THE LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE

Changing paradigms in the management of Multiple Sclerosis

White Paper

Panos Kanavos and Jean Mossman • November 2018

This research was commissioned via LSE Consulting which was set up by the London School of Economics and Political Science to enable and facilitate the application of its academic expertise and intellectual resources.

LSE Consulting
LSE Enterprise Limited
London School of Economics and Political Science

Houghton Street
London
WC2A 2AE

(T) +44 (0)20 7955 7128
(E) lseenterprise.consulting@lse.ac.uk
(W) lse.ac.uk/consultancy

Acknowledgements

The authors are grateful for the financial contribution received from F. Hoffmann-La Roche Ltd through an unrestricted educational grant to support the research presented in this paper.

Table of contents

Executive Summary

MS, a progressive neurological disease which causes both physical and mental disability in early adulthood, is thought to affect 2.5 million people globally and to be responsible for €15.5 billion worth of indirect and direct medical and non-medical costs in Europe each year. These costs are higher than the equivalent for long-term conditions such as asthma and diabetes.

While the overall causative factor is not yet known, what is known is that the immune system mistakenly attacks and damages the myelin sheath around the axons of nerves in the brain, spinal cord and optic nerve. The resulting inflammation, damage and destruction is generally irreversible and leads to brain atrophy and a host of symptoms including reduced fine motor control, cognitive impairment, depression and anxiety.

There are three main 'types' of MS; most common is the relapsing remitting form (RRMS) where acute symptom attacks are interspersed with remission periods when the symptoms abate due to CNS repair and the use of neurological reserves. Many people with RRMS go on to develop secondary progressive MS (SPMS). SPMS can lead to increased disability and a resulting increase in costs both to the people with MS (PwMS) and their caregivers, and to society as a whole. Less common than RRMS is primary progressive MS (PPMS) in which the PwMS has no or very few periods of remission and disability usually develops more rapidly than for RRMS.

New MRI-based diagnostic criteria and the development of novel disease modifying therapies (DMTs) have led to enhanced debate around optimised MS diagnostic and management pathways and the application of new treatment paradigms which allow the active monitoring of disease progression. Evidence shows that DMTs are most effective when used in the initial stages of the condition and treatment is aimed at preventing or controlling evidence of disease activity, an approach used in other chronic long-term conditions such as rheumatoid arthritis. In MS, no evidence of disease activity (NEDA) is most commonly associated with no relapses; no disability progression and no new or newly enlarged lesions or active lesions on MRI. There is an increasing move to offer people the opportunity to switch to an alternative DMT when treatment fails based on MRI changes without waiting for clinical relapse.

Despite the evolution of the diagnostic and treatment paradigm for MS, there is still evidence that both within- and between-country variation remains in management approaches. This report summarises a number of recommendations made in two recent reports which highlighted these differences. These recommendations span four areas: (a) diagnosis, (b) treatment initiation, (c) management and (d) evidence base/data generation (and associated healthcare system response).

Delay in diagnosis must be reduced as this is a significant barrier to early MS treatment.

- **Prompt action upon initial symptoms** – Awareness campaigns are needed to reduce delays between onset of first symptom and presentation at the family physician or primary care physician by educating the public on the typical symptoms and the importance of prompt action;
- **Educate** primary care physicians **about prompt referral to a specialist** – Family doctors must be educated about the need for prompt referral to a specialist as too often people with MS symptoms make multiple visits to their family doctors before a diagnosis is reached;

- **Improve access to specialist MS services –** Encourage more neurologists to specialise in MS as MS neurologists are best placed to provide diagnosis and management of those with the condition;
- **Adopt latest diagnostic criteria** –MRI-based diagnosis for both initial disease and recurrence is hampered by a lack of MRI machines in some countries. Countries need to ensure they have the equipment required to adopt the latest diagnostic criteria.

Early diagnosis must be followed by early treatment initiation. Once neurological reserve has been exhausted physical and mental ability decline. Once such disability is in place, pharmacological treatment fails – there are no approved drug treatments for secondary progressive MS.

- **Align prescribing guidelines with diagnostic criteria -** Despite updated diagnostic evidence there are still some countries where prescribing guidelines for MS do not match diagnostic guidelines. Healthcare authorities must work towards ensuring that modern prescribing guidelines build on work done in the early diagnosis arena;
- **Education around brain health -** Preserving brain volume and cognitive reserve are central tenets to MS care as they protect against disability progression and disease-related cognitive decline. Education from health professionals and MS specialists is key to ensure that patients have all the information they need on the benefits of early treatment to make an informed decision;
- **Make the full range of DMTs readily available in a timely manner -** The DMTs currently licensed for treatment are not all equally effective. Treatment sequence restrictions based on cost are unacceptable and treatment decisions should be made between patients and their doctor based on clinical reasons only.

Patients should be evaluated regularly for disease progression. The benefits of early diagnosis and treatment initiation are significantly diminished in the absence of continued evaluation of both treatment effectiveness and treatment safety.

- **Use evidence from MRI monitoring during treatment decision making -** MRI monitoring can detect novel lesions, as used in the diagnosis of MS, and is thought to be a more sensitive index of inflammatory disease activity than clinical relapse;
- **Implement collection of an agreed data set at a national level -** Patient monitoring is vital but achieving lasting benefit for all PwMS is only feasible if such data is usable. Results from monitoring should be available via a clinical management tool to facilitate decision making for PwMS;
- **Shared decision process** – An individual's MS treatment should be agreed in a dialogue between the person and their specialist MS healthcare professional based on all relevant information.

New data should be acted on promptly. Continued work will be required to generate a novel evidence base as new treatment options are developed and new data around management comes to light.

- **Standardised data collection –** The status of national disease registries is minimal. A key recommendation is the development of standardised data collection protocols and the generation of real-world evidence of long term DMT safety and effectiveness;

- **Economic evaluations from a societal perspective** - Caregivers lose on average €31,155 per year due to lost productivity as a direct result of caring for someone with MS. Economic evaluations should take a societal perspective and include all potential health benefits to all parties, including caregivers;
- **Cost effectiveness taking account of HRQoL** – PwMS do not believe generic quality of life measures capture issues important to them. Patient views need to be incorporated into HTA decision-making more effectively;
- **Greater consistency in economic data collection and use –** There is limited consistency in the use of health-related quality of life (HRQoL) data across countries leading to variation in access. Standardised processes for cost-effective analysis of medicines should be implemented;
- **Cost-effective therapeutic strategies –** Access to novel DMTs can be restricted in some countries. A focus on alternative financing models, such as patient access schemes, risk sharing and capitation is needed to improve access to treatment.
- **Responsive healthcare systems -** Healthcare systems need to respond dynamically to new evidence on MS diagnosis and treatment. New evidence generated by trials currently under way should quickly be incorporated into updated guidance on MS management.

PPMS brings particular challenges and in a separate, recent initiative by a group of physicians and patient organisations has developed a call to action to policy makers and the MS research community to raise the ambition for engaging, diagnosing and treating people with PPMS. This call to action encompasses research recommendations in two areas, improved diagnosis and treatment and the treatment benefits most meaningful to patients. The key recommendations are set out below:

- **Improve diagnosis and treatment in PPMS:**
    - Accelerate early diagnosis: Since PPMS is a relentlessly progressive disease from onset, rapid and accurate diagnosis leading to timely treatment provides the best chance of minimizing disability
    - Improve measurement instruments: Better instruments are needed to provide an explicit understanding of the disease, its natural history, and treatment effects.
    - Ensure shared decision-making throughout the care pathway: Information should be available to patients over the course of their disease to reduce uncertainty and enable informed decision-making.
- **Capture the benefits most meaningful to patients and their caregivers in PPMS:**
    - Assess and track independence: Measures are needed which capture attributes of independence over the different stages of life for people with PPMS.
    - Capture the true cost of PPMS:PPMS creates significant care responsibilities for the patient's family and friends, who typically provide the majority of care and needs to be characterized and quantified.

1. Introduction

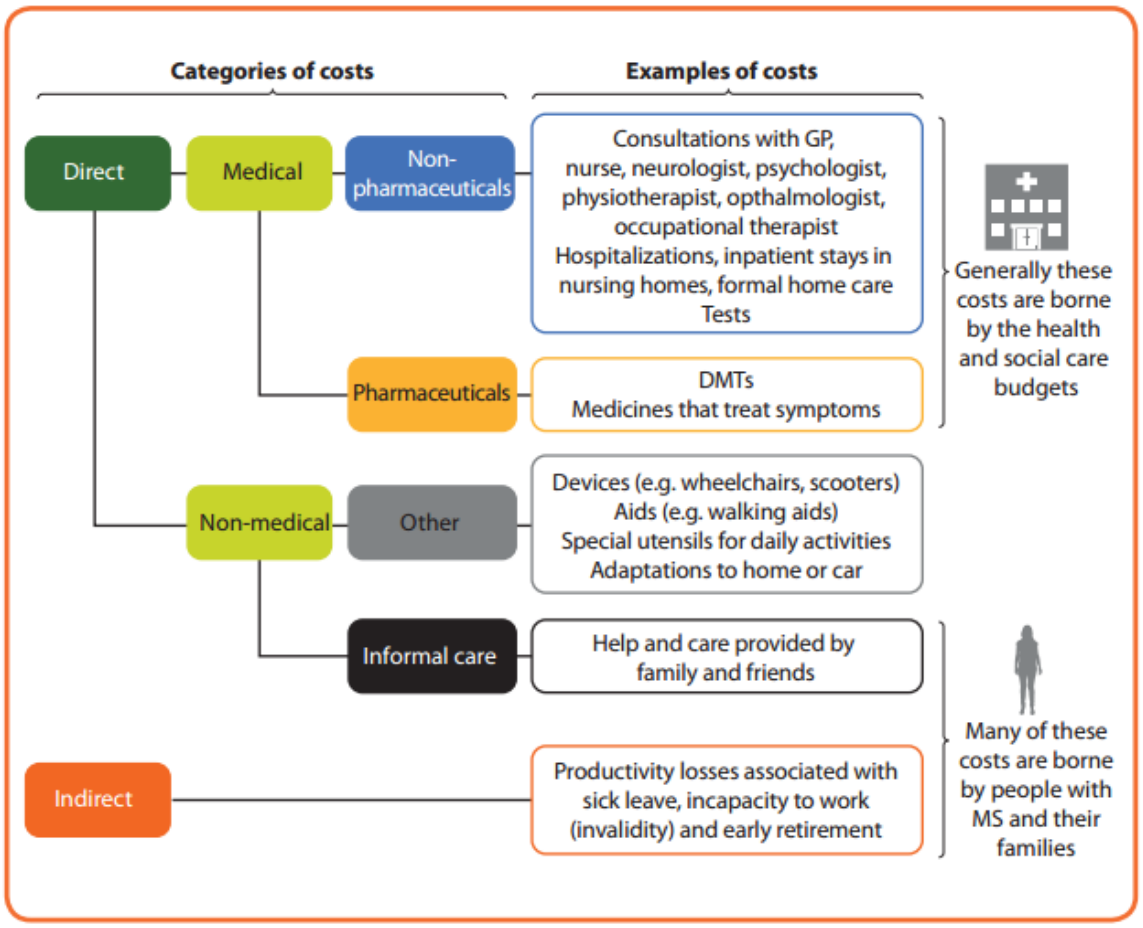
Multiple Sclerosis (MS) is a serious, progressive neurological disease which causes irreversible physical and mental disability in people in early adulthood and leads to significant long-term health and economic burdens in both the patient and their families and caregivers. The leading cause of non-traumatic disability in young and middle-aged people in developed countries (MS Society 2015b) and the second most common cause of disability among central nervous system diseases, data suggest that between 3 and 7 people per 100,000 population are diagnosed with the condition each year.

