Brain health

Time matters in multiple sclerosis

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Preparation of the report and its recommendations was funded by an educational grant from F. Hoffmann-La Roche, who had no influence on the content.
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These organizations endorse the recommendations made in this report.
Acknowledgements

Preparation of the report and its recommendations was funded by an educational grant from F. Hoffmann-La Roche, who had no influence on the content.

Support for the independent writing and editing of this publication was provided by Oxford PharmaGenesis Ltd, UK, and was funded by an educational grant from F. Hoffmann-La Roche, who had no influence on the content.

Publication of the report and its recommendations was funded by grants from AbbVie and Genzyme and by educational grants from Biogen, F. Hoffmann-La Roche and Novartis, all of whom had no influence on the content.

This publication is available online at www.msbrainhealth.org
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Endorsements

The organizations listed below endorse the recommendations made in this report.

- Accelerated Cure Project for Multiple Sclerosis
- ACTRIMS (Americas Committee for Treatment and Research in Multiple Sclerosis)
- BCTRIMS (Brazilian Committee for Treatment and Research in Multiple Sclerosis)
- Consortium of Multiple Sclerosis Centers
- Czech MS Society (Unie ROSKA)
- ECTRIMS (European Committee for Treatment and Research in Multiple Sclerosis)
- European Brain Council
- European Multiple Sclerosis Platform
- French MS Society (Société Francophone de la Sclérose en Plaques)
- International Organization of Multiple Sclerosis Nurses
- International Society of Neuroimmunology
- LACTRIMS (Latin-American Committee for Treatment and Research in Multiple Sclerosis)
- MENACTRIMS (Middle East North Africa Committee for Treatment and Research in Multiple Sclerosis)
-MexCTRIMS (Mexican Committee for Treatment and Research in Multiple Sclerosis)
- Multiple Sclerosis Australia
- Multiple Sclerosis International Federation
- Multiple Sclerosis Ireland
- Multiple Sclerosis Research Australia
- Multiple Sclerosis Society
- Multiple Sclerosis Trust
- National Multiple Sclerosis Society
- PACTRIMS (Pan-Asian Committee for Treatment and Research in Multiple Sclerosis)
- RUCTRIMS (Russian Committee for Treatment and Research in Multiple Sclerosis)
- Shift.ms
Preface

This report presents an expert, evidence-based position for policy recommendations aimed at improving outcomes for people with multiple sclerosis (MS). It summarizes the evidence and consensus findings from the structured discussions of a global author group, comprising clinicians, researchers, specialist nurses, health economists and representatives from patient groups, all with expertise and experience in the area of MS.

In summarizing the available data, this report:

- demonstrates the personal and economic impact of MS (Section 1)
- examines the reasons behind delays in diagnosis (Section 2)
- presents the evidence base for a therapeutic strategy that aims to maximize lifelong brain health, centred around a more urgent approach to management, which involves:
  - early intervention with therapies most likely to provide optimal benefit and safety for each person with MS on an individualized basis (Section 3)
  - regular monitoring of disease activity and safety parameters (Section 4)
  - switching therapy based on evidence of disease activity (Section 5)
- provides guidance on how to improve access to treatment in order to create the optimal environment for this therapeutic strategy (Section 6).

Our vision is that the report and its recommendations will be used widely among those committed to creating a better future for people with MS and their families. Healthcare professionals, patient groups, healthcare authorities, health technology assessors, insurance companies, payers, regulatory authorities, government bodies, pharmaceutical companies and other relevant stakeholders who influence care quality can affect these outcomes; all have a responsibility to strive towards the highest possible standards of care.

A word on language

This report is aimed at a wide range of audiences and has been written in language that we hope can be easily understood by all readers. A glossary at the back of the document provides definitions of terms that may be unfamiliar.

In this report, the term established DMTs refers to disease-modifying therapies approved for relapsing forms of MS during the 1990s, and to reformulations and generic versions of these substances.

