirect (€15,390 vs. €18,521) and DMT (€18,942

vs. €20,044) costs and a higher VAS score (65 vs. 62) compared to those receiving late treatment, although these differences were not statistically significant (p>0.05). Reflecting on our study sample, even though our results suggest that a shift towards early treatment had comparable effects to late treatment in terms of overall costs and health outcomes, a larger sample of respondents followed over time would be needed to generate more robust conclusions on the long-term socioeconomic impact of early DMT initiation. Importantly, using real world data on a larger scale across international settings would be crucial to better understand the impact of a paradigm shift in the management of MS on long-term productivity loss in different healthcare systems. This could also provide robust results to inform country specific, as well as international, policy developments. Healthcare systems need to be able to respond dynamically as new evidence emerges on the diagnosis and treatment of MS, along with more evidence on the psychosocial support requirements for PWMS, and the long-term economic evidence on the impact of MS.

7.1.3 Using the economic and socioeconomic data from this to create a health benefit design package for PWMS in the countries of interest

Value-based benefit design (VBBD)[78] advocates better alignment between copayment and clinical value. The rationale behind VBBD is that many valuable treatments for chronic illnesses, such as MS medications, are often used sub-optimally, potentially leading to undesirable outcomes such as an increase in complications and avoidable hospitalizations (e.g. falls, urinary tract infections). Copayment should be reduced to improve clinical outcomes for high-value therapy such as DMTs. In the long run, the improved clinical outcomes may translate into cost savings in terms of reduction in hospitalization events, disabilities, absenteeism, presenteeism, and overall direct and indirect costs[79,80]. Direct and socioeconomic cost data from the PWMS survey can be used to inform policy change in the way a health care system views a debilitating chronic disease such as MS.

7.2 What the Clinician survey suggests about policy change in MS

The primary analysis of the PWMS and clinician data sets provided evidence on whether the views of PWMS and treating physicians are aligned on MS management and allowed the exploration of factors which influence these views.

7.2.1 Diagnosis and treatment

Both PWMS and clinicians reported that PWMS experience a first symptom of MS at about 20-30 years, whereas they receive formal diagnosis of MS at 30-40 years old. Mixed views were reported when commenting on the delay between first symptoms and diagnosis (1 year for the clinicians vs. 5 years for PWMS) and the delay between diagnosis and treatment with DMTs (2 months vs. 2 years, respectively). When looking at treatment management, about 75% of the clinicians were treating their patients with oral DMTs whereas only 55% of the PWMS reported that they were treated with DMTs. Current clinical guidance suggests that some clinicians may consider starting DMT treatment for individuals within 12 months after first symptoms if MRI establishes evidence of MS diagnosis (2010 McDonald criteria)[21]. However factors such as poor rates of clinician adherence to treatment guidelines, relative lack of available neurologists and low treatment affordabilitymay explain the longer delays in access to treatment as reported by PWMS[58].

When choosing a DMT, the most important attributes for clinicians are effectiveness, safety and tolerability (and they believed that similar aspects drove PWMS' decisions). PWMS, on the other hand, placed greater value on convenience, doctor's advice and safety. Responses showed that safety and efficiency data may be valued by clinicians and PWMS in their choice of treatment. A lack of long-term safety and efficacy data for the newer DMTs may have led to conservatism among some clinicians and PWMS regarding initiating treatment with a DMT[1].

7.2.2 When treatment should be started

In line with current guidance about 92% (11) of clinicians did not consider starting treatment with DMTs in a person with a normal MRI as they considered it unnecessary at that stage. They would consider starting treatment with DMTs only in the presence of brain lesions, optic neuritis or severe initial relapse. The PWMS had mixed views on the matter; for example, they were aware of the side effects of treatments and preferred to delay possible risks as much as possible; but they were also knowledgeable about the irreversible effect of MS on brain volume and the attached disabilities. The individual personal circumstances, variability in access to relevant information on MS and individual involvement in the decision making process appeared to be the driving factors in MS management. Those factors may give reasons for promoting joint decision for both patients and clinicians [1].

7.3 What does the analysis of HTAs suggest about policy change in MS

Evidence from the analysis of HTA assessments showed that input from external stakeholders is already part of the HTA decision making in different country settings. Stakeholder input from patient associations was more commonly considered by NICE compared to other HTA agencies. Key stakeholders should be actively engaged by those conducting HTAs, and have their views reflected in the HTA process[81]. The key messages extrapolated from the evidence included the following:

- **There is a need for a standardized approach when including PWMS' views in HTA decision making.** Given that MS is a disease that can have a profound impact on the HRQoL of PWMS, the HTA bodies should pay particular attention in their assessments on the HRQoL factors. The HTAi Interest Group on Patient and Citizen Involvement in HTA (PCIG) has developed a patient group submission template that is available for people to use[82].
- **Greater homogeneity across HTA bodies is needed when taking into account HRQoL elements.**
- **Health gain and quality of life data should take account of dimensions that patients say have a significant impact on their daily lives; many of these items are not captured by the generic tools (e.g. EQ-5D-5L) often used by HTA agencies internationally.**
- **There is a need for standardized approaches when including "other factors" in HTA decision making and a wide range of evidence and outcomes must be considered.** A wide array of considerations and assessments related to the clinical and economic evidence are considered in HTA assessments across case studies and DMTs of interest. Appropriate guidelines and systematic approaches to evidence synthesis and analysis during an HTA assessment is important, particularly when more complex statistical and methodological techniques are used to address gaps in the available data for a technology[81]. HTA assessments should take account of the items patients say have a significant impact on their daily lives; however, many of these items are not captured by generic tools such as the EQ-5D-5L questionnaire.
- **Moving beyond HTAs and leveraging the potential of risk-sharing to improve cost-effectiveness and affordability.** HTA assessments can have a substantive impact on access to DMTs for PWMS. Specifically for England and Scotland, fingolimod was originally not recommended by NICE and SMC, respectively, and the decision was only reversed after a patient access scheme was introduced. This data is confirmed by the literature[6].
- **Discussion on an earlier use of DMTs to reduce accumulation of irreversible long term damage and decrease socioeconomic burden is missing from HTA assessment.** The lack of real world data on the clinical and economic benefits of the technology is a key issue commonly reported by HTA bodies[81]. The literature on MS management reported a lack of evidence on long term clinical and economic benefit of DMTs as these treatments have only recently been introduced into clinical practice and the collection of such data is currently under way.
- **HTA assessments should be conducted in a timely manner.** The collection of long-term benefit of DMTs using real world evidence is a necessary step forward and currently underway but should not inflict unwanted delays to HTA decision-making.

8. The way forward for MS management: achieving better outcomes for PWMS

MS is associated with a high cost of illness, both in terms of direct and indirect costs. Given that the onset of MS is generally in early adult life and the disease lasts over an individual's lifetime, there are huge costs relating to productivity losses. In addition, there is a clear deterioration in health outcomes of PWMS and their caregivers in comparison to the healthy population, with impact potentially increasing in line with the severity of the disease. The primary data analysis from this study expanded previous knowledge on the socioeconomic burden and health related quality of life (HRQoL) of PWMS and their caregivers across country settings. Results confirmed that there is an urgent need to achieve better outcomes for people with MS and 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.

8.1 Improve the quality of care and health outcomes for every person with MS: Diagnosis, treatment and management goals should be set to provide the best health outcome for every person with MS

8.1.1 Early diagnosis and treatment

Although it seems entirely plausible that early diagnosis and treatment with DMTs would help reduce relapse rates and MRI lesion accumulation and, therefore, would favourably influence the long-term prognosis, they have been only recently introduced in MS management and there are no published and peer-reviewed controlled trial results showing long-term benefit. **Therefore, the harmonised collection of real world data with the support of national registries is urgently needed; analysis of this data will allow clarification of the benefit of early diagnosis and treatment with DMTs on long-term outcomes.**

8.1.2 More intense monitoring regimens should be routinely available in practice

Understanding of MS disease activity has developed significantly over the past 15 years. This can largely be attributed to improved use of MRI scanning, which provides a more sensitive tool for identifying inflammatory damage in MS. MRI is an effective way of capturing disease activity early and it is increasingly used in practice; this was confirmed by the clinicians participating in this study. Ongoing debate also considers the use of MRI to monitor disease activity in patients on DMTs. Current recommendations on 'treating to target' mean 'treat until no evidence of disease activity is reached', including no relapses, no increase in disability and no new or active (enhancing) lesions on patients' MRI scans. Meeting this objective implies regular monitoring of not only clinical relapse and disability progression, but also MRI activity. Regular use of MRI to monitor disease activity and the effects of treatment is still not common practice (for example see the UK[1]), though it is increasingly used as an outcome measure for clinical trials and the sample of clinicians interviewed confirmed that MRI is routinely available in their practice across different country settings. **Therefore, more research is needed to measure the effectiveness of more intense monitoring with more frequent MRI scans. Updated and internationally comparable evidence on the use of diagnostic imaging as a means of capturing disease activity should be generated as a priority. Registry data should be amended to allow for collection and use of standardised information on MRI use across countries to better monitor diagnosis and treatment goals across settings.**

8.1.3 MS management

Current clinical guidance suggests that some clinicians may consider starting DMT treatment for individuals within 12 months after first symptoms appear if MRI establishes evidence of MS diagnosis (2010 McDonald criteria) [21]. In this report the majority of the clinicians interviewed were treating their patients with oral DMTs whereas only half the PWMS reported that they were treated with DMTs. There seem to be a number of barriers in accessing treatment, for example, delays in diagnosis, lack of available neurologists, poor adherence to clinical guidelines by clinicians and problems with DMT reimbursement by a number of national health systems. Although the incidence and intensity of these barriers is not the

same across settings, they reflect the PWMS views reported in this paper. Given perceived uncertainties around efficacy, risk and tolerability, limitations in prescribing guidelines and access to treatment, the treatment decision is quite often "no treatment". For example in UK there is a preference to "wait and see", with less frequent prescribing compared to other countries, particularly early in the disease course[83].