The global estimated number of people with the condition stands at 2.5 million, an increase of 400,000 since 2008, although such an increase may partly be due to better reporting and diagnostic processes. Prevalence increases as distance from the equator increases, such that countries including Canada, North America, UK and Germany have higher prevalence rates than Sub-Saharan Africa, East Asia and South Eastern European countries like Romania and Bulgaria. These discrepancies in incidence have led to various hypotheses related to the causative factor, still unknown despite the condition having been identified as early as 1868.

In MS the immune system mistakenly attacks and damages the myelin sheath, which in normal situations facilitates neuronal impulse conduction, around the axons of the nerves in the brain, spinal cord and optic nerve. The inflammation, damage and destruction of these crucial nerves, which can be seen as lesions visible in brain MRI scans, is generally irreversible leading to brain atrophy. Commonly occurring symptoms can include problems with vision, depression, anxiety, limitations in mobility, reduced fine motor control, unclear speech, incontinence and cognitive impairment.

The tendency of the condition to affect young adults means that it is affecting those with the potential for many years of employment resulting in high indirect costs. It has been predicted that the total costs of MS to society, including indirect and direct medical and non-medical costs, in Europe stands at €15.5 billion per annum, or €37,000 per person with MS, with similar costs in the US (€39,000) and Australia (€33,000) (Kobelt 2009). This cost is higher than the equivalent for long-term conditions such as asthma, chronic obstructive pulmonary disease and diabetes. The progressive nature of the condition increases levels of disability which can affect individuals' and their informal caregivers' quality of life, involvement in society and productivity leading to an increased burden on the health system (direct costs) and significant productivity losses (indirect costs) (see **Figure 1**). In Europe, evidence shows that total mean annual costs per individual with MS can be as high as €62,000 in someone with severe disease (Kobelt *et al.* 2006).

Figure 1: The total societal costs of MS are borne by health and social care services, people with MS and their families

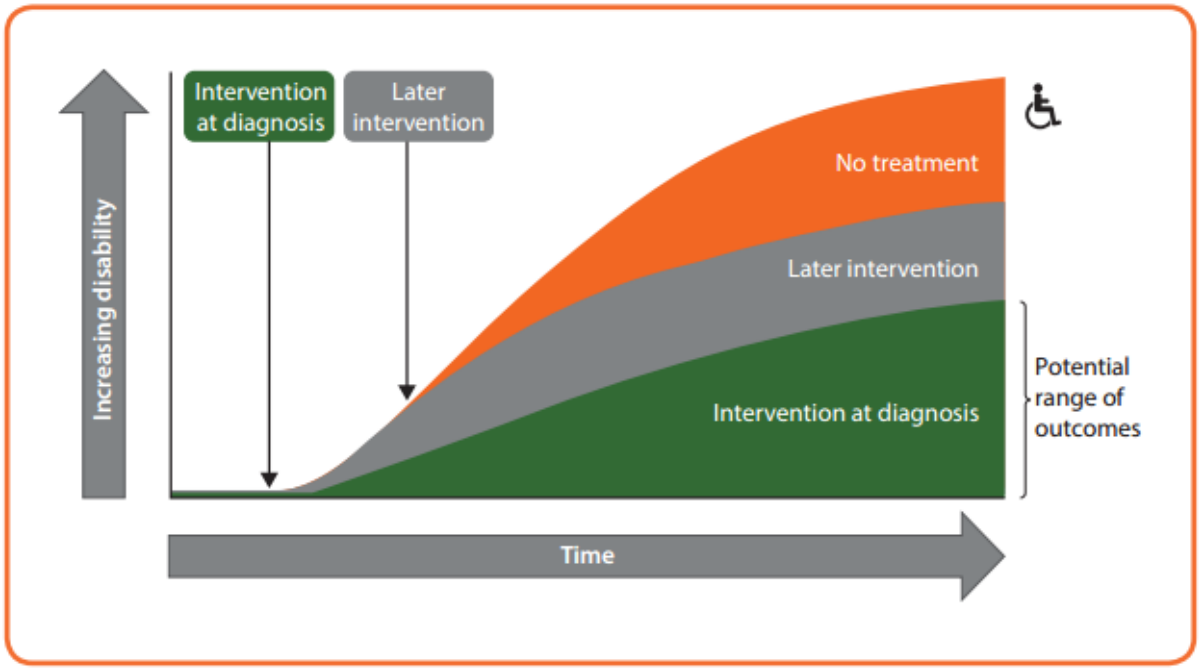


Source: Giovannoni et al. 2015a.

There are three forms of MS: the majority of people (80-90%) will initially suffer from the relapsing remitting form (RRMS) where acute attacks of symptoms are interspersed with remission periods when symptoms abate and disability may disappear due to CNS repair and the use of neurological reserves which can remodel and compensate for damage to a certain extent. While complete 'recovery' from these relapses can appear to occur, relapses often lead to unrecognised disability progression. As the disease progresses the relapsing-remitting patterns are no longer evident and secondary progressive MS (SPMS) develops. If RRMS is left untreated, more than half of people will develop SPMS within 15-20 years (Scalfari *et al.* 2014). In around ten per cent of patients there is a progressive disease course from the outset without the remission periods. This primary progressive MS (PPMS) is associated with underlying neurodegeneration, rather than the inflammation responsible for RRMS.

The finite capacity of neurological reserve and repair mechanisms in the CNS contribute to the importance of early diagnosis. If MS-related brain damage is undetected MS may go untreated leading to exhaustion of brain reserve and an early progression into the SPMS state. Early treatment with disease modifying therapies (DMT) will work towards reserving brain tissue (see **Figure 2**). Over and above pharmacological treatment initiation early diagnosis means that appropriate steps can be taken to improve brain health, including exercise, smoking cessation, weight loss and control of co-morbidities such as hypertension, which could all contribute towards improving brain health.

Figure 2: Early intervention with a DMT in MS and CIS is thought to give the best long-term prognosis



Source: Giovannoni et al. 2015a.

Access to MRI scanning, which can identify lesions as a result of inflammation, has improved understanding of the disease and revolutionised investigation, diagnosis and treatment of the condition. Initial criteria for MS diagnosis (Shumacher, 1965 and Poser, 1983) were based on observable events – at least two acute clinical relapses. The advent of MRI scanning led to the development of the McDonald criteria with the most recent update allowing a diagnosis of MS to be made in a person who has had just one relapse (Polman *et al.* 2011) which generally means that individuals can be diagnosed more quickly and start treatment earlier.

Alongside diagnostics, treatment options have also evolved over the past decade. There are now around ten DMTs available for treating PwMS. Platform therapies Interferon (IFN) and Glatiramer Acetate (GA) have been in use since the mid-1990s and reduce relapse rate by around a third, although evidence on their effectiveness on disability progression is mixed. Since 2000 a number of newer MS therapies have been developed and approved. These have different modes of action and side-effect profiles such that it is not always straightforward choosing the DMT that is most appropriate for each person with MS.

The development of new diagnostic criteria and novel therapeutic agents has led to enhanced debate around optimised MS diagnostic and management pathways as well a discussion around new treatment paradigms. Two recent papers – IMPrESS (International MultiPlE Sclerosis Study) (Kanavos *et al.* 2016) and Brain Health: Time matters in multiple sclerosis (Giovannoni *et al.* 2015a) highlighted instances where MS management and treatment is still not considered ideal in order to direct the policy discussion with the goal of policy change. Each paper made a number of recommendations and the current paper summarises these to provide a framework for engaging policy makers to facilitate progress in the treatment of MS.