In this report, the term newer DMTs refers to disease-modifying therapies approved for relapsing forms of MS after the 1990s that have different mechanisms of action from established DMTs; some newer DMTs have an evidence base supporting efficacy superior to that of an established DMT, which may include head-to-head clinical trials or real-world evidence.
Executive summary

Multiple sclerosis (MS) is an incurable chronic disease in which the body’s own immune system destroys tissue in the brain and spinal cord. It is the leading cause of non-traumatic disability among young and middle-aged adults in many developed countries, and it affects 2.3 million people worldwide. Although there is no cure for MS, therapies exist that can alter the disease course by reducing disease activity and slowing down the accumulation of disability. This report recommends specific actions that aim to achieve the best possible outcome for every person with MS.

A therapeutic strategy that offers the best chance of preserving brain and spinal cord tissue early in the disease course needs to be widely accepted – and urgently adopted. Even in the early stages of MS, cognition, emotional well-being, quality of life, day-to-day activities and ability to work can be markedly affected by the damage occurring in the brain and spinal cord. As the disease progresses, increasing disability – such as difficulties in walking – imposes a heavy burden on people with MS and on their families. It also leads to substantial economic losses for society, owing to diminished working capacity.

Significant delays often occur before a person with symptoms suggestive of MS sees a neurologist for diagnosis and treatment. This is despite diagnosis being 10 times more rapid now than in the 1980s and substantial evidence that early treatment is more effective than later treatment. Campaigns to raise awareness of MS among the general public and among clinicians who make referrals are urgently needed, as they have the potential to improve outcomes by enabling earlier diagnosis. Initiatives to improve access to specialist MS healthcare professionals and specialized diagnostic procedures are also needed.

Early intervention is vital. Appropriate lifestyle interventions, treatment with a therapy that can reduce disease activity and consideration of rapid switching to another therapy if monitoring reveals a suboptimal response are crucial elements of the strategy. Involving people with MS proactively in decision-making and in managing their disease is also key to the successful management of MS. Healthcare professionals should encourage those in their care to play a fully informed, shared role in treatment decisions and to live a ‘brain-healthy’ lifestyle.

Regular monitoring of disease activity and recording this information formally are the cornerstone of the strategy recommended by the authors. The results of clinical examinations and brain scans will enable personalized treatment for every person with MS and will generate long-term real-world evidence that can be used by regulatory bodies, health technology assessors, payers and clinicians for evaluating therapeutic strategies.

Offering the full range of therapies that can reduce disease activity improves the chance of finding the best option for each person with MS. The number of effective therapies continues to grow, providing increasing scope to tailor treatment to individual needs. In many jurisdictions, however, access to therapies is limited by licensing stipulations, prescribing guidelines or reimbursement decisions; these typically lag behind the most recent clinical trial data and real-world evidence. We therefore call on regulatory bodies, healthcare authorities, insurance companies, health technology assessors and payers to improve access to therapies, so that personalized treatment can be optimized. We also recommend that the relevant bodies consider all costs to all parties when conducting economic evaluations and that they encourage the continuing investigation, development and use of cost-effective therapeutic strategies and alternative financing models.
Major public policy changes are needed in order to translate recent advances in the diagnosis and treatment of MS into improved outcomes. Enabling and promoting widespread adoption of the therapeutic strategy for MS recommended in this report has the potential to minimize disease activity and maximize lifelong brain health for those with the disease. It is time to make a real difference to the lives of people with MS and their families – and to avoid many of the long-term economic and personal costs that result from unnecessary irreversible disability.
Multiple sclerosis has a profound personal, social and economic impact. Better outcomes for people with MS and those who care for them can be achieved if organizations implement the following three sets of recommendations.

1. **Minimize delays in the diagnosis of MS and in the time to treatment initiation as these can result in irreversible disability progression.**

   - **Educate the general public to take prompt action if early symptoms of MS develop, by visiting a healthcare professional.**
     Awareness campaigns that highlight the typical initial symptoms, the negative impact of delaying treatment and the personal and societal costs of the disease would support this.