PWMS mentioned that they were aware of the side effects of individual treatments and preferred to delay potential risks as much as possible; but they were also knowledgeable about the irreversible effect of MS on brain volume and the attached disabilities. **The individual personal circumstances, variability in access to relevant information on MS and individual involvement in the decision making process appeared to be the driving factors in MS management and shared decision making may be more satisfactory for both patients and clinicians. Health systems should involve more actively PWMS in decisions about their disease management.**

8.1.4 Better evaluation of the health outcomes for PWMS and their caregivers

The use of generic measures of utility such as EQ-5D-5L in people with MS does not capture all of the domains that are impacted by the condition. The primary data from PWMS presented in the report sought to address this issue and to evaluate which health status aspects are particularly important to PWMS beyond EQ-5D-5L. Many of these items (e.g. fatigue and weakness, balance and dizziness, or bladder problems) are not captured by the generic tools (e.g. EQ-5D-5L) often used by HTA agencies internationally.

There is some evidence in the literature and from our analysis that the socioeconomic burden and distress on caregivers is substantial, and it varies by the PWMS' level of disability, but more robust evidence is needed to elucidate the full impact of MS on caregivers and the overall family across countries. **Given that MS is a disease that can have a profound impact on the HRQoL of both PWMS and their caregivers, the HTA bodies should pay particular attention in their assessments on the HRQoL factors and consider a wider range of evidence and outcomes beyond EQ-5D for PWMS.**

8.2 (Further) robust evidence should be generated and used in order to make appropriate decisions about care management MS strategies

8.2.1 MS registries

MS registries act as a powerful instrument for population level measurements of disease specific characteristics, long-term benefits of DMTs and dissemination of information about treatments and services in a given region. Unfortunately, most of the registries do not collect harmonised epidemiological, clinical, economic and utility data on PWMS across countries. This lack of data can affect the quality of the evidence available and possible estimation of the impact of management strategies on economic and health outcomes. For example, in the UK, there is no complete national registry of people with MS[18], whereas in Germany and Sweden databases exist which cover more than 90% of the MS population[19]. The European Register for Multiple Sclerosis (EUReMS) demonstrated that international MS data collection is possible and has the potential to lead to better outcomes for those living with multiple sclerosis in Europe[107]. **More robust epidemiological, clinical and disease management data are needed internationally to inform better decisions for priority setting and healthcare policy in MS.**

8.2.2 HTA evidence

Key stakeholders should be actively engaged by those conducting HTAs in order to understand stakeholder perspectives on the HTA process. Health gain and quality of life data should take account of dimensions that patients say have a significant impact on their daily lives; many of these items are not captured by generic tools often used by HTA agencies internationally (e.g. EQ-5D-5L questionnaire). **There is a need for a standardized approach when including PWMS' views in HTA decision-making** and **assessments should take account of dimensions that patients say have a significant impact on their daily lives.**

Greater consistency is needed in collecting economic data and evaluating the economic impact of MS to ensure that comparisons across settings can be made. **Health gain and quality of life data in HTA assessments should incorporate appropriate standardized methods for economic evaluations and grading evidence.**

8.3 Increase responsiveness of health care systems to new evidence on MS

Although guidelines for MS management are available at local and international levels there is still limited **use of standardized protocols** across settings and this has been confirmed by the clinicians participating in this study. **Widespread adoption of current guidelines would avoid inappropriate variations in eligibility for DMT initiation across local settings84 and strengthen diagnosis, treatment and monitoring. Finally, a reward system should be in place across healthcare systems to improve clinical practice (quality of care and health outcomes) and incorporate updated harmonised evidence on MS management (available from MS registries) into health care decision-making.**

9. References

1. MS Society Time to Act – September 2015. A consensus on early treatment.
2. Dutta R, Trapp BD. Pathogenesis of axonal and neuronal damage in multiple sclerosis. *Neurology.* 2007;68(22 Suppl 3):S43-54.
3. Scalfari A, Neuhaus A, Daumer M, Muraro PA, Ebers GC. Onset of secondary progressive phase and long-term evolution of multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2014;85(1):67-75.
4. Leray E, Yaouanq J, Le Page E, et al. Evidence for a two-stage disability progression in multiple sclerosis. *Brain.* 2010;133(Pt 7):1900-1913.
5. Warren S WKGWHO, 2001. Multiple Sclerosis. ISBN: 92-4-156203-X. 2001.
6. Wilsdon T., Barron A., Mitchell-Heggs A., Ginoza S. Access to medicines for multiple sclerosis: Challenges and opportunities. Charles Rivers Associates, February 2014. Available online at: http://www.crai.co.uk/sites/default/files/publications/CRA-Biogen-Access-to-MS-Treatment-Final-Report.pdf.
7. Kobelt and Kasteng. Access to innovative treatments in multiple sclerosis in Europe, a report prepared for the European Federation of Pharmaceutical Industry Associations (EFPIA). 2009. Available at: http://www.comparatorreports.se/Access%20to%20MS%20treatments%20-%20October%202009.pdf
8. Trisolini M HA, Wiener J, Lesesne S. Global Economic Impact of Multiple Sclerosis. *Multiple Sclerosis International Federation UK, London, United Kingdom.* 2010.
9. Goodin DS, Frohman EM, Garmany GP, Jr., et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology.* 2002;58(2):169-178.
10. Tremlett H, Yousefi M, Devonshire V, Rieckmann P, Zhao Y. Impact of multiple sclerosis relapses on progression diminishes with time. *Neurology.* 2009;73(20):1616-1623.
11. Fox RJ, Hersh CM. Multiple sclerosis. Cleveland Clinic Disease Management Project. The Cleveland Clinic Foundation. Published June 2014. http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/neurology/multsclerosis/multsclerosis.htm. Accessed April 29, 2015.
12. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology.* 2014;83(3):278-286.
13. Goodin DS, Reder AT, Ebers GC, et al. Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFNbeta-1b trial. *Neurology.* 2012;78(17):1315-1322.
14. Mackenzie IS, Morant SV, Bloomfield GA, MacDonald TM, O'Riordan J. Incidence and prevalence of multiple sclerosis in the UK 1990-2010: a descriptive study in the General Practice Research Database. *J Neurol Neurosurg Psychiatry.* 2014;85(1):76-84.
15. Hoer A, Schiffhorst G, Zimmermann A, et al. Multiple sclerosis in Germany: data analysis of administrative prevalence and healthcare delivery in the statutory health system. *BMC Health Serv Res.* 2014;14(381):1472-6963.
16. Kingwell E, Marriott JJ, Jette N, et al. Incidence and prevalence of multiple sclerosis in Europe: a systematic review. *BMC Neurol.* 2013;13(128):1471-2377.
17. Pugliatti M, Rosati G, Carton H, et al. The epidemiology of multiple sclerosis in Europe. *Eur J Neurol.* 2006;13(7):700-722.
18. Trust. M. A to Z of MS. Types of MS. *Available online at http://www.nationalmssociety.org/What-is-MS/Types-of-MSPrevalence and incidence of multiple sclerosis http://www.mstrust.org.uk/atoz/prevalence_incidence.jsp..* 2013. Accessed February 20, 2015..
19. MSIF. The Atlas of MS 2013, Mapping multiple sclerosis around the world. Available at http://www.atlasofms.org/./ 2013.
20. Finkelsztejn A, Gabbai AA, Fragoso YD, et al. Latin American algorithm for treatment of relapsing-remitting multiple sclerosis using disease-modifying agents. *Arq Neuropsiquiatr.* 2012;70(10):799-806.
21. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol.* 2011;69(2):292-302.
22. Cutter GR, Zimmerman J, Salter AR, et al. Causes of death among persons with multiple sclerosis. *Mult Scler Relat Disord.* 2015;4(5):484-490.
23. Shirani A, Zhao Y, Karim ME, et al. Association between use of interferon beta and progression of disability in patients with relapsing-remitting multiple sclerosis. *Jama.* 2012;308(3):247-256.
24. Giovannoni. blog (http://multiple-sclerosis-research.blogspot.com/2015/06/early-intervention-in-ms.html). 2015
25. Banwell B, Giovannoni G, Hawkes C, Lublin F. *Editors' welcome and a working definition for a multiple sclerosis cure.* Mult Scler Relat Disord. 2013 Apr;2(2):65-7. doi: 10.1016/j.msard.2012.12.001. Epub 2013 Jan 21.
26. J.M. WHLaS. Multiple Sclerosis: Diagnosis and Therapy. *Wiley-Blackwell by John Wiley & Sons.* 2012.
27. Kappos L, Antel J, Comi G, et al. Oral fingolimod (FTY720) for relapsing multiple sclerosis. *N Engl J Med.* 2006;355(11):1124-1140.