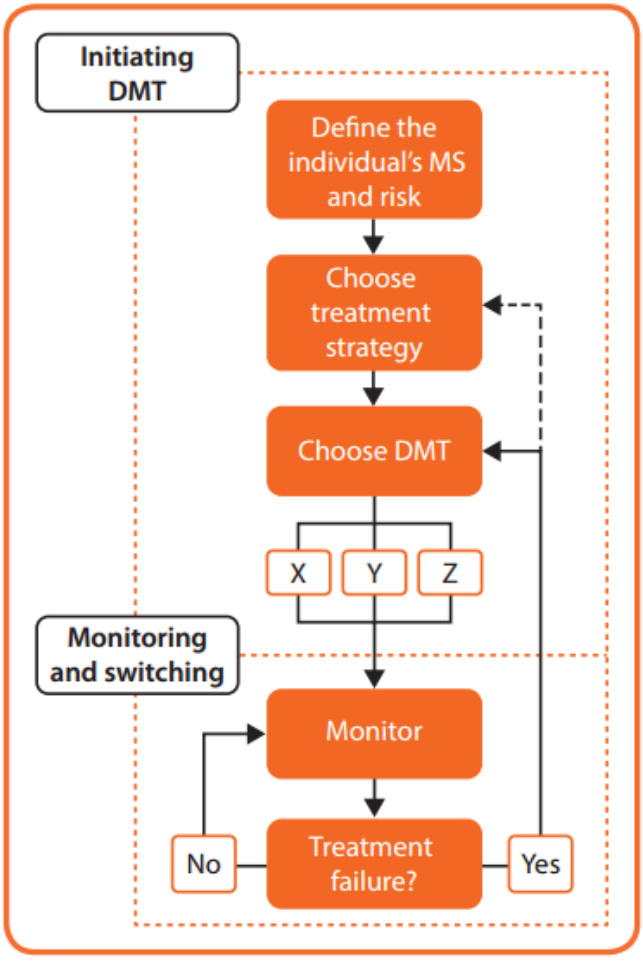
2. A Novel Treatment Paradigm?

Traditionally the MS treatment paradigm has been based on reducing relapse rates and the consequences of relapses. The introduction of more easily accessible MRI scanning and additional DMTs for the treatment of RRMS has led to a change in treatment goals which now require the setting of targets and the active monitoring of outcomes (Giovannoni *et al.* 2015b). All too often treatment in countries such as the UK has been on a 'watchful waiting' basis with the most common approach being no active treatment. However, evidence now shows that DMTs are most effective when used in the initial stages of the condition – this is reflected in the 2015 Association of British Neurologist guidelines (Scolding *et al.* 2015) where the focus is on the right treatment at the right time.

As well as treating at the right time the aim of treatment has shifted towards 'no evidence of disease activity' (NEDA) as seen in other chronic long-term conditions such as rheumatoid arthritis. In MS the most widely used definition of disease activity for NEDA is based on three separate measures of disease activity: 1) no relapses; 2) no disability progression and 3) no MRI activity (i.e. no new or newly enlarged lesions or active lesions). Experts suggest that PwMS should be offered the opportunity to switch to an alternative DMT when there is still evidence of disease according to the above criteria (see **Figure 3**). Although the NEDA hypothesis has been suggested by a number of experts there is not yet a body of evidence which backs up the idea

of a single relapse triggering treatment escalation (Scolding *et al.* 2015). As a result some neurologists delay change to a different DMT until there is clinical evidence of disease activity (i.e. relapses or disability progression) even when this is suggested by MRI (Hanson *et al.* 2014). Brain atrophy rate, or brain volume loss (BLV) has been proposed as an additional fourth component of NEDA (NEDA-4) due to its relationship with disease activity and disability progression (Popescu *et al.* 2013). Similarly, a fifth marker, 'no neuronal inflammation in the cerebrospinal fluid or blood', makes up NEDA-5 (Kanavos *et al.* 2016).

Figure 3: The importance of treatment initiation and monitoring



Source: Giovannoni et al. 2015a.

Despite potential progress in the areas of early diagnosis, early treatment, treating to target and the general evolution of the treatment paradigm for MS there is still evidence that there is both within- and between-country variation in terms of best practice.

3. Recommendations

Both IMPrESS and Brain Health focus on new treatment paradigms in MS, and associated policy change required, but from a different perspective. The main aim of the IMPrESS report was to address the significant impact of MS on the health and wellbeing of people with the disease and their caregivers and on society. Both primary and secondary data sources were used with the primary sources including collection of data from PwMS and their caregivers together with insights about treatment pathways from clinicians. A series of surveys captured information around 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 DMTs.

Brain Health: Time matters in multiple sclerosis presents an expert, evidence-based position for policy recommendations aimed at improving outcomes for PwMS. It summarises evidence and consensus findings from the structured discussions of a global author group made up of clinicians, researchers, specialist nurses, health economists and representatives from patient groups, all with expertise and experience in the area of MS.

Across the two papers 17 recommendations spanning four different areas (diagnosis; treatment initiation; disease management; and evidence) were defined.

Diagnosis

Delayed diagnosis (more than 12 months after first symptoms) has been shown to be a barrier to early access to MS treatments in all countries studied in the IMPrESS report (France, Germany, Greece, Italy, Romania, Sweden, UK and US). The survey of PwMS and clinicians showed a disconnect between opinions on diagnosis delay. The majority of clinicians said that their patients generally reported a diagnosis delay of around one year for their patients; in contrast PwMS said that they had to wait an average of 4.8 years between first symptom and diagnosis, although half of those PwMS asked did report an early diagnosis. It is possible that the patients asked were misremembering the date of onset of their or that they could retrospectively identify early, unrecognised, symptoms when they looked back. It is difficult to define exactly when MS begins due to variation in signs and symptoms experienced between individuals. Furthermore, misdiagnosis is common as many of the symptoms are similar to other, more common conditions like a trapped nerve. A recent survey found that 80% of people with MS in the UK were misdiagnosed leading to a wait of more than a year for a correct diagnosis (MS Society 2015a). A key recommendation of both reports was to decrease diagnosis delay in order to initiate treatment as early as possible.

Prompt action upon initial symptoms

Evidence shows that delays in the referral pathway are common and generally occur at two key stages (**Figure 4**). Initial delay can develop between the onset of first observable/clinical symptoms and presentation at a healthcare practitioner (general practitioner or family doctor). Such delays are common and can last more than a year in some cases (Fernández *et al.* 2010). Awareness campaigns are needed to educate the public on typical initial symptoms, the importance of prompt action, and personal and societal costs of the disease.

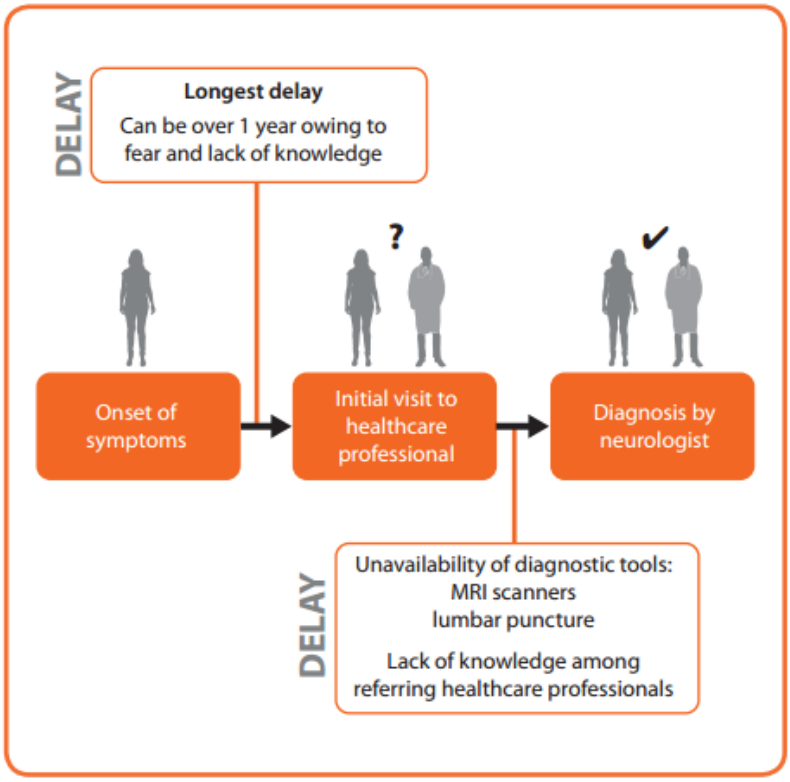
Educate family doctors about prompt referral up

Over a quarter of people with symptoms of MS have to visit their family doctor over four times before they are referred to a neurologist (MS Society 2015a). The similarity of MS symptoms with other, more common, neurological diseases may well be the reason for this and in England, many family doctors feel that they would benefit from further training and support on the identification of the signs and symptoms of neurological conditions in general (The Neurological Alliance 2016).

Local guidelines may also affect the speed at which patients with potential MS can be referred to a neurologist. For example, National Institute for Health and Clinical Excellence (NICE) - the English body of the UK Department of Health that publishes guidance on the use of medicines, treatments and procedures as well as clinical practice to be followed by English clinicians - guidelines advise GPs to exclude alternative diagnoses by performing blood tests including: full blood count; inflammatory markers; liver function tests; renal function tests; calcium; glucose; thyroid function tests; vitamin B_{12} and HIV serology which may delay referral.

Family doctors need to be trained to understand the need for prompt referral upwards.

Figure 4: Delays between the initial onset of MS symptoms and diagnosis are common and can last more than 2 years



Source: Giovannoni et al. 2015a.

Improve access to specialist MS neurologist and neurology services

The complexity of MS means that MS neurologists are best placed to diagnose and manage those with the condition. Unfortunately lack of neurologists specialising in MS is one of the main barriers to access in some countries, particularly UK and Romania which both had the lowest levels of MS neurologists (64%) compared to all other countries. Low levels of specialist neurologists can lead to excessive waiting times and an increase in diagnosis delay.

A key recommendation is to increase the number of MS neurologists available within a country by encouraging neurologists to specialise in MS management, maybe with the use of training incentives.

Adopt latest diagnostic criteria

The advent of MRI scanning has allowed MS to be diagnosed in a person who has had just one relapse as lesion patterns suggestive of MS can now be elucidated rather than using the directly

observable clinical effects. A 2013 international survey found that 8% of the 105 countries asked did not use the recognised McDonald criteria for diagnosis (Multiple Sclerosis International Federation 2013). These were low income countries with the potential for limited access to MRI scanners – there are around 120 times more MRI scanners per capita in high-income countries than in low-income countries. The apparent lack of use of modern diagnosis criteria could also be representative of the levels of priority given to MS in such countries, which were all close to the equator or in southern regions. It is therefore likely that they have lower prevalence of MS than countries further away from the Equator in the northern hemisphere, which may result in reduced health priority.