   - **Educate family and primary care physicians about the importance of promptly referring people with suspected MS to a neurologist, and ultimately to a specialist clinic, to speed up diagnosis and treatment initiation.**

   - **Recommend that general neurologists refer people suspected of having the disease to specialist MS neurologists.**

   - **Improve access to specialist care for MS: make diagnostic and monitoring procedures more widely accessible, increase the numbers of healthcare professionals who specialize in the management of MS, and ensure that these specialists provide prompt diagnostic and support services for people with suspected MS and those who have been newly diagnosed with the disease.**

   - **Adopt the latest accepted diagnostic criteria, in order to diagnose MS as early as possible.**

   - **Align prescribing guidelines with the latest accepted diagnostic criteria to give people with MS the opportunity to start treatment and receive support promptly, as soon as diagnosis is confirmed.**

National bodies may include government departments or private organizations, depending on the country in question.
### 2. Set goals for treatment and ongoing management that aim for the best possible outcome for every person with MS.

- **Ensure that MS healthcare professionals can take the time to educate people with MS about strategies to manage their disease.** Emphasize the importance of a ‘brain-healthy’ lifestyle, the benefits of early treatment with therapies that can modify the disease course, the likely consequences of inadequate or suboptimal treatment and the goal of minimizing disease activity while optimizing safety. 
  - National bodies
  - Professional bodies
  - Healthcare providers

- **Implement a shared decision-making process** that embodies dialogue between people with MS and healthcare professionals. A well-informed and proactive collaboration between people with MS and their healthcare team is vital to successful management of the disease. 
  - National bodies
  - Professional bodies
  - Healthcare providers

- **Make the full range of disease-modifying therapies available** to people with active relapsing forms of MS, regardless of their treatment history, to speed up adoption of the most appropriate treatment strategy that optimizes effectiveness and safety for each individual. 
  - Regulatory authorities
  - Healthcare providers
  - Health technology assessors
  - Reimbursement agencies

- **Include evidence from monitoring via regular clinical evaluation and scheduled/unscheduled MRI brain scans in any definitions of disease activity or suboptimal response,** in order to assist in the rapid identification of treatment failure and the decision to switch treatment. 
  - Healthcare providers
  - Regulatory authorities

- **Ensure that MS healthcare professionals can take the time to monitor disease activity** in people with MS. 
  - National bodies
  - Healthcare providers

- **Agree and implement standardized data collection techniques, protocols and data sets,** nationally and internationally, to track clinical and subclinical events in routine practice. **Incorporate these into a clinical management tool** to facilitate individualized practice. 
  - National and international bodies
  - Healthcare providers
  - Curators of registries and databases

- **Maintain treatment with a disease-modifying therapy** for as long as a person with MS would be at risk of inflammatory disease activity if they were not receiving treatment; in the case of a suboptimal response, make a prompt decision about whether or not to switch therapy. 
  - Healthcare providers
  - Reimbursement agencies

- **Seek regulatory and health technology assessment approvals** to implement these recommendations. 
  - Pharmaceutical companies
  - Professional bodies
  - Patient groups
  - Any other stakeholders

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National bodies may include government departments or private organizations, depending on the country in question.
3. Consult the most robust evidence base possible, and generate further evidence, in order to make good decisions about therapeutic and management strategies for MS.

- **Carry out economic evaluations of therapies and other healthcare interventions from a societal perspective**, considering the health benefits and costs to all parties, to improve assessments of true cost-effectiveness.

  - Health technology assessors
  - Reimbursement agencies
  - Patient groups

- **Encourage the continuing investigation, development and use of cost-effective therapeutic strategies**, of approaches that reduce the costs of managing MS and of alternative financing models, to improve access to treatment.