28. O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med.* 2011;365(14):1293-1303.
29. Kappos L, Gold R, Miller DH, et al. Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. *Lancet.* 2008;372(9648):1463-1472.
30. Goodin DS, Bates D. Treatment of early multiple sclerosis: the value of treatment initiation after a first clinical episode. *Mult Scler.* 2009;15(10):1175-1182.
31. Kappos L, Freedman MS, Polman CH, et al. Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study. *Lancet.* 2007;370(9585):389-397.
32. Johnson KP, Brooks BR, Ford CC, et al. Glatiramer acetate (Copaxone): comparison of continuous versus delayed therapy in a six-year organized multiple sclerosis trial. *Mult Scler.* 2003;9(6):585-591.
33. Comi G. Clinically isolated syndrome: the rationale for early treatment. *Nat Clin Pract Neurol.* 2008;4(5):234-235.
34. Jacobs LD, Beck RW, Simon JH, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. *N Engl J Med.* 2000;343(13):898-904.
35. Comi G, De Stefano N, Freedman MS, et al. Comparison of two dosing frequencies of subcutaneous interferon beta-1a in patients with a first clinical demyelinating event suggestive of multiple sclerosis (REFLEX): a phase 3 randomised controlled trial. *Lancet Neurol.* 2012;11(1):33-41.
36. Comi G, Filippi M, Barkhof F, et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. *Lancet.* 2001;357(9268):1576-1582.
37. Comi G, Martinelli V, Rodegher M, et al. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2009;374(9700):1503-1511.
38. Jeffrey. TOPIC: Teriflunomide delays clinically definite MS. www.medscape.com/viewarticle/803177. 2013.
39. Gold R, Wolinsky JS, Amato MP, Comi G. Evolving expectations around early management of multiple sclerosis. *Ther Adv Neurol Disord.* 2010;3(6):351-367.
40. Filippi M, Rovaris M, Inglese M, et al. Interferon beta-1a for brain tissue loss in patients at presentation with syndromes suggestive of multiple sclerosis: a randomised, double-blind, placebo-controlled trial. *Lancet.* 2004;364(9444):1489-1496.
41. Rieckmann P. Neurodegeneration and clinical relevance for early treatment in multiple sclerosis. *Int MS J.* 2005;12(2):42-51.
42. Gout O, Lebrun-Frenay C, Labauge P, Le Page GE, Clavelou P, Allouche S. Prior suggestive symptoms in one-third of patients consulting for a "first" demyelinating event. *J Neurol Neurosurg Psychiatry.* 2011;82(3):323-325.
43. Putzki N, Fischer J, Gottwald K, et al. Quality of life in 1000 patients with early relapsing-remitting multiple sclerosis. *Eur J Neurol.* 2009;16(6):713-720.
44. Salter AR, Cutter GR, Tyry T, Marrie RA, Vollmer T. Impact of loss of mobility on instrumental activities of daily living and socioeconomic status in patients with MS. *Curr Med Res Opin.* 2010;26(2):493-500.
45. Scott TF, Schramke CJ. Poor recovery after the first two attacks of multiple sclerosis is associated with poor outcome five years later. *J Neurol Sci.* 2010;292(1-2):52-56.
46. Fernandez O, Fernandez V, Arbizu T, et al. Characteristics of multiple sclerosis at onset and delay of diagnosis and treatment in Spain (the Novo Study). *J Neurol.* 2010;257(9):1500-1507.
47. Kingwell E, Leung AL, Roger E, Duquette P, Rieckmann P, Tremlett H. Factors associated with delay to medical recognition in two Canadian multiple sclerosis cohorts. *J Neurol Sci.* 2010;292(1-2):57-62.
48. Kelly SB, Chaila E, Kinsella K, et al. Multiple sclerosis, from referral to confirmed diagnosis: an audit of clinical practice. *Mult Scler.* 2011;17(8):1017-1021.
49. Miller RM, Happe LE, Meyer KL, Spear RJ. Approaches to the management of agents used for the treatment of multiple sclerosis: consensus statements from a panel of U.S. managed care pharmacists and physicians. *J Manag Care Pharm.* 2012;18(1):54-62.
50. Giovannoni G, Nath A. *After the storm: neurofilament levels as a surrogate endpoint for neuroaxonal damage.* Neurology. 2011 Apr 5;76(14):1200-1. doi: 10.1212/WNL.0b013e3182143345. Epub 2011 Feb 23.
51. Giovannoni G. Cerebrospinal fluid neurofilament: the biomarker that will resuscitate the 'Spinal Tap'. *Mult Scler.* 2010;16(3):285-286.
52. Castrop F, Haslinger B, Hemmer B, Buck D. Review of the pharmacoeconomics of early treatment of multiple sclerosis using interferon beta. *Neuropsychiatr Dis Treat.* 2013;9:1339-1349.
53. http://www.euroqol.org/.
54. Collin C, Wade DT, Davies S, Horne V, The Barthel Index, Disability and Rehabilitation 2008, 10:2 61-63.
55. Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. *Gerontologist.* 1980;20(6):649-655.

56. Scolding N, Barnes D, Cader S, et al. Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. *Pract Neurol.* 2015;15(4):273-279.

57. Nicod E, Kanavos P. Developing an evidence-based methodological framework to systematically compare HTA coverage decisions: A mixed methods study. *Health Policy.* 2016;120(1):35-45.

58. Holloway E, Redford-Totts D (MS Society). Right Treatment, right time? How people with MS make decisions about disease modifying drugs http://www.treatmerightms.org.uk/wp-content/ uploads/2014/04/Right-treatment-right-time.pdf.

59. Giovannoni G. Any evident MRI T2-lesion activity should guide change of therapy in multiple sclerosis—yes. *Mult Scler.* 2015;21(2):134-136.

60. Giovannoni G, Nath A. After the storm: neurofilament levels as a surrogate endpoint for neuroaxonal damage. *Neurology.* 2011;76(14):1200-1201.

61. WHO. Worl Health Organization. Health statistics and information systems database, Disease burden, Available via http://www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html.

62. Ashaye. Multiple Sclerosis and Variation in Health Utilities: A Systematic Review of the Literature. *Conference: 2014 Joint ACTRIMS-ECTRIMS Meeting, At Boston, Massachusetts USA,.* 2014.

63. Kobelt G, Berg J, Lindgren P, Fredrikson S, Jonsson B. Costs and quality of life of patients with multiple sclerosis in Europe. *J Neurol Neurosurg Psychiatry.* 2006;77(8):918-926.

64. Adelman G, Rane SG, Villa KF. The cost burden of multiple sclerosis in the United States: a systematic review of the literature. *J Med Econ.* 2013;16(5):639-647.

65. Kolasa K. How much is the cost of multiple sclerosis—systematic literature review. *Przegl Epidemiol.* 2013;67(1):75-79.

66. Pike. Poster from the 1st European Academy of Neurology (EAN) Congress, Berlin June 2015 (http://www.eaneurology.org/berlin2015/uploads/media/Biogen.pdf). 2015.

67. Naoshy. Poster from the 1st European Acadmy of Neurology Congress, Berlin June 2015

68. Sidovar MF, Limone BL, Lee S, Coleman CI. Mapping the 12-item multiple sclerosis walking scale to the EuroQol 5-dimension index measure in North American multiple sclerosis patients. *BMJ Open.* 2013;3(5).

69. Goldman MD, Motl RW, Rudick RA. Possible clinical outcome measures for clinical trials in patients with multiple sclerosis. *Ther Adv Neurol Disord.* 2010;3(4):229-239.

70. Available at: http://multiplesclerosis.net/ms-in-america-2014/.

71. Available at: http://multiplesclerosis.net/ms-in-america-2014/.

72. Kobelt G, Berg J, Atherly D, Hadjimichael O. Costs and quality of life in multiple sclerosis: a cross-sectional study in the United States. *Neurology.* 2006;66(11):1696-1702.

73. Naci H, Fleurence R, Birt J, Duhig A. Economic burden of multiple sclerosis: a systematic review of the literature. *Pharmacoeconomics.* 2010;28(5):363-379.

74. Rieckmann P, Boyko A, Centonze D, et al. *Achieving patient engagement in multiple sclerosis: A perspective from the multiple sclerosis in the 21st Century Steering Group.* Mult Scler Relat Disord. 2015 May;4(3):202-218. doi: 10.1016/j.msard.2015.02.005. Epub 2015 Mar 2.; 2015.