Ensuring that countries have a sufficient number of accessible MRI machines should enable doctors to follow the McDonald criteria at all times – there should be no excuse for patients having a delay in diagnosis because their neurologist is using an outdated method of diagnosis. All neurologists in all countries should be educated on the importance of early diagnosis and encouraged to use the modern equipment and methods available to them.

Box 1: Diagnosis related recommendations

The following recommendations are related to improving the route to diagnosis for those with MS:

Prompt action upon initial symptoms – Develop awareness campaigns to educate the public on typical MS symptoms, the importance of prompt action as well as the personal and societal costs of the disease to reduce delays between onset of fist symptom and presentation at family doctor.

Educate family doctor **about prompt referral to a specialist** –Enhance family doctor education around MS such that they understand the need for prompt referral upwards.

Improve access to specialist MS neurologist and neurology services – Adopt programmes to encourage more neurologists to specialise in MS.

Adopt latest diagnostic criteria – Ensure all countries have a sufficient number of MRI machines to allow them to adopt and retain the latest diagnostic criteria for MS.

Early treatment initiation

Early diagnosis is of limited worth if it is not accompanied by prompt treatment and to maximise lifelong brain health. MS causes irreversible damage to the brain and spinal cord and once neurological reserve has been exhausted there are steady increases in physical and mental disability. At this stage pharmacological treatment fails – there are no approved drug treatments for non-relapsing secondary progressive MS. Effective DMT and lifestyle interventions (see

below) must therefore be initiated as soon as MS is diagnosed in order to protect neurological reserve as much as possible.

Starting DMTs around two years earlier in people with RRMS can result in longer time to sustained disability, fewer new lesions, lower relapse rate, reduced risk of transition to SPMS and better-long term outcomes based on a variety of RCTs and real-world evidence(The PRISMS Study Group & The University of British Columbia MS/MRI Analysis Group 2001; Johnson *et al.* 2005; Kappos *et al.* 2006b;Rovaris *et al.* 2007; Trojano *et al.* 2007; Trojano *et al.* 2009; Bermel *et al.* 2010; Ebers *et al.* 2010; Goodin *et al.* 2012a; Goodin *et al.* 2012b; Agius *et al.* 2014; Kappos *et al.* 2015). Evidence also shows that PwMS treated earlier in the course of their disease showed a trend towards a lower total indirect and direct cost, although an enhanced study over a longer time course is essential to observe the financial benefits of early treatment (Kanavos *et al.* 2016).

Despite the overwhelming evidence there are situations where people have a delayed treatment initiation. In 2013 a WHO study of global MS highlighted that only half of the treatment eligible population in countries contributing to the 2013 Atlas of MS received a DMT. Potential reasons for not being treated with one included patient choice, reimbursement policy, clinical practice and access to MS healthcare professionals (Multiple Sclerosis International Federation 2013). The IMPrESS study found that 73% of PwMS with RRMS asked were started on a DMT, although two-thirds of patients wanted to delay treatment initiation until clinical diagnosis (with the remainder wanting treatment from first symptoms) as they were aware of the side-effect risks of DMTs. When the irreversible effects of MS on brain volume and attached disabilities are discussed with their clinician many may chose early treatment. Clinicians reported a gap between diagnosis and initiation of treatment of less than 2 months whereas PwMS reported delays in treatment of around 2 years (calculated as their age of treatment subtracted from their age at diagnosis).

Align prescribing guidelines with diagnostic criteria

Treatment delay could be due to issues around national/local prescribing. A central aim should be to ensure that these are aligned with modern diagnostic criteria, i.e. The McDonald 2010 diagnostic criteria, which allow a diagnosis of MS to be made based on one relapse and MRI evidence. Despite the diagnostic evidence there are still situations in some countries where prescribing guidelines for MS do not match diagnostic guidelines. For example, the 2013 MS Atlas survey found that in 14 of the 27 countries responding people diagnosed with RRMS were

required to have at least two clinically significant relapses within two years, as opposed to MRI observed lesions, in order to be prescribed a DMT.

It is essential that prescribing guidelines are aligned with diagnostic criteria. The national and local healthcare authorities must work towards ensuring that modern prescribing guidelines build on work done in the early diagnosis arena.

Education around brain health

Greater awareness among PwMS that their disease is irreversible, and that brain atrophy and deterioration in cognitive reserve may not manifest as clinical symptoms until later, is required. Education from health professionals and MS specialists is key to ensure that those patients who are inclined to delay DMT use until clinical symptoms start have all the information they need on the benefits of early treatment to make an informed decision.

Lifestyle intervention also has a place in MS management and a key recommendation is to ensure that lifelong brain health is maximised in people with MS.]Much like other long-term conditions such as hypertension there are a number of lifestyle-related factors that can exacerbate MS. Cardiovascular health is correlated with brain volume and cognitive reserve in people with MS – improving it by adopting a healthy lifestyle should be encouraged. Lack of aerobic exercise, cigarette smoking and alcohol consumption have all been associated with worse outcomes in those with MS (Pittas *et al.* 2009; D'hooghe *et al.* 2010; Özcan *et al.* 2014; Jick *et al.* 2015; Kappus *et al.* 2016). Intellectually enriching activities such as reading, education, hobbies and creative expression may also enhance cognitive reserve and protect against cognitive impairment. It is vital that those with a diagnosis of MS are made aware of the concept of brain health and what they can do to maximise it.

Make the full range of DMTs readily available in a timely manner

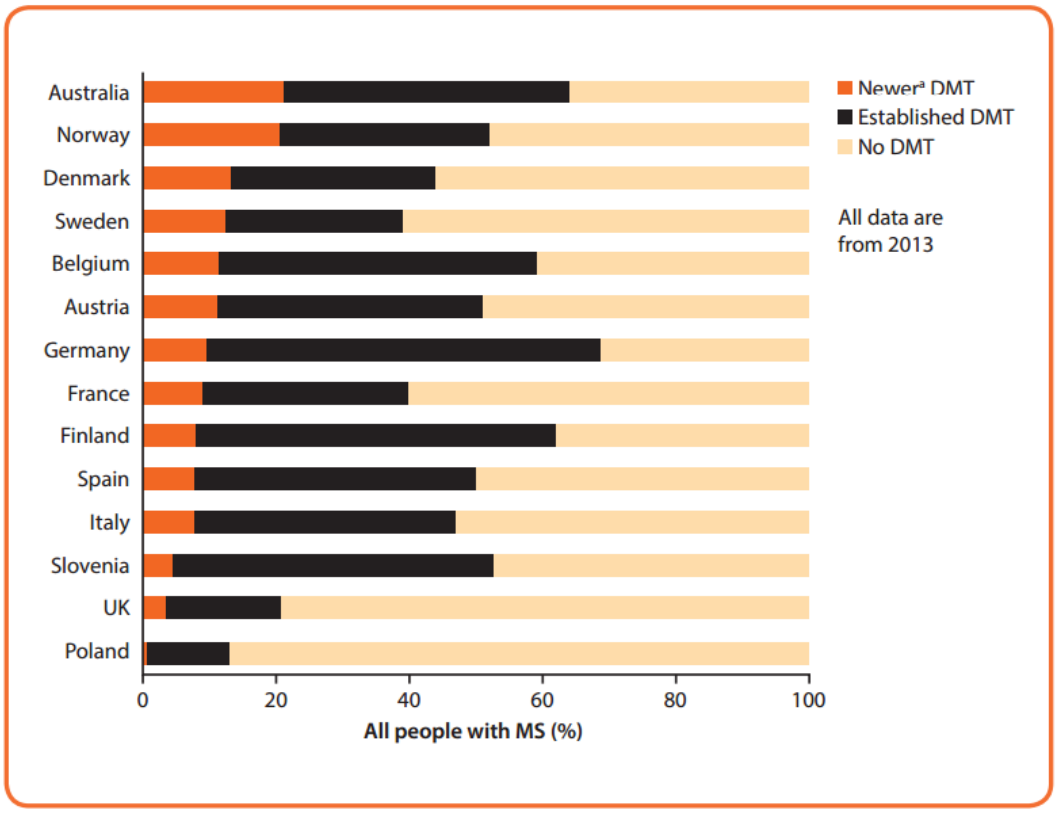
Alongside early treatment initiation it is essential that a full range of treatment options are available for those who need them. The DMTs licensed for treatment are not all equally effective, and there is no agreed gold standard treatment. A number of newer DMTs, developed from the beginning of the 21st century onwards, have been shown to be more effective than established DMTs at reducing disability progression, relapse rate and/or burden of lesions in clinical trials (Rudick *et al.* 2006; The CAMMS223 Trial Investigators 2008; Cohen *et al.* 2010; Cohen *et al.* 2012; Coles *et al.* 2012a; Coles *et al.* 2012b). Despite this most people with MS who receive DMTs will start with an established treatment (Tornatore *et al.* 2012; Bonafede *et al.* 2013;

Jokubaitis *et al.* 2013). In this respect 'escalation' strategies seem to be the most common, when a PwMS is started on the drug that is considered the least toxic but still expected to control the patient's disease before escalating to more potent therapies if there is continued disease activity. The alternative, an 'induction' process, involves giving powerful drugs with potentially significant side effects early in the disease course.

All DMTs have a unique mode of action, route of delivery and side effect profile such that treatment choice is an individual process for all PwMS and their clinical teams. As far as PwMS surveyed in the IMPrESS project are concerned the most important attributes for them when choosing medication are convenience, doctor's advice, tolerability and effectiveness, whilst clinicians were more concerned with effectiveness, safety and tolerability. A lack of long-term safety and efficacy data for the newer DMTsmay well lead to conservatism regarding newer DMT therapy and it is important that real world data on their long term impact is collected.

There are global examples of regulators and insurers imposing specific treatment sequence restrictions on MS patients, only allowing them to try newer DMTs after they have experienced treatment failure with an established DMT. This is the case with some insurance companies in the USA (Edlin & Sonnenreich 2008), and some European countries have national reimbursement guidelines that place greater restrictions on the circumstance when newer DMTs will be funded than the licence issuers (Wilsdon *et al.* 2014). As a result, there are between country differences in the proportion of people treated with newer versus established DMTs (**Figure 5**).

Figure 5: The proportion of people with all forms of MS receiving a newer DMT in 2013 varied considerably between countries.



Source: Giovannoni et al. 2015a.

Despite their systematic nature there are instances where the results of HTA based decision-making processes, and the evidence used in these processes, differ significantly across countries which can lead to different coverage decisions for MS medicines. Furthermore, HTA and reimbursement processes can also impact on the time it takes for countries to gain access to novel DMTs leading to significant time lags. In Europe Germany, Sweden, Austria and Denmark are systematically among the first countries to gain access to innovative medicines with the UK and Finland experiencing delays of between 12 and 18 months, and Poland experiencing delays for market entry of just over 2 years (Wilsdon *et al.* 2014). Treatment choice also plays a key role in condition management, recommendations for which will be discussed in the next section.

Box 2: Expedite treatment initiation

The following recommendations aim to ensure that people diagnosed with MS start the most effective treatment as quickly as possible:

Align prescribing guidelines with diagnostic criteria - Healthcare authorities should ensure that modern prescribing guidelines are aligned with diagnostic criteria to enable PwMS to start DMTs based on MRI observed lesions, rather than clinically significant relapses.

Education around brain health – Develop programmes to educate PwMS on the importance of early treatment and lifestyle adaptation for maximisation of brain health.

Make the full range of DMTs readily available in a timely manner – Ensure that treatment decisions are made between PWMS and their clinicians on the basis of clinical evidence only, as opposed to economic, regulatory or reimbursement-based evidence.

Management

The benefits of early diagnosis and treatment initiation are significantly diminished in the absence of continued condition management and monitoring. Regular monitoring allows evaluation of both treatment effectiveness and treatment safety (two key factors involved with medication choice). Such monitoring is common place in conditions that can cause irreversible organ damage such as diabetes, but in MS similar approaches are not yet routine (MS Society 2015b). Treat-to-target – where regular monitoring of composite measures of disease activity is used to work towards clinical remission – is also a common feature of the treatment of conditions like rheumatoid arthritis but has not yet been incorporated into routine clinical practice for MS. A key recommendation is that regular monitoring of clinical and subclinical disease activity becomes central to MS management.

Include evidence from MRI monitoring during treatment decision making

MRI monitoring can detect novel lesions, as used in diagnosis of MS, and is thought to be a more sensitive index of inflammatory disease activity than clinical relapse (Scolding *et al.* 2015). Such monitoring is crucial to ensure that DMT therapy is working effectively and UK guidelines suggest that MRI scanning be included in an annual review.

MRI evidence of subclinical disease can guide treatment decisions in a more timely manner than the presence of relapses alone. A prompt switch to an alternative DMT is vital as disease activity during treatment with a DMT is predictive of poor prognosis. While there is no widely agreed definition of how to manage people who are not responding well to a specific DMT, and no agreed definition of suboptimal response, NEDA has been suggested as a treatment target with PwMS being offered the opportunity to switch to an alternative DMT when they have existing evidence

of disease. Only a third of PwMS questioned in IMPrESS switched DMTs during the course of their treatment, although this may be because they experienced effective control of their MS with their initial DMT.

There are some instances where neurologists will not switch a person with MS to a different DMT without clinical evidence of disease activity, even when clear MRI evidence of disease activity is available (Tornatore *et al.* 2012; Hanson *et al.* 2014) and in the UK almost three quarters of MS specialist nurses responding to a 2014 survey said that they would only refer a PwMS for a DMT review following two or more relapses.

Of those switching it is more common to change to another established treatment than it is to move to a newer DMT (Bonafede *et al.* 2013). Potential reasons for this include perceived expense of newer DMTs, concerns over different side effect profiles of newer DMTs and general unfamiliarity with the mechanisms of action of the newer drugs. This is despite evidence showing that people who switch from an established DMT to a newer DMT (which is known to be superior to the original DMT) are more likely to be free from relapses, disability progression and new MRI activity compared with switching to another established DMT (Prosperini *et al.* 2012; Bergvall *et al.* 2014; He *et al.* 2015; Spelman *et al.* 2015).

A key recommendation is that, when a sub-optimal response is experienced. the decision to switch should be made promptly so that all gaps in treatment can be minimised. Treatment gaps in those with active MSare thought to be equivalent, or worse than, periods of non-adherence, having a significant impact on disease and increasing the chance of relapse (Jokubaitis *et al.* 2014). Guidelines should be updated to reflect increased understating around the maximum length of treatment gaps but allowing a flexible approach to treatment for patients wish to take small breaks to accommodate, for example, a holiday, as this might increase long-term adherence (Lugaresi *et al.* 2012).

Agree set data collection protocol

Patient monitoring is vital and results should be recorded in national databases or registries which can be accessed via a clinical management tool to facilitate individual decision making. Developing guidelines around the type of data that is to be collected in registries, and the use of this data, will help generate a real-world evidence base that could be used to inform future clinical and regulatory practice.

Shared decision process

The treatment of MS should be based around a dialogue between the PwMS and their MS healthcare professional. DMT choice is a complex process and should reflect the patient's perceptions of the side effect profiles and expected benefits of treatment alongside monitoring requirements and their personal preferences in terms of their work, family and other factors that may be important to them. In the UK 84% of PwMS have been reported as wanting to have an involvement in their treatment decision making process, with 50% wanting to make the final decision on their own. Similar findings have been found in the US.

A key recommendation is that MS healthcare professionals take time to ensure that PwMS have all the information they need to make an informed choice about treatment. All patients should be involved in their treatment process as it has been shown that people with MS who have good, open, trust-based relationships with their healthcare professionals and feel that they are well informed about their disease and its treatment have improved adherence to their DMT. Furthermore, their choice of DMT is improved when they understand their disease and the risks of inefficient treatment.

Box 3: Enhance condition management

The following recommendations aim to ensure that PWMS have their condition managed in a clinically effective manner:

Include evidence from MRI monitoring during treatment decision making – Ensure that MRI evidence is included, over and above diagnosis, in condition monitoring and is given more weight as an index of inflammatory disease than clinical relapse.

Agree set data collection protocol – Develop robust and universal protocols for the collection of data from condition monitoring and ensure that this data is recorded in databases or registries accessible via clinical management tools.

Shared decision process - MS healthcare professionals should ensure PWMS have all the information they need to make an informed choice about treatment and that there is an efficient and trusting dialogue between PWMS and all parties involved in their care.

Generating a novel evidence base

The development of a new treatment paradigm for MS care, focused on early diagnosis, expedited treatment plans and thorough management and monitoring, is an example of the use of an evidence base to improve clinical practice and outcomes for people with MS. Continued work is needed to extend the evidence base as new treatment options are developed and new data around management comes to light.

Standardised data collection

There is a major requirement for a standardised process of data collection and storage encompassing epidemiological, clinical and disease management data to inform future decision making. The current status of national disease registries is minimal; those that exist, in countries such as Germany, Sweden and Denmark where registries cover 50-90% of the population with MS (Multiple Sclerosis International Federation 2013; Wilsdon *et al.* 2014), have been set up independently, have information on different sets of people, use non-standardised data collection techniques and follow no set parameter of what data is collected (Flachenecker *et al.* 2014).

A key recommendation is the development of standardised data collection protocols incorporating dimensions for which little validated information exists, for example the use of MRI across countries. Furthermore, standardising and recording results of treatment and routine monitoring will enable the generation of real-world evidence on the long-term effectiveness and safety of DMTs.

The generation of real-world evidence will also help regulatory authorities, HTA bodies and payers, who currently tend to use data from short-term clinical trials to make economic decisions about DMTs, ensure that they are using the most up-to-date information to gain a modern perspective on the cost/benefit of novel DMTs.

Economic evaluations from a societal perspective

When performing cost-analysis calculations to decide where healthcare resources are allocated, national HTA bodies tend to only use information on costs borne by healthcare and social services to assess the value of a new medicine to decide whether or not the public budget will be responsible for funding its use. This payer-centric perspective of cost-effective analysis ignores costs outside the healthcare system (which can make up two thirds of all costs) like informal care from caregivers and incapacity to work (for both the caregiver and the PWMS).

IMPrESS showed that over and above PwMS' indirect costs (€16,061) caregivers lost on average €31,155 per year due to lost productivity as a direct result of caring for someone with MS and their health status was around 70% of perfect health.

It is recommended that economic evaluations take a societal perspective and include all potential health benefits to all parties, including caregivers. If such important domains are missing there may be situations where DMTs that have the potential to provide an economic benefit to society

as a whole may not be considered cost effective leading to funding restrictions which limit access to novel, potentially useful, medication.

Cost effectiveness taking account of HRQoL

Over and above the tangible costs related to MS there are a host of intangible costs to consider. These include costs related to pain, quality of life impacts, stress and the impact of quality of life on family and friends and are estimated to amount to around €13,000 per person (in 2005).

In treatments where quality of life is a factor, long-term benefits of medication or other interventions are difficult to quantify. Measures of health-related quality of life (HRQoL), for use in cost-effectiveness analysis, are generally captured in both caregivers and PwMS using the generic EuroQol 5 dimensions 5 levels (EQ-5D-5L) utility measure. Using the EQ-5D-5L shows that on average PWMS have 60% of perfect health, a loss of 25% compared to the general population (Kanavos *et al.* 2016).