75. Marrie RA, Elliott L, Marriott J, et al. Dramatically changing rates and reasons for hospitalization in multiple sclerosis. *Neurology.* 2014;83(10):929-937.

76. Broadley SA, Barnett MH, Boggild M, et al. A new era in the treatment of multiple sclerosis. *Med J Aust.* 2015;203(3):139-141.

77. Noyes K, Weinstock-Guttman B. Impact of diagnosis and early treatment on the course of multiple sclerosis. *Am J Manag Care.* 2013;19(17 Suppl):s321-331.

78. Chernew ME, Rosen AB, Fendrick AM. Value-based insurance design. *Health Aff.* 2007;26(2):30.

79. Mahoney JJ. Reducing patient drug acquisition costs can lower diabetes health claims. *Am J Manag Care.* 2005;11(5 Suppl):S170-176.

80. Goldman DP, Joyce GF, Karaca-Mandic P. Varying pharmacy benefits with clinical status: the case of cholesterol-lowering therapy. *Am J Manag Care.* 2006;12(1):21-28.

81. Available at: https://www.ispor.org/workpaper/International-survey-of-methods-used-in-HTA.pdf.

82. http://www.htai.org/interest-groups/patient-and-citizen-involvement.html Aa.

83. MS Society. A lottery of treatment and care – MS Services across England at the UK, 2013. Available at: http://mslottery.mssociety.org.uk/wpcontent/uploads/2013/04/UK-ms-lottery.pdf.

84. Pozzilli C, Romano S, Cannoni S. Epidemiology and current treatment of multiple sclerosis in Europe today. *J Rehabil Res Dev.* 2002;39(2):175-185.

85. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Ann Neurol.* 1996;39(3):285-294.

86. Group PPoRaDbIb-aSiMSS. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis.. *Lancet.* 1998;352(9139):1498-1504.

87. Paty DW, Li DK. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. UBC MS/MRI Study Group and the IFNB Multiple Sclerosis Study Group. *Neurology.* 1993;43(4):662-667.

88. Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. *Neurology.* 1995;45(7):1268-1276.

89. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med.* 2006;354(9):899-910.

90. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet.* 2012;380(9856):1819-1828.

91. O'Connor PW, Li D, Freedman MS, et al. A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. *Neurology.* 2006;66(6):894-900.

92. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med.* 2012;367(12):1098-1107.

93. Multiple sclerosis: management of multiple sclerosis in primary and secondary care. NICE 2014.

94. Multiple sclerosis study group [GRESEP]. Guidelines for the treatment of MS

95. Guidelines from The Italian Neurological and Neuroradiological Societies for the use of magnetic resonance imaging in daily life clinical practice of multiple sclerosis patients (2013). Neurol Sci. 2013.

96. Guidelines on the clinical use for the detection of neutralizing antibodies (NAbs) to IFN beta in multiple sclerosis therapy: report from the Italian Multiple Sclerosis Study group Neurol Sci. 2014.

97. Gold R, Oreja-Guevara C. Advances in the management of multiple sclerosis spasticity: multiple sclerosis spasticity guidelines. *Expert Rev Neurother.* 2013;13(12 Suppl):55-59.

98. German Association of Neurologists guidelines for the diagnosis and treatment of MS eurologie DGf: Diagnostik Und Therapie Der Multiplen Sklerose. Leitlinien Für Diagnostik Und Therapie in Der Neurologie. Stuttgart: Georg Thieme Verlag; 2013..

99. Freedman MS, Selchen D, Arnold DL, et al; Canadian Multiple Sclerosis Working Group. Treatment optimization in MS: Canadian MS Working Group updated recommendations. Can J Neurol Sci. 2013.

100. American Academy of Neurology Neurology 2014 available at https://www.aan.com.

101. European Academy of Neurology (European Federation of Neurological Societies) 2011.

102. Multiple sclerosis: EFNS guidelines on the use of imaging in multiple sclerosis: M. Filippi et al.; European handbook of neurological management: volume 1, 2nd edition. Edited by N. E. Gilhus, M. P. Barnes and M. Brainin. 2011 Blackwell Publishing Ltd.

103. Multiple sclerosis: EFNS guidelines on the use of anti-interferon beta antibody measurements in multiple sclerosis: P. S. Sørensen et al.; European handbook of neurological management: volume 1, 2nd edition. Edited by N. E. Gilhus, M. P. Barnes and M. Brainin. 2011 Blackwell Publishing Ltd..

104. Multiple sclerosis relapses: efns guidelines on acute relapses of multiple sclerosis: f. Sellebjerg et al.; European handbook of neurological management: volume 1, 2nd edition. Edited by N. E. Gilhus, M. P. Barnes and M. Brainin. 2011 Blackwell Publishing Ltd.

105. The European MS Platform's Code of Good Practice 2008 , 2010

106. Kantarci O, Wingerchuk D. Epidemiology and natural history of multiple sclerosis: new insights. *Curr Opin Neurol.* 2006;19(3):248-254.

107. The EUReMS project website, available from http://eurems.eu/index.php/project-backgroud.

10. Appendices

Appendix Table 1: Main DMTs – Platform therapies

Molecule name		Branded name	Introduced to market	Administration	Efficacy	Main side effects	Recommendations/indications from the literature
Interferons	interferon β-1a	Rebif (EMD Serono, Inc)	1998	Injectable (SC thrice weekly)	Reduction of 32% in RR, 37% in DP, 52% compared to placebo[85]	flu-like side-effects (myalgias, headache, malaise)	Active non aggressive RRMS (first line), SPMS with exacerbations, CIS
		Avonex (Biogen)	1996	Injectable (IM once weekly)	Reduction of 32% in RR, 31% in DP compared to placebo[86]		
	interferon β-1b	Betaferon (Bayer); Extavia (Novartis)	1993	Injectable (SC every other day)	Reduction of 34% in RR, 29% in DP compared to placebo[87]		
Glatiramer acetate (GA)		Copaxone (Teva Pharmaceuticals)	1996	Injectable (SC daily)	Reduction of 29% in RR, 12% in DP compared to placebo[88]	skin injection site reactions, lipoatrophy	

Appendix Table 2: Main DMTs – Non-platform therapies

Molecule name		Branded name	Introduced to market	Administration	Efficacy	Main side effects	Recommendations/indications from the literature
Infusion	Mitoxantrone	Novantrone (EMD Serono)	2000	Infusion at a hospital		Cardiotoxicity and leukemia	In US: active non aggressive RRMS (second line), SPMS with exacerbations
	Natalizumab	Tysabri (Biogen)	2004 (reintroduced 2006)	Infusion every 28 days	Reduction of 68% in RR, 42% in DP compared to placebo[89]	Progressive multifocal leukoencephalopathy (PML)	Active non aggressive RRMS (second line), aggressive RES MS
	Alemtuzumab	Lemtrada (Genzyme)	2012	Infusion twice yearly	Reduction of 50-55% in RR and 42% in DP compared to βIFNs[90]	Thrombocytopenic purpura (ITP), thyroid problems	Active non aggressive RRMS (first line)
Oral agents	Fingolimod	Gilenya (Novartis)	2010	Oral (once daily)	Reduction of 54% in RR, 30% in DP compared to placebo[27]	Bradycardia and atrioventricular block. Few cases of PML reported	Active non aggressive RRMS (second line), aggressive RES MS
	Teriflunomide	Aubagio (Genzyme)	2012	Oral (once daily)	Reduction of 30% in RR, 30% in DP compared to placebo[91]	Hepatic irritation and alopecia	Active non aggressive RRMS (first line)
	Dimethyl fumarate, (BG-12)	Tecfidera (Biogen)	2013	Oral (twice daily)	Reduction of 53% in RR, 38% in DP compared to placebo[92]	Flushing and gastrointestinal symptoms. Few cases of PML reported	Active non aggressive RRMS (first line)

SC= subcutaneous, IM=intramuscular, II= intravenous infusion, RR= relapse rate, DP=disability progression

Appendix Table 3: MS guidelines across country settings

Country	Country specific guideline	Reference
England	yes	Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis BMJ 2015[56] Multiple sclerosis: management of multiple sclerosis in primary and secondary care. NICE 2014[93]
France	yes	Multiple sclerosis study group [GRESEP]. Guidelines for the treatment of MS[94]
Sweden	no	See European guidance below
Italy	yes	Guidelines from The Italian Neurological and Neuroradiological Societies for the use of magnetic resonance imaging in daily life clinical practice of multiple sclerosis patients (2013). Neurol Sci. 2013[95] Guidelines on the clinical use for the detection of neutralizing antibodies (NAbs) to IFN beta in multiple sclerosis therapy: report from the Italian Multiple Sclerosis Study group Neurol Sci. 2014[96]
Germany	yes	Gold et al. Advances in the management of multiple sclerosis spasticity: multiple sclerosis spasticity guidelines. Expert Rev Neurother. 2013[97] German Association of Neurologists guidelines for the diagnosis and treatment of MS eurologie DGf: Diagnostik Und Therapie Der Multiplen Sklerose. Leitlinien Für Diagnostik Und Therapie in Der Neurologie. Stuttgart: Georg Thieme Verlag; 2013.[98]
Romania	no	See European guidance. The European MS Platform's Code of Good Practice
Canada	yes	Freedman MS, Selchen D, Arnold DL, et al; Canadian Multiple Sclerosis Working Group. Treatment optimization in MS: Canadian MS Working Group updated recommendations. Can J Neurol Sci. 2013[99]
USA	yes	American Academy of Neurology Neurology. 2014100 Summary of Evidence-Based Guideline: Complementary and Alternative Medicine in Multiple Sclerosis Assessment and Management of Psychiatric Disorders in Individuals with Multiple Sclerosis
European guidelines	yes	European Academy of Neurology (European Federation of Neurological Societies) 2011[101] Multiple sclerosis: EFNS guidelines on the use of imaging in multiple sclerosis: M. Filippi et al.; European handbook of neurological management: Volume 1, 2nd edition. Edited by N. E. Gilhus, M. P. Barnes and M. Brainin. 2011 Blackwell Publishing Ltd.[102] Multiple sclerosis: EFNS guidelines on the use of anti-interferon beta antibody measurements in multiple sclerosis: P. S. Sørensen et al.; European handbook of neurological management: Volume 1, 2nd edition. Edited by N. E. Gilhus, M. P. Barnes and M. Brainin. 2011 Blackwell Publishing Ltd.[103] Multiple sclerosis relapses: EFNS guidelines on acute relapses of multiple sclerosis: F. Sellebjerg et al.; European handbook of neurological management: Volume 1, 2nd edition. Edited by N. E. Gilhus, M. P. Barnes and M. Brainin. 2011 Blackwell Publishing Ltd.[104]
		The European MS Platform's Code of Good Practice 2008 , 2010[105]

Appendix Table 4: Total annual costs and utility per PWMS by country

Countries	Total direct medical costs Mean (SD)	Total direct non-medical costs Mean (SD)	Total indirect costs Mean (SD)	Total costs Mean (SD)	Utility (EQ-5D-5L)	Utility lost	Original data, publication date
UK (Euro, 2006 exchange rate)	**EDSS 0 – 3:** €4,577 (3,057) [£6,714 (4,484)] **EDSS 4 – 5:** €5,524 (3,594) [£8,101 (5,271)] **EDSS 6 – 8:** €4,131 (3,897) [£6,059 (5,716)]	**EDSS 0 – 3:** €1,304 (5,043) [£1,913 (7,396)] **EDSS 4 – 5:** €7,022 (8,303) [£10,299 (12,178)] **EDSS 6 – 8:** €28,121 (20,514) [£41,242 (30,086)]	**EDSS 0 – 3:** €2,191 (4,562) [£3,214 (6,691)] **EDSS 4 – 5:** €5,110 (6,184) [£7,494 (9,069)] **EDSS 6 – 8:** €7,989 (6,583) [£11,717 (9654)]	**EDSS 0 – 3:** €8,074 (9,060) [£11,841 (13,288)] **EDSS 4 – 5:** €17,656 (11,872) [£25,894 (17,411)] **EDSS 6 – 8:** €40,241 (23,479) [£59,018 (34,435)]	**EDSS 2.0:** 0.725 **EDSS 6.5**: 0.477	0.27	2006 data from [72] UK 2012 (£ 2009) from [61]
France (Euro)	**All:** €23,654 (32,494) **EDSS 0 – 3:** €11,806 (13,514) **EDSS 4 – 5:** €19,817(20,845) **EDSS 6 – 8:** €38,774 (44,518)		**All:** €20,730 (27,123) **EDSS 0 – 3:** €12,250 (22,541) **EDSS 4 – 5:** €24,306 (27,959) **EDSS 6 – 8:** €27,666 (28,698)	**All:** €44,384 (45,687)	**EDSS 0 – 3:** 0.686 (0.217) **EDSS 4 – 5:** 0.520 (0.238) **EDSS 6 – 8**: 0.333 (0.283)	0.28	2006 data from [72] France 2009 from [61]
Sweden (Euro)	**All:** €v15,186 (24,638)	**All:** €21,264 (45,056)	**All:** €17,151 (18,497)	**All:** €53,601 (58,108)	**EDSS 2.0:** 0.696 **EDSS 6.5:** 0.462	0.23	2006 data from [72] Sweden 2006 from [61]
Italy (Euro)	**EDSS 0 – 3:** €21,418 (13,719) **EDSS 4 – 5:** €30,507 (23,868) **EDSS 6 – 8:** €13,646 (21,141)	**EDSS 0 – 3:** €447 (2007) **EDSS 4 – 5:** €5634 (8,874) **EDSS 6 – 8:** €15,826 (10,260)	**EDSS 0 – 3:** €596 (2,737) **EDSS 4 – 5:** €5,185 (8,134) **EDSS 6 – 8:** €10,120 (11,686)	**EDSS 0 – 3:** €22,461 (13,799) **EDSS 4 – 5:** €41,327 (31,263) **EDSS 6 – 8:** €39,592 (37,785)	**EDSS 2.0:** 0.677 **EDSS 6.5:** 0.477	0.31	2006 data from [72] Italy 2012 (Euro 2009) from [61]

Appendix Table 4: Total annual costs and utility per PWMS by country (continued)

Countries	Total direct medical costs Mean (SD)	Total direct non-medical costs Mean (SD)	Total indirect costs Mean (SD)	Total costs Mean (SD)	Utility (EQ-5D-5L)	Utility lost	Original data, publication date
Germany (Euro)	**EDSS 0 – 3:** €16,954 (9,886) **EDSS 4 – 5:** €17,841 (12,458) **EDSS 6 – 8:** €30,348 (24,911)	**EDSS 0 – 3:** €1,163 (3,629) **EDSS 4 – 5:** €12,373 (21,513) **EDSS 6 – 8:** €22,926 (16,515)	**EDSS 0 – 3:** €3,057 (8,938) **EDSS 4 – 5:** €9710 (15,789) **EDSS 6 – 8:** €10,996 (16,940)	**EDSS 0 – 3:** €21,174 (16,287) **EDSS 4 – 5:** €39,923 (33,335) **EDSS 6 – 8:** €64,270 (15,472)	**EDSS 2.0:** 0.721 **EDSS 6.5:** 0.440	0.2	2006 data from [72] 2012 (Euro 2009) from [61]
Canada (Euro, 2012 exchange rate)	**EDSS 0 – 3:** €25,476 (62,182) [CAN$ 19,837 (48,419)] **EDSS 4 – 6.5:** €18,054 (15,421) [CAN$ 14,058 (12,008)] **EDSS 7 – 9:** €12,172 (12,785) [CAN$ 9,478 (9,955)]	**EDSS 0 – 3:** €4,942 (13,732) [CAN$ 3,848 (10,693)] **EDSS 0 – 3:** €16,325 (26,805) [CAN$ 12,712 (20,872)] **EDSS 7 – 9:** €56,535 (69,873) [CAN$ 4,4022 (54,408)]	**EDSS 0 – 3:** €9,184 (18,655) [CAN$ 7,151 (14,526)] **EDSS 0 – 3:** €25,496 (24,964) [CAN$ 19,853 (19,439)] **EDSS 7 – 9:** €31,438 (28,761) [CAN$ 24,480 (22,395)]	**EDSS 0 – 3:** €39,601 (66,512) [CAN$ 30,836 (51,791)] **EDSS 0 – 3:** €59,874 (43,961) [CAN$ 46,622 (34,231)] **EDSS 7 – 9:** €100,147 (80,018) [CAN$ 77,981 (62,307)]	(using HUI) **EDSS 1-2:** utility 0.75 **EDSS 3-4:** utility 0.65 **EDSS 5-6:** utility 0.75	-	2012 from [61] And [107]
USA (Euro, 2011 exchange rate)	**Mean cost:** €8,547 – 48,010 (adjusted to 2011) [US$6144 - 34,511] **RRMS:** €18,453 [US$13,265] (2010 – 2011)		**Mean cost** €2,638 – 27,451 (adjusted to 2011) [US$1896- 19,733] **RRMS:** €125 – 7,374 [US$90 (2012) – US$5,301 (2010 – 2011)] **SPMS:** €527 – 1029 [US$379 – $740 (2012)]	**Mean cost** €11,864 – 75,461 (adjusted to 2011) [US$ 8,528- 54,244] **RRMS:** €8,190 – 49,013 [US$5,887 (2006) – US$35,232 (2009)] **PPMS /PMS:** €32,873 [US$23,630 (2006)]	0.70	0.22	2011 from Adelman et al 2013 USA 2012 from [61] 2006 from [7]