Evidence shows that PwMS do not believe that the EQ-5D-5L accurately captures issues around HRQoL specific to their condition. Six aspects of health status that patients have reported as being most important to them include: mobility, usual activities (work, housework, family etc), pain/discomfort, fatigue and weakness, balance and dizziness, and bladder problems. and PwMS do not believe that the impact of the latter three aspects is accurately captured by EQ-5D-5L (Kanavos *et al.* 2016). If such important domains are missing from these generic measures, then comparisons across interventions will be invalid.

Patient Relevant Outcome Measures (PROMs) have recently become more important in MS outcome assessment. They encompass information provided by PwMS reflecting their functioning health and well-being from their perspective, including how disease and medical interventions impact on their quality of life. There are a number of validated MS-specific measures of HRQoL available including the PRIMUS[1], MSQLI[2] and the MSWS-12[3] and integrating these PROMS into cost-effective analysis has the potential to capture increased levels of benefits.

A standardised approach for incorporating patients' views into HTA decision making, with a particular focus on HRQoL, is urgently needed. The HTAi Interest Group on Patient and Citizen

[1] *Patient Reported Outcome Indices for Multiple Sclerosis*
[2] *Multiple Sclerosis Quality of Life Inventory*
[3] *12-item Multiple Sclerosis Walking Scale*

Involvement in HTA (PCIG) has produced a patient group submission template which considers the impact of the condition on the caregivers as well as the patient.

Greater consistency in economic data collection and use

There is an issue around the consistency which is required for comparisons of cost-effectiveness to be made across settings. HRQoL evidence is used differently across agencies analysing cost effectiveness of MS medications and economic data collection is also inconsistent across HTA agencies.

IMPrESS analysed the HTA process for a number of MS DMTs in the UK, Sweden, France, Scotland, Germany and Canada and found variations in the use of comparators, primary and secondary endpoints, HRQoL evidence and QoL endpoints, and levels of stakeholder input. The result was a difference in the time lag between regulatory approval and completion of HTA assessments and in rejection status of the same DMT across different countries. Such discrepancies could lead to lack of access, affecting treatment of those with MS. It could also result in parallel trade, or black-market exports from countries where medicines have been approved to those where they are unavailable.

Standardised methods should be in place for measuring the cost-effectiveness of new DMTs. Ensuring that HTA bodies have access to standardised registries and databases (see above) may also improve the consistency of data for the evaluation of the economic impact of MS which will allow for comparison across settings to be made.

Cost-effective therapeutic strategies

Access to treatment can often depend on affordability (as well as clinical effectiveness, and the decisions of regulatory authorities) with low income countries reimbursing fewer DMTs than higher income countries. In Romania reimbursement for treatment with DMTs is approved on a case by case basis according to the availability of funds. In 2013 500 MS patients were on the waiting list for state-funded DMTs with approximately 200 new patients approved to receive the subsidised treatment each year. In Poland patients are only treated with a DMT for five years; after this time the treatment is transferred to someone on the waiting list (Wilsdon *et al.* 2014).

Even in high income countries access to more expensive, newer DMTs can be restricted due to cost. In the US costs are two to three times higher than countries such as Australia, Canada and UK (Hartung *et al.* 2015) leading to some patients having to pay significantly out of pocket for DMTs if their insurance companies do not pay for a particular medicine.

New approaches, such as managed entry schemes which collect effectiveness data while allowing patients to be treated, are needed. Risk sharing schemes have been used in the UK for MS; for example, when β -interferon and glatiramer acetate received a negative HTA assessment, eligible patients were given access to the treatment, funded by the NHS, and were monitored for ten years to gather long-term data in the hope of finding the medicines to be cost effective. Six year analysis, published in 2015, showed that the effects of the drugs over six years are cost effective (Palace *et al.* 2015).

Responsive healthcare system

The final recommendation is based on the responsiveness of the healthcare system. It is vital that healthcare systems respond dynamically as new evidence emerges on the diagnosis, treatment and long-term impact of MS as well as novel DMTs. Any new evidence generated by long-term trials currently under way should quickly be incorporated into updated guidance on condition management.

Evidence discussed in this paper shows that there are still situations where guidelines are available but there is still limited use of standardised protocols. If the long-term impact of a new treatment paradigm for MS is to be effectively quantified then such protocols should be uniformly implemented within and across countries.

Box 4: Generate a novel evidence base

The following recommendations aim to ensure that novel evidence around the treatment and management of PWMS is utilised to enhance future care:

Standardised data collection – Develop standardised data collection protocols and generate real world evidence on the long-term safety and effectiveness of novel DMTs and make this available to HTA bodies to aid with standardised health technology assessment processes.

Economic evaluations from a societal perspective – Include a societal perspective in all economic evaluations of novel DMTs, medical devices and non-drug interventions related to the treatment and management of MS to achieve an accurate estimation of cost effectiveness.

Cost effectiveness taking account of HRQoL – Adapt generic quality of life measures to ensure they fully capture all issues important to PwMS, and incorporate HRQoL measures into health technology assessments so that patient views are taken into account.

Greater consistency in economic data collection and use – Develop a standardised process for the use of HRQoL data as well as standardised comparators, primary and secondary endpoints and levels of stakeholder input in cost effectiveness analysis of novel DMTs and non-drug interventions to limit between-country variation in access to treatment.

Cost-effective therapeutic strategies – Increase the use of alternative financing models such as patient access schemes, risk sharing and capitation to improve access to treatment in all countries.

Responsive healthcare system – Ensure that new evidence on MS diagnosis and treatment-related issues, generated via long-term trials currently under way, is incorporated into updated guidance on condition management as efficiently as possible as soon as it is available.

PPMS

This paper has tended to focus on RRMS, as does most of the literature. But there are major issues facing those with PPMS, who are likely to be less well served with healthcare delivery compared to those with RRMS and SPMS. Many patient groups report that people with PPMS are lost to the system: in the absence of an effective treatment they don't attend regular follow up appointments. This will hopefully change as treatments for PPMS become available. In the meantime, a call to action on the research needs in PPMS has been defined (see **Figure 6**) which will provide a blueprint for improving care for this group of MS patients.

Figure 6: Call to action on primary progressive multiple sclerosis (PPMS)

Lisbon declaration on Primary Progressive Multiple Sclerosis

Purpose

This declaration represents a call to action to policy makers and the MS research community to raise the ambition for engaging, diagnosing and treating people with PPMS. The MS community – including patients, clinicians, regulators, health authorities, industry and academia – need to work together to advance understanding of PPMS and close key evidence gaps that limit our diagnosis and management of the condition.

Imperatives for the MS community to promote patient independence

Primary progressive multiple sclerosis (PPMS), the more rapidly progressing form of MS, is a degenerative disease that has been neglected due to the historic lack of efficacious treatments. Over time, PPMS can erode a patient's ability to live their desired life and increases their dependence on others, and does so more rapidly than other forms of MS[i]. It is time to bring about a shift in focus to protect and sustain patient independence and quality of life. Independence is crucial as it contributes to living full and satisfying lives in accordance with the individual's wishes. In order to sustain independence in the face of PPMS, we have agreed the following research agenda.

Research priorities

Improve diagnosis and treatment

- **Accelerate early diagnosis:** Time is of the essence. Since PPMS is a relentlessly progressive disease from onset, rapid and accurate diagnosis leading to timely treatment provides the best chance of minimizing disability. Evidence shows people with PPMS can experience years in limbo awaiting diagnostic clarity. We must understand and address the causes for delays in presentation, referral, investigation and diagnosis, by mapping the natural history of PPMS and its early-presenting symptoms, along with identifying common barriers to diagnosis.
- **Improve measurement instruments:** We must develop better instruments to measure the impact of, and changes in PPMS, and how people with PPMS feel and function so that we have an explicit understanding of the disease, its natural history, and treatment effects. Such tools need to be conceptually grounded, scientifically strong and able to detect meaningful changes in function. We support the use of a wide range of measurement methods to enhance patient-professional partnerships and aid diagnosis, monitoring and rehabilitation.
- **Ensure shared decision-making throughout the care pathway:** We need to understand the optimal care pathway to best utilize any new treatment available, along with ideal roles for healthcare providers such as neurologists, general practitioners, and specialist nurses. The care pathway should include holistic support for patients and carers, while enhancing the information available to patients over the course of their disease to reduce uncertainty and enable informed decision-making.

Capture the benefits most meaningful to patients and their carers

- **Assess and track independence:** Many people with PPMS, and their families cite preservation of independence as their most important goal.[ii] There is a need for measures capturing attributes of independence over the different stages of life. Such measures will allow care and treatment interventions to be evaluated in light of how they support participation in activities that matter most to patients.
- **Capture the true cost of PPMS:** Methods for evaluation of the cost of PPMS are imperfect and the impact is often underestimated. PPMS creates significant care responsibilities for the patient's family and friends, who typically provide the majority of care. The impact of PPMS on informal caregivers, including the impact of progression on caregiver wellbeing, employment, education, and quality of life needs to be characterized and quantified.

Signatories

- *Birgit Bauer, Journalist, MS blogger and social media expert*
- *Trishna Bharadia, MS Advocate and Disability Awareness campaigner*
- *Giovanni Fattore, Professor of Health Policy, University of Bocconi*
- *Jeremy Hobart, Professor of Clinical Neurology and Health Measurement, University of Plymouth, UK*
- *Gisela Kobelt, President, European Health Economics*
- *Amanda Montague, Vice President of Education & Healthcare Relations, Multiple Sclerosis Association of America*
- *Jo Sopala, Director of Health Professional Programmes, MS Trust*
- *Michela Tinelli, Assistant Professorial Research Fellow, London School of Economics*

[i] Time to fixed disability milestones was shorter in PPMS than in Relapsing-Onset MS (Expanded Disability Status Scale (EDSS) 4.0:8.1 vs 17.1 years, p <0.001; EDSS 6.0: 9.6 vs 22.1 years, p<0.001; ; EDSS 8.0: 20.7 vs 39.7 years, p<0.001): Harding KE, Wardle M, Moore P et al. *Modelling the natural history of primary progressive multiple sclerosis. J Neurol Neurosurg Psychiatry* 2015;86:13–9. *See also* Confavreux, *et. al., Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process*, Brain. 2003 Apr;126(Pt 4):770-82.

ii Holland NJ, Schneider DM, Rapp R, Kalb RC. *Meeting the needs of people with primary progressive multiple sclerosis, their families, and the health-care community*. Int J MS Care 2011;13:65–74

This declaration was developed in June 2018 at the PPMS Independence Policy roundtable in Lisbon, which was supported by Roche

4. Future steps

This report has highlighted a number of recommendations, based on those discussed in two recent papers on MS, in four broad areas related to the management of MS - *Diagnosis; Early treatment initiation; Management; and Generating a novel evidence base*.