Appendix Table 5: Clinical uncertainties

Clinical Uncertainties	Description
Clinical Benefits	Uncertainties related to the real magnitude of the clinical benefit given by the drug appraised such as assuming the long-term effect of the medicines or the assumptions on retreatment rates or assumption on the discontinuation of treatment or on a return to a rate of progression equivalent to the natural history of the disease or on the choice of data.
Study Design	Uncertainties related to the statistical methodology or the conduct of the trial such as the loss of patients to follow-up, the inclusion of patient preferences during the trial conduct, the reliance of non-phase III trials results considered less robust, the uncertain nature of indirect comparisons, the assumptions around the trial design or randomisation the methodologies used for the subgroup analyses or pooling of trials, the unverifiable nature of the evidence, the risk of attrition bias, the primary endpoint that is not powered by the study, the appropriateness of the statistical methods used, or the use of historical control data.
Population	Uncertainties around the population generalizability of the trial results to local clinical practice, and the representation of the trial population to the indication being appraised, including issues around the baseline characteristics of patients.
Sample Size	Uncertainties stemming from the trial not being statistically powered due to small sample sizes.
Safety	Uncertainties relate to the safety profile of the drug studied such as if adverse events provoked by the drug are manageable considering the life extension and the health benefit gained or whether the withdrawals are possibly associated with the toxicity profile of the treatment, the higher risk of adverse events compared to the control arm, or the lack of comparative safety data.
Comparator	Uncertainties related to the suitability of the comparator(s) chosen in the analysis or the trial.
HRQoL	Uncertainties related to the absence of any quality of life data in the submission, absence of any improvement in quality of life, or the uncertain nature of its magnitude of improvement.
Cross-over	Uncertainties related to the possibility to crossover after the first trial period leading to a possible bias in the real magnitude of clinical benefit of the drug.
Resource Use	Uncertainties related to the proper use of resource respect the country setting (e.g. hospitalisation days) from the treatment in the trials or the possibility of a change in the resource used by introducing the new drug (e.g effect of an oral administration of a particular drug on the health service)
Duration of the trial	Uncertainties related to the trial period considered too short to capture the drug's long-term benefits or reflect clinical practice (e.g. interim data having been used as main evidence).
Clinical Practice	Uncertainties relate to the lack of optimal treatment sequence, or change in clinical practice in the last years or to the generalizability of the trial to the clinical practice of the country.
Administration provision	Uncertainties around the additional requirements from receiving a treatment (e.g. implications for service delivery, monitoring or need for hospital visits) or the uncertainties around the optimal dosage of treatment.

Appendix table 6: Economic uncertainties relating to the clinical and economic evidence submitted

Economic Uncertainties	Description
	Clinical Uncertainties
Clinical Benefit	Uncertainties around the estimates of clinical benefit of both the treatment and comparator
Clinical Practice	Uncertainties on the place of the treatment in clinical practice, such as issues around a lack of agreement as to the best treatment pathway or that the use of therapies not commonly used in the clinical practice.
Comparator	Uncertainties around the appropriateness of the comparator used in the model
Conduct and design	Uncertainties around the bias steaming from the conduct of the trial used to populate the economic model data
Evidence and study design	Uncertainties around the evidence used to populate the economic model data
	Economic Uncertainties
Utility	Uncertainties around the estimation given for the utility and disutility in the model such as such as whether it provides a good fit to the data, or whether the models enables to account for longer term data, or the inclusion of certain elements in the model.
Methods	Uncertainties around the methods used in the economic model
Effects	Uncertainties around the estimation of the effects of the drug studied or the comparators
Costs	Uncertainties related to the inclusion or exclusion on certain costs.
Resource Use	Uncertainties related to the estimation of the resource used by the health sector.
PAS	Uncertainties related to the introduction of the Patients Access Scheme in the economic modelling leading to a underestimation of the ICER
Modelling	Uncertainties related to the proper application of statistical model and the modelling assumption made in the model
Model Structure	Uncertainties related to the structure of the model such as its length.
Exploratory Multivariate analysis	Uncertainties on how the effects of the treatment were extrapolated.
Clinical Assumptions	Uncertainties related to Structural assumptions used in the analysis, including those around the cost, effect, utilities or treatment pathway of the treatment.

Appendix Table 7: Time lapse between marketing authorization and completion of the HTA process

Marketing authorisation from EMA	DRUG NAME	NICE	Lag (months)	TLV	Lag (months)	HAS	Lag (months)	SMC	Lag (months)	IQWIG	Lag (months)
12/09/13	Alemtuzumab	01/05/14	8.00	20/02/14	5.00	N/A	N/A	01/04/14	7.00	N/A	N/A
30/01/14	Dimethyl fumarate	01/08/14	7.00	01/08/14	7.00	01/05/14	4.00	01/07/14	6.00	01/07/14	6.00
17/03/11	Fingolimod	01/08/12	17.00	N/A	N/A	01/07/11	4.00	01/11/14	44.00	01/01/12	10.00
27/06/06	Natalizumab	01/08/07	14.00	01/12/06	6.00	01/01/07	7.00	01/05/14	95.00	N/A	N/A
26/08/13	Teriflunomide	01/01/14	5.00	01/05/14	9.00	01/06/14	10.00	01/02/14	6.00	01/12/13	4.00
13/03/97	Interferon Beta - Avonex	01/01/02	58.00	01/05/14	206.00	01/06/10	159.00	01/11/03	80.00	N/A	N/A
04/05/98	Interferon Beta - Rebif	01/01/02	44.00	01/09/09	136.00	01/06/10	145.00	01/10/12	173.00	N/A	N/A
Median Lag			21.86		61.50		54.83		58.71		6.67

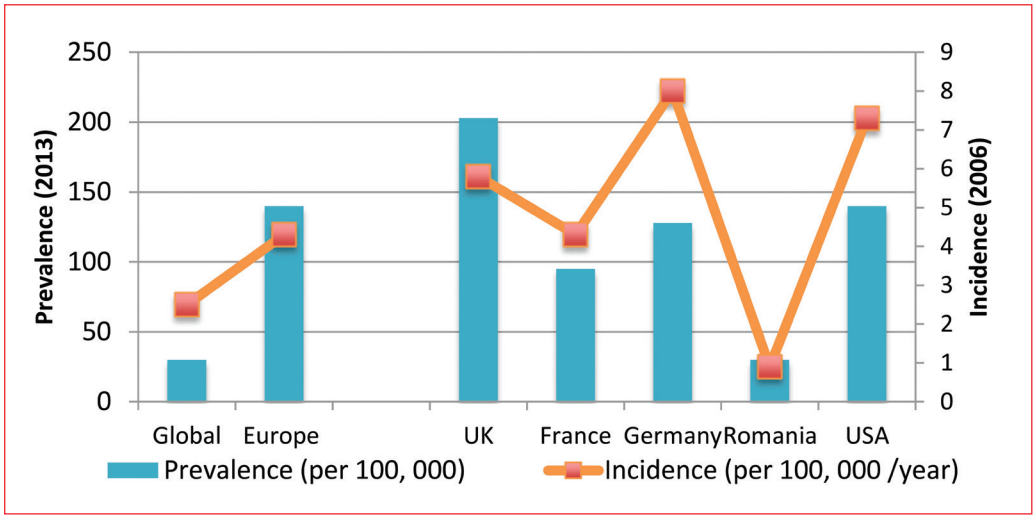
Appendix Table 8: Patient survey: Responses and socio-demographic data
(Entire sample and country sub-groups)

Characteristics, country specific case studies	All	USA	UK	France	Germany	Romania
Questionnaires completed	271	70	26	103	11	45
Questionnaires used for analysis*	246	70	25	97	10	44
Age, mean (SD)	43.7 (6)	54.3 (11.2)	38.2 (12.5)	42.6 (10.7)	42.5 (10.2)	41 (9)
Gender, Female (n, %)	205 (83%)	59 (85.5%)	18 (72%)	83 (85.6%)	10 (100%)	35 (80%)
Marital status, % (n):						
Single	42 (17.1%)	8(11.4%)	10(40%)	14(15%)	2(20%)	8(18.2%)
Married or cohabiting	165 (67.1%)	47(67.1%)	12(48%)	67(70%)	7(70%)	32(72.7%)
Divorced	26 (10.6%)	12(17.1%)	1(4%)	8(8%)	1(10%)	4(9.1%)
Separated	9 (3.7%)	1(1.4%)	2(16%)	6(6%)	0%	0%
Widow	3 (1.2%)	2(2.9%)	0%	1(5%)	0%	0%
Level of education, % (n):						
Primary	6 (4.2%)	4 (5.7%)	1 (4%)	0%	1 (10%)	0%
Secondary School Certificate	29 (11.8%)	8 (11.4%)	3 (12%)	14 (14.4%)	4 (40%)	0%
A levels	73 (29.7%)	3 (4.3%)	7 (28%)	35 (36.1%)	3 (30%)	25 (56.8%)
University	112 (45.5%)	54 (77%)	14 (56%)	41 (42.3%)	2 (20%)	1 (2.3%)
None	21 (8.5%)	1 (1.4%)	0%	2 (2.1%)	0%	18 (41%)
Number of household members where you live, mean (sd)	2.6 (0.2)	2.3 (1.1)	2.4(1.0)	2.6 (1.2)	2.7(1.1)	2.8(1.0)
Age @ 1st symptoms , mean (sd)	30.4 (3.1)	32.6 (12.4)	25.7 (9.7)	30.2 (9.9)	33.7 (9.3)	30 (8.9)
Age @ diagnosis, mean (sd)	35.2 (4.4)	42.1 (12.3)	30.3 (6.5)	34.2 (10.4)	36.3 (8.4)	33.3 (7.5)
Gap from symptoms to diagnosis (yrs), mean (sd)	4.8 (2.8)	9.5 (10.5)	4.6 (7.12)	3.9 (6.1)	2.6 (3.3)	3.3 (6.0)
EARLY DISEASE MANAGEMENT**, n(%)	118 (48%)	20 (28.6%)	14 (56%)	51 (52.6%)	6 (24%)	27 (61.4%)
LATE DISEASE MANAGEMENT, n(%)	128 (52%)	50 (71.4%)	11 (44%)	46 (47.4%)	4 (16%)	17 (38.6%)
Type of MS, % (n)						
RRMS	175 (66%)	53 (73.6%)	20 (74%)	59 (53.2%)	10 (100%)	33 (73.3%)
SPMS	30 (11.3%)	16 (22.2%)	2 (7.4%)	9 (8.1%)	0%	3 (6.7%)
PPMS	26 (9.8%)	1 (1.4%)	4 (14.8%)	16 (14.4%)	0%	5 (11.1%)
Unknown	34 (12.8%)	2 (2.8%)	1 (3.7%)	27 (24.3%)	0%	4 (8.9%)