Acting on these recommendations will require a number of policy proposals. Countries should consider developing a national, focused strategy for MS which local payers must follow. Goals of any guidelines produced should be clear and MS specialists should be encouraged to follow these as much as possible, not just for treatment-based decisions but for management reviews. There must be an end to blanket bans on certain drugs for certain groups of people – authorities should be encouraged to make recommendations on a case-by-case basis to account for the highly individualised treatment sometimes required. Countries could also consider appointing a neurology Tsar responsible for devising a targeted national strategy for neurological conditions to address service variations seen in MS.

Some countries will need greater investment in the healthcare infrastructure devoted to MS, for example to increase the number of MS neurologists and MS nurses. Reliable recording of indirect costs, such as lost employment related profitability, should be encouraged to enable enhanced value-based decisions around drug supply. International standards on data collection are needed for the development of registries/databases for MS.

Focused education should also be a key policy aim. The population should be educated in issues around brain health, as they are for cardiovascular health, the early signs and symptoms of MS and the importance of early diagnosis and treatment; general practitioners, and other generalist health care workers should be made aware of the possible symptoms of MS and the importance of urgent referral to a specialist; and MS specialists should be aware of the importance of following up to date guidelines in terms of diagnosis and treatment. They should also be encouraged to include all patients in discussions and decisions about their own care.

Only when these changes are implemented will we see the improvements in MS that patients – and their caregivers – deserve.

References

Agius M., Meng X., Chin P., Grinspan A. & Hashmonay R. (2014) Fingolimod Therapy in Early Multiple Sclerosis: An Efficacy Analysis of the TRANSFORMS and FREEDOMS Studies by Time Since First Symptom. *CNS Neuroscience & Therapeutics* **20**, 446-51.

Bergvall N., Makin C., Lahoz R., Agashivala N., Pradhan A., Capkun G., Petrilla A.A., Karkare S.U., McGuiness C.B. & Korn J.R. (2014) Relapse Rates in Patients with Multiple Sclerosis Switching from Interferon to Fingolimod or Glatiramer Acetate: A US Claims Database Study. *PLoS ONE* **9**, e88472.

Bermel R., Weinstock-Guttman B., Bourdette D., Foulds P., You X. & Rudick R. (2010) Intramuscular interferon beta-1a therapy in patients with relapsing-remitting multiple sclerosis: a 15-year follow-up study. *Multiple Sclerosis* **16**, 588-96.

Bonafede M.M., Johnson B.H., Wenten M. & Watson C. (2013) Treatment Patterns in Disease-Modifying Therapy for Patients With Multiple Sclerosis in the United States. *Clinical Therapeutics* **35**, 1501-12.

Cohen J.A., Barkhof F., Comi G., Hartung H.-P., Khatri B.O., Montalban X., Pelletier J., Capra R., Gallo P., Izquierdo G., Tiel-Wilck K., de Vera A., Jin J., Stites T., Wu S., Aradhye S. & Kappos L. (2010) Oral Fingolimod or Intramuscular Interferon for Relapsing Multiple Sclerosis. *New England Journal of Medicine* **362**, 402-15.

Cohen J.A., Coles A.J., Arnold D.L., Confavreux C., Fox E.J., Hartung H.-P., Havrdova E., Selmaj K.W., Weiner H.L., Fisher E., Brinar V.V., Giovannoni G., Stojanovic M., Ertik B.I., Lake S.L., Margolin D.H., Panzara M.A. & Compston D.A.S. (2012) Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *The Lancet* **380**, 1819-28.

Coles A.J., Fox E., Vladic A., Gazda S.K., Brinar V., Selmaj K.W., Skoromets A., Stolyarov I., Bass A., Sullivan H., Margolin D.H., Lake S.L., Moran S., Palmer J., Smith M.S. & Compston D.A.S. (2012a) Alemtuzumab more effective than interferon β-1a at 5-year follow-up of CAMMS223 Clinical Trial. *Neurology* **78**, 1069-78.

Coles A.J., Twyman C.L., Arnold D.L., Cohen J.A., Confavreux C., Fox E.J., Hartung H.-P., Havrdova E., Selmaj K.W., Weiner H.L., Miller T., Fisher E., Sandbrink R., Lake S.L., Margolin D.H., Oyuela P., Panzara M.A. & Compston D.A.S. (2012b) Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *The Lancet* **380**, 1829-39.

D'hooghe M., Nagels G., Bissay V. & De Keyser J. (2010) Modifiable factors influencing relapses and disability in multiple sclerosis. *Multiple Sclerosis* **16**, 773-85.

Ebers G.C., Traboulsee A., Li D., Langdon D., Reder A.T., Goodin D.S., Bogumil T., Beckmann K., Wolf C., Konieczny A. & Study f.t.I.o.t.-y.L.-T.F.-U. (2010) Analysis of clinical outcomes according to original treatment groups 16 years after the pivotal IFNB-1b trial. *Journal of Neurology, Neurosurgery & Psychiatry* **81**, 907-12.

Edlin M. & Sonnenreich P. (2008) Trends in Managing Multiple Sclerosis. *Pharmacy and Therapeutics* **33**, 611-4.

Fernández O., Fernández V., Arbizu T., Izquierdo G., Bosca I., Arroyo R., García Merino J.A. & de Ramón E. (2010) Characteristics of multiple sclerosis at onset and delay of diagnosis and treatment in Spain (The Novo Study). *Journal of Neurology* **257**, 1500-7.

Filippi M., Rocca M.A., Ciccarelli O., De Stefano N., Evangelou N., Kappos L., Rovira A., Sastre-Garriga J., Tintorè M., Frederiksen J.L., Gasperini C., Palace J., Reich D.S., Banwell B., Montalban X. & Barkhof F. (2016) MRI CRITERIA FOR THE DIAGNOSIS OF MULTIPLE SCLEROSIS: MAGNIMS CONSENSUS GUIDELINES. *The Lancet. Neurology* **15**, 292-303.

Flachenecker P., Buckow K., Pugliatti M., Kes V.B., Battaglia M.A., Boyko A., Confavreux C., Ellenberger D., Eskic D., Ford D., Friede T., Fuge J., Glaser A., Hillert J., Holloway E., Ioannidou E., Kappos L., Kasilingam E., Koch-Henriksen N., Kuhle J., Lepore V., Middleton R., Myhr K.-M., Orologas A., Otero S., Pitschnau-Michel D., Rienhoff O., Sastre-Garriga J., Schyns-Liharska T., Sutovic D., Thalheim C., Trojano M., Vlasov Y.V., Yaldizli Ö. & Consortium* f.t.E. (2014) Multiple sclerosis registries in Europe – results of a systematic survey. *Multiple Sclerosis Journal* **20**, 1523-32.

Giovannoni G., Butzkueven H., Dhib-Jalbut S., Hobart J., Kobelt G., Pepper G., Sormani M., Thalheim C., Traboulsee A. & Vollmer T. (2015a) Brain Health: Time matters in multiple sclerosis.

Giovannoni G., Turner B., Gnanapavan S., Offiah C., Schmierer K. & Marta M. (2015b) Is it time to target no evident disease activity (NEDA) in multiple sclerosis? *Multiple Sclerosis and Related Disorders* **4**, 329-33.

Goodin D.S., Ebers G.C., Cutter G., Cook S.D., O'Donnell T., Reder A.T., Kremenchutzky M., Oger J., Rametta M., Beckmann K. & Knappertz V. (2012a) Cause of death in MS: long-term follow-up of a randomised cohort, 21 years after the start of the pivotal IFNβ-1b study. *BMJ Open* **2**.

Goodin D.S., Reder A.T., Ebers G.C., Cutter G., Kremenchutzky M., Oger J., Langdon D., Rametta M., Beckmann K., DeSimone T.M. & Knappertz V. (2012b) Survival in MS: A randomized cohort study 21 years after the start of the pivotal IFNβ-1b trial. *Neurology* **78**, 1315-22.

Hanson K.A., Agashivala N., Wyrwich K.W., Raimundo K., Kim E. & Brandes D.W. (2014) Treatment selection and experience in multiple sclerosis: survey of neurologists. *Patient preference and adherence* **8**, 415-22.

Hartung D.M., Bourdette D.N., Ahmed S.M. & Whitham R.H. (2015) The cost of multiple sclerosis drugs in the US and the pharmaceutical industry: Too big to fail? *Neurology* **84**, 2185-92.

He A., Spelman T., Jokubaitis V. & et al. (2015) COmparison of switch to fingolimod or interferon beta/glatiramer acetate in active multiple sclerosis. *JAMA Neurology* **72**, 405-13.

Jick S.S., Li L., Falcone G.J., Vassilev Z.P. & Wallander M.-A. (2015) Epidemiology of multiple sclerosis: results from a large observational study in the UK. *Journal of Neurology* **262**, 2033-41.

Johnson K.P., Ford C.C., Lisak R.P. & Wolinsky J.S. (2005) Neurologic consequence of delaying glatiramer acetate therapy for multiple sclerosis: 8-year data. *Acta Neurologica Scandinavica* **111**, 42-7.