*16 questionnaires were received from countries not included in the study (1:Thailand, 1:Netherlands, 1:Hong Kong, 2:Poland, 2:Belgium, 3:Austria, 1:Czech Rep, 1:Spain, 1:Serbia, 2:Ireland, 1:Morocco)

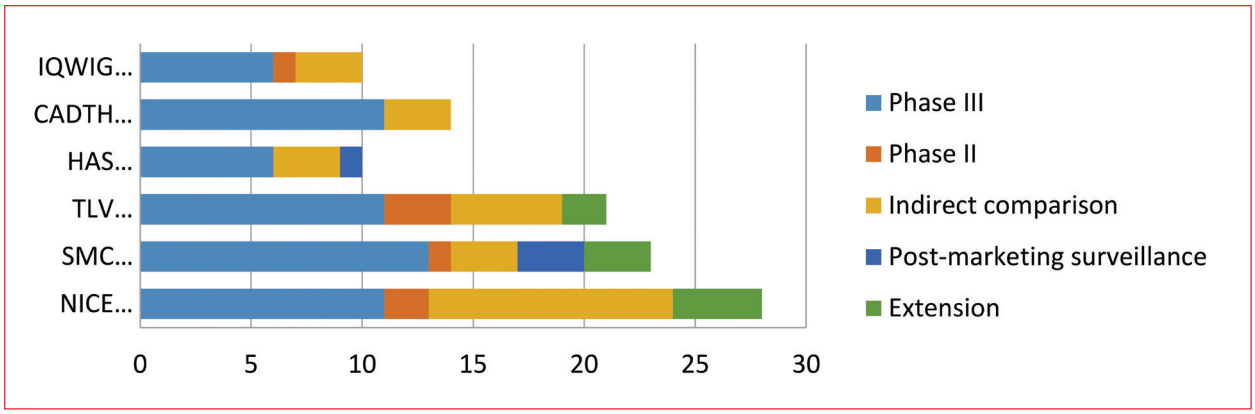
** Early disease management:= initiation of DMT within 12 months of a single neurological attack (Clinically Isolated Syndrome – CIS) with MRI enhancing lesions [55, 76,77,51].

Appendix Figure 1: Mean estimated prevalence and incidence
(Global, Europe and each country case study)

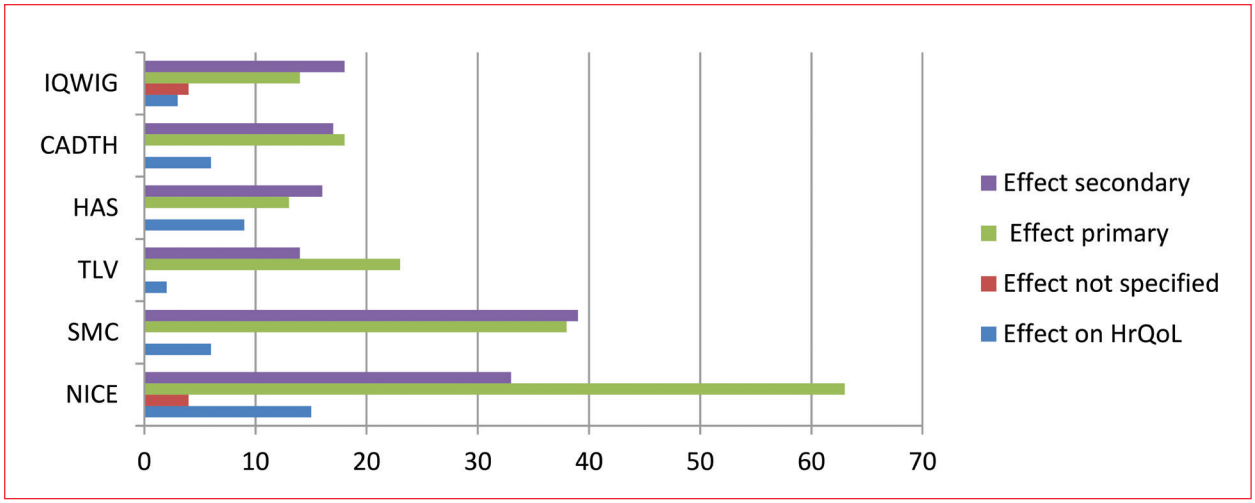


Note: Prevalence rates were kept consistent with figures reported by Multiple Sclerosis International Federation (MSIF)[19], whereas incidence rates were consistent with results reported from EU[17] and USA[106] epidemiological studies.

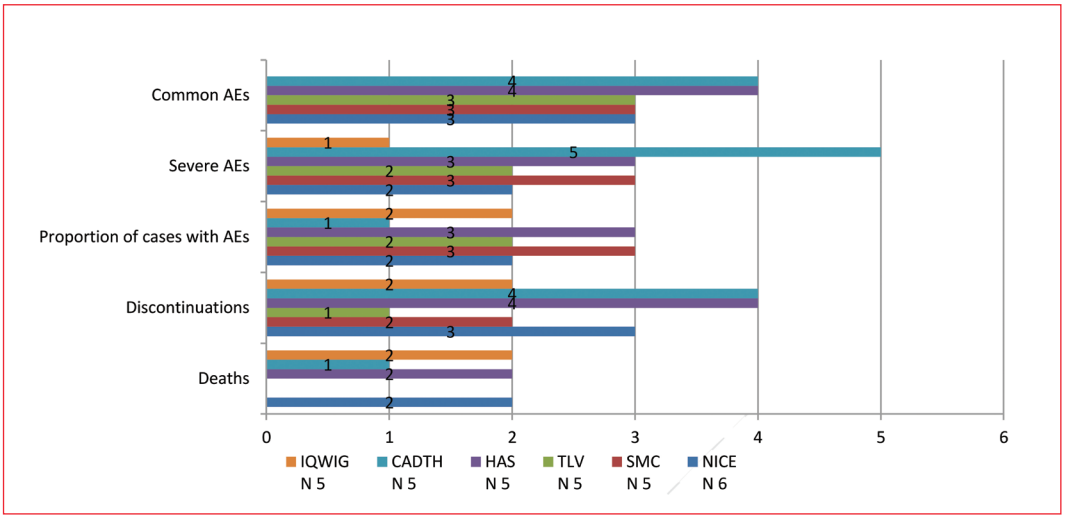
Appendix Figure 2: HTAs of MS-DMTs: Types of clinical trials examined
(Cumulative numbers by agencies)



Appendix Figure 3: HTAs of MS DMTs: Clinical endpoints used in clinical trials
(Cumulative numbers by agencies)



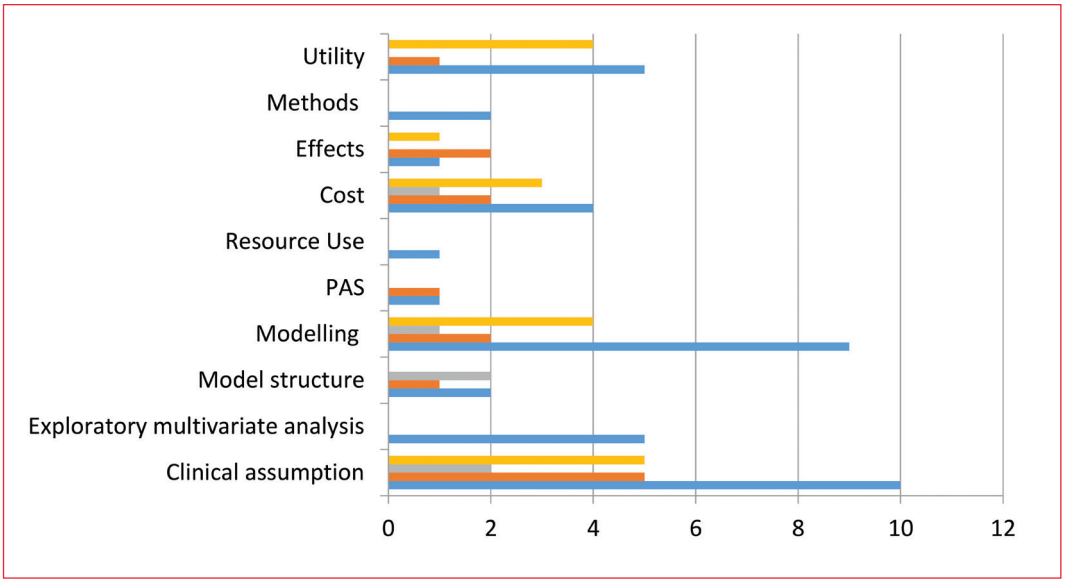
Appendix Figure 4: HTAs of MS DMTs: Safety indicators
(Cumulative numbers by agencies)



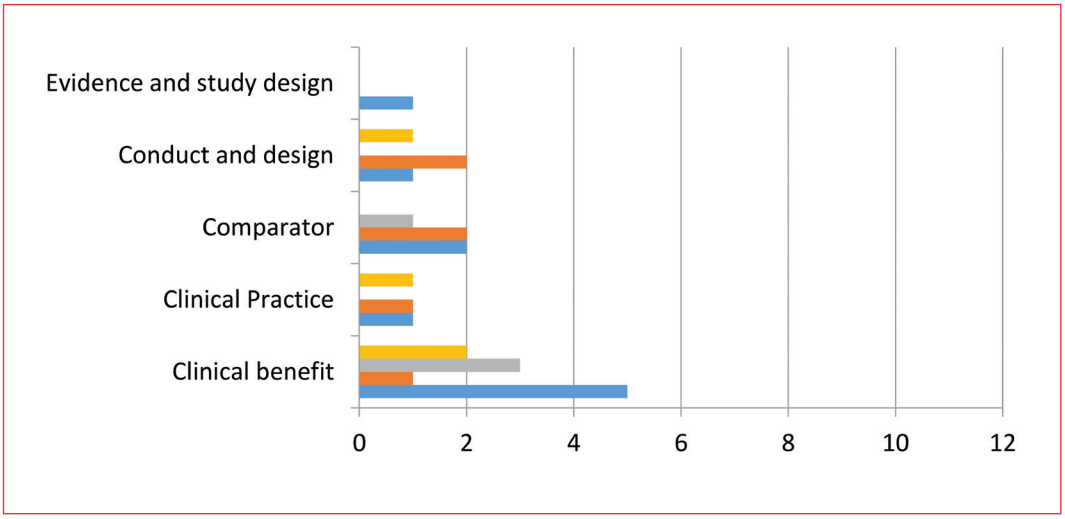
Note: AEs = adverse events

Appendix Figure 5: HTAs of MS DMTs: Economic evidence uncertainties
(Cumulative numbers by agencies)

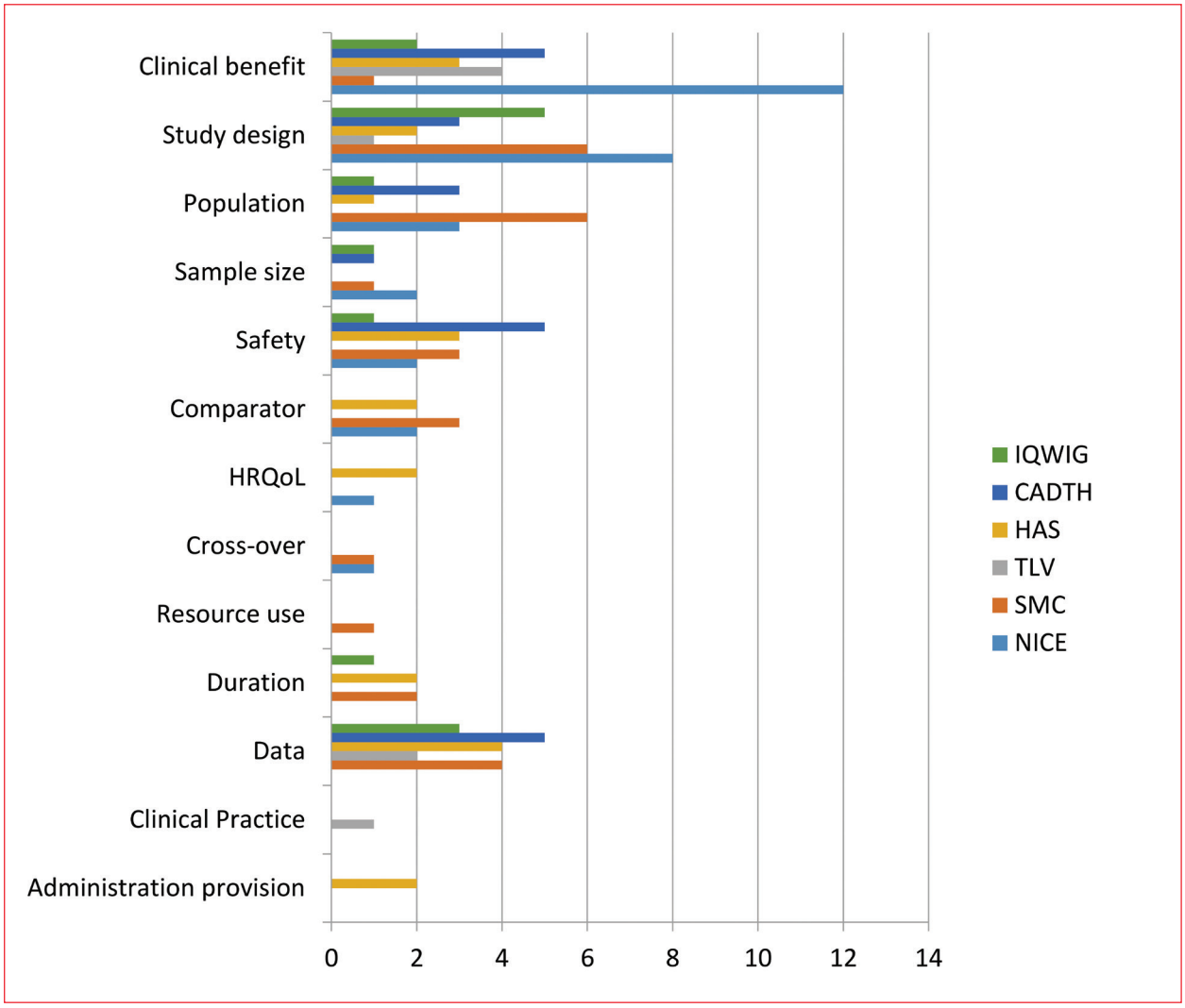
(Economic model)



(Clinical evidence used in the economic model)



Appendix Figure 6: HTAs of MS DMTs: Clinical evidence uncertainties
(Cumulative numbers by agencies)



List of abbreviations

AAN	American Association of Neurology
ABN	Association of British Neurologists
AE	Adverse Event
AIFA	Italian medicines agency (Italy, Agenzia Italiana del Farmaco)
CADTH	Canadian Agency for Drugs and Technologies in Health (Canada)
CNS	Central Nervous System
CSF	Cerebro Spinal Fluid
CDMS	Clinically Definite Multiple Sclerosis
CIS	Clinical Isolated Syndrome
CQG	Cost per QALY gained
DALYs	Disability-Adjusted Life Years
DMTs	Disease Modifying Treatments
EDSS	Expanded Disability Status Scale
EQ-5D-5L	EuroQol 5 dimensions 5 levels
GA	Glatiramer Acetate
HAS	Haute Autorité de Santé (France)
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
IQWiG	Institute for quality and efficiency in healthcare (Germany, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)
IFN	Interferon
MS	Multiple Sclerosis
MSQLI	Multiple sclerosis Quality of Life Inventory
MRI	Magnetic Resonance Imaging
MSIF	Multiple Sclerosis International Federation
NEDA	No Evidence of Disease Activity
NICE	National Institute for Health and Care Excellence (England)
PAS	Patient Access Scheme (England)
PROMs	Patient Relevant Outcome Measures
PRIMUS	Patient Reported outcome Indices for MUltiple Sclerosis
PWMS	People With Multiple Sclerosis
PPMS	Primary Progressive Multiple Sclerosis
QALY	Quality Adjusted Life Year
RES	Rapidly Evolving Severe relapsing remitting multiple sclerosis
RRMS	Relapsing Remitting Multiple Sclerosis
SMC	Scottish Medicines Consortium (Scotland)
SPMS	Secondary Progressive Multiple Sclerosis
SF-36	Short Form health survey 36-Item
TLV	Dental and Pharmaceutical Benefits Board (Sweden, Tandvårds-och läkemedelsförmånsverket)