Jokubaitis V.G., Li V., Kalincik T., Izquierdo G., Hodgkinson S., Alroughani R., Lechner-Scott J., Lugaresi A., Duquette P., Girard M., Barnett M., Grand'Maison F., Trojano M., Slee M., Giuliani G., Shaw C., Boz C., Spitaleri D.L.A., Verheul F., Haartsen J., Liew D. & Butzkueven H. (2014) Fingolimod after natalizumab and the risk of short-term relapse. *Neurology* **82**, 1204-11.

Jokubaitis V.G., Spelman T., Kalincik T., Izquierdo G., Grand'Maison F., Duquette P., Girard M., Lugaresi A., Grammond P., Hupperts R., Cabrera-Gomez J., Oreja-Guevara C., Boz C., Giuliani G., Fernández-Bolaños R., Iuliano G., Lechner-Scott J., Verheul F., van Pesch V., Petkovska-Boskova T., Fiol M., Moore F., Cristiano E., Alroughani R., Bergamaschi R., Barnett M., Slee M., Vella N., Herbert J., Shaw C., Saladino M.L., Amato M.P., Liew D., Paolicelli D., Butzkueven H., Trojano M. & the M.S.G. (2015) Predictors of disability worsening in clinically isolated syndrome. *Annals of Clinical and Translational Neurology* **2**, 479-91.

Jokubaitis V.G., Spelman T., Lechner-Scott J., Barnett M., Shaw C., Vucic S., Liew D., Butzkueven H., Slee M. & on behalf of the Australian M.S.G. (2013) The Australian Multiple Sclerosis (MS) Immunotherapy Study: A Prospective, Multicentre Study of Drug Utilisation Using the MSBase Platform. *PLoS ONE* **8**, e59694.

Kanavos P., Tinelli M., Efthymiadou O., Visintin E., Grimaccia F. & Mossman J. (2016) Towards better outcomes in multiple sclerosis by addressing policy change.

Kappos L., O'Connor P., Radue E.-W., Polman C., Hohlfeld R., Selmaj K., Ritter S., Schlosshauer R., von Rosenstiel P., Zhang-Auberson L. & Francis G. (2015) Long-term effects of fingolimod in multiple sclerosis: The randomized FREEDOMS extension trial. *Neurology* **84**, 1582-91.

Kappos L., Traboulsee A., Constantinescu C., Erälinna J.-P., Forrestal F., Jongen P., Pollard J., Sandberg-Wollheim M., Sindic C., Stubinski B., Uitdehaag B. & Li D. (2006b) Long-term subcutaneous interferon beta-1a therapy in patients with relapsing-remitting MS. *Neurology* **67**, 944-53.

Kappus N., Weinstock-Guttman B., Hagemeier J., Kennedy C., Melia R., Carl E., Ramasamy D.P., Cherneva M., Durfee J., Bergsland N., Dwyer M.G., Kolb C., Hojnacki D., Ramanathan M. & Zivadinov R. (2016) Cardiovascular risk factors are associated with increased lesion burden and brain atrophy in multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry* **87**, 181-7.

Kobelt G. (2009) Access to innovative treatments in multiple sclerosis in Europe

Kobelt G., Berg J., Lindgren P., Fredrikson S. & Jönsson B. (2006) Costs and quality of life of patients with multiple sclerosis in Europe. *Journal of Neurology, Neurosurgery, and Psychiatry* **77**, 918-26.

Lugaresi A., Ziemssen T., Oreja-Guevara C., Thomas D. & Verdun E. (2012) Improving patient–physician dialog: commentary on the results of the MS Choices survey. *Patient preference and adherence* **6**, 143-52.

MS Society (2015a) Symptoms of MS are mistaken for other conditions, survey reveals. URL https://www.mssociety.org.uk/ms-news/2015/05/symptoms-ms-are-mistaken-other-conditions-survey-reveals.

MS Society (2015b) Time to Act – a consensus on early treatment.

Multiple Sclerosis International Federation (2013) Atlas of MS database data export: diagnosis URL http://www.atlasofms.org.

NHS England & Monitor (2014) Local payment examples - Capitation: a potential new payment model to enable integrated care.

Özcan M.E., İnce B., Bingöl A., Ertürk S., Altınöz M.A., Karadeli H.H., Koçer A. & Asil T. (2014) Association between smoking and cognitive impairment in multiple sclerosis. *Neuropsychiatric Disease and Treatment* **10**, 1715-9.

Palace J., Duddy M., Bregenzer T., Lawton M., Zhu F., Boggild M., Piske B., Robertson N.P., Oger J., Tremlett H., Tilling K., Ben-Shlomo Y. & Dobson C. (2015) Effectiveness and cost-effectiveness of interferon beta and glatiramer acetate in the UK Multiple Sclerosis Risk Sharing Scheme at 6 years: a clinical cohort study with natural history comparator. *The Lancet Neurology* **14**, 497-505.

Pittas F., Ponsonby A.-L., van der Mei I.A.F., Taylor B.V., Blizzard L., Groom P., Ukoumunne O.C. & Dwyer T. (2009) Smoking is associated with progressive disease course and increased progression in clinical disability in a prospective cohort of people with multiple sclerosis. *Journal of Neurology* **256**, 577-85.

Polman C.H., Reingold S.C., Banwell B., Clanet M., Cohen J.A., Filippi M., Fujihara K., Havrdova E., Hutchinson M., Kappos L., Lublin F.D., Montalban X., O'Connor P., Sandberg-Wollheim M., Thompson A.J., Waubant E., Weinshenker B. & Wolinsky J.S. (2011) Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. *Annals of Neurology* **69**, 292-302.

Popescu V., Agosta F., Hulst H.E., Sluimer I.C., Knol D.L., Sormani M.P., Enzinger C., Ropele S., Alonso J., Sastre-Garriga J., Rovira A., Montalban X., Bodini B., Ciccarelli O., Khaleeli Z., Chard D.T., Matthews L., Palace J., Giorgio A., De Stefano N., Eisele P., Gass A., Polman C.H., Uitdehaag B.M.J., Messina M.J., Comi G., Filippi M., Barkhof F., Vrenken H. & Group o.b.o.t.M.S. (2013) Brain atrophy and lesion load predict long term disability in multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry* **84**, 1082-91.

Prosperini L., Giannì C., Leonardi L., De Giglio L., Borriello G., Galgani S., Pozzilli C. & Gasperini C. (2012) Escalation to natalizumab or switching among immunomodulators in relapsing multiple sclerosis. *Multiple Sclerosis Journal* **18**, 64-71.

Rovaris M., Comi G., Rocca M., Valsasina P., Ladkani D., Pieri E., Weiss S., Shifroni G., Wolinsky J., Filippi M. & European/Canadian Glatiramer Acetate Study Group (2007) Long-term follow-up of patients treated with glatiramer acetate: a multicentre, multinational extension of the European/Canadian double-blind, placebo-controlled, MRI-monitored trial. *Multiple Sclerosis* **13**, 502-8.

Rudick R.A., Stuart W.H., Calabresi P.A., Confavreux C., Galetta S.L., Radue E.-W., Lublin F.D., Weinstock-Guttman B., Wynn D.R., Lynn F., Panzara M.A. & Sandrock A.W. (2006) Natalizumab plus Interferon Beta-1a for Relapsing Multiple Sclerosis. *New England Journal of Medicine* **354**, 911-23.

Scalfari A., Neuhaus A., Daumer M., Muraro P.A. & Ebers G.C. (2014) Onset of secondary progressive phase and long-term evolution of multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry* **85**, 67-75.

Scolding N., Barnes D., Cader S., Chataway J., Chaudhuri A., Coles A., Giovannoni G., Miller D., Rashid W., Schmierer K., Shehu A., Silber E., Young C. & Zajicek J. (2015) Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. *Practical Neurology*.

Spelman T., Kalincik T., Zhang A., Pellegrini F., Wiendl H., Kappos L., Tsvetkova L., Belachew S., Hyde R., Verheul F., Grand-Maison F., Izquierdo G., Grammond P., Duquette P., Lugaresi A., Lechner-Scott J., Oreja-Guevara C., Hupperts R., Petersen T., Barnett M., Trojano M., Butzkueven H., the M.I. & the T.O.P.i. (2015) Comparative efficacy of switching to natalizumab in active multiple sclerosis. *Annals of Clinical and Translational Neurology* **2**, 373-87.

The CAMMS223 Trial Investigators (2008) Alemtuzumab vs. Interferon Beta-1a in Early Multiple Sclerosis. *New England Journal of Medicine* **359**, 1786-801.

The Neurological Alliance (2016) Neurology and primary care: Improving the transition from primary care for people with neurological conditions.

The PRISMS Study Group & The University of British Columbia MS/MRI Analysis Group (2001) PRISMS-4: Long-term efficacy of interferon-β-1a in relapsing MS. *Neurology* **56**, 1628-36.

Tornatore C., Phillips J.T., Khan O., Miller A.E. & Barnes C.J. (2012) Practice patterns of US neurologists in patients with CIS, RRMS, or RIS: A consensus study. *Neurology. Clinical Practice* **2**, 48-57.

Trojano M., Pellegrini F., Fuiani A., Paolicelli D., Zipoli V., Zimatore G.B., Di Monte E., Portaccio E., Lepore V., Livrea P. & Amato M.P. (2007) New natural history of interferon-β–treated relapsing multiple sclerosis. *Annals of Neurology* **61**, 300-6.

Trojano M., Pellegrini F., Paolicelli D., Fuiani A., Zimatore G.B., Tortorella C., Simone I.L., Patti F., Ghezzi A., Zipoli V., Rossi P., Pozzilli C., Salemi G., Lugaresi A., Bergamaschi R., Millefiorini E., Clerico M., Lus G., Vianello M., Avolio C., Cavalla P., Lepore V., Livrea P., Comi G. & Amato M.P. (2009) Real-life impact of early interferonβ therapy in relapsing multiple sclerosis. *Annals of Neurology* **66**, 513-20.

Wilsdon T., Barron A., Mitchell-Heggs A. & Ginoza S. (2014) Access to medicines for multiple sclerosis: Challenges and opportunities.