  - Regulatory authorities
  - Healthcare providers
  - Health technology assessors
  - Reimbursement agencies

- **Agree and implement standardized data collection techniques, protocols and data sets**, nationally and internationally, to track clinical and subclinical events in routine practice. **Incorporate these into national and international MS registries and databases** to generate real-world evidence of the long-term effectiveness and safety of therapeutic strategies; such evidence can be used by regulatory bodies and payers, and will enable differences in practice patterns to be assessed and addressed.

  - National and international bodies
  - Healthcare providers
  - Curators of registries and databases

- **Ensure that access to multiple sclerosis registries and databases is available** for those carrying out health technology assessments and economic evaluations.

  - National and international bodies
  - Healthcare providers
  - Curators of registries and databases

National bodies may include government departments or private organizations, depending on the country in question.
1. Raise awareness of the global burden of multiple sclerosis

Key points

- In multiple sclerosis (MS), tissue in the brain, spinal cord and optic nerve is destroyed by the body’s own immune system, often leading to physical disability and cognitive impairment.

- MS typically affects young adults in the prime of life. For many, bouts of symptoms (relapses), disability progression, fatigue and cognitive impairment markedly reduce their quality of life and ability to work or study.

- As disability worsens, personal and economic costs soar. Most of this additional burden falls on people with MS and on family members, many of whom become lifelong caregivers.

- Early and appropriate treatment can markedly reduce disease activity and accumulation of disability, but there is currently no cure for MS.

Multiple sclerosis affects young adults worldwide

MS is a progressive neurodegenerative disease that typically affects young adults in the prime of life, causing irreversible physical and mental disability. It is the leading cause of non-traumatic disability among young and middle-aged people in many developed countries.\(^1\) MS is the most common cause of wheelchair use among those aged 18–64 years,\(^2\) and the third most common cause of paralysis (after stroke and spinal cord injury) across all age groups\(^3\) in the USA. The disease thus negatively affects the lives of people with MS and their families, and leads to large, long-term health and economic burdens.

Globally, the estimated number of people with MS has increased from 2.1 million in 2008\(^4\) to 2.3 million in 2013.\(^1\) Better reporting and diagnosis\(^1\) and improved survival\(^8\) may have contributed to this change, although the disease has been shown to be on the increase in a UK population.\(^5\) MS is found worldwide but it becomes more common with increasing distance from the equator, particularly in the northern hemisphere.\(^7\) It is most prevalent in North America, Europe, Australia, New Zealand,\(^1\) other countries with Caucasian populations\(^8\) and Iran.\(^9\) The causes of MS are unclear, but risk is partially determined by a complex interaction between genetic\(^10\text{-}13\) and environmental\(^14\text{-}27\) factors.

Typically, MS is diagnosed in young, active people in their 20s or 30s,\(^28\) and about two-thirds of those affected are women.\(^1\) MS therefore affects people with the potential for many decades of employment ahead of them, who also may be making decisions about starting and raising families.

Multiple sclerosis is progressive and irreversible

Brain tissue is damaged and brain volume is lost

In MS, the immune system mistakenly attacks and damages tissue in the brain, spinal cord and optic nerve, collectively known as the central nervous system (CNS). This results in lesions (areas of acute injury) that can be seen in a brain scan or post-mortem examination, as well as diffuse damage that is more difficult to observe.\(^29\) Although repair mechanisms operate in the CNS, repair is often incomplete, some nerve tissue is irreversibly destroyed and the brain begins to atrophy (decrease in volume) more rapidly than in people unaffected by MS.\(^30\text{-}35\)

In healthy adults, a small amount of brain atrophy occurs with ageing – in the region of 0.1–0.5% per year.\(^36\) However, in many people with untreated MS the brain typically atrophies at a much higher rate, at about
1. Raise awareness of the global burden of multiple sclerosis

0.5–1.35% per year (Figure 1).36,37 Accelerated brain atrophy starts early, often before a diagnosis of MS (Figure 2a), and proceeds throughout the course of the disease if left untreated.31 The goal of treating MS should be to prevent damage to the brain and spinal cord that leads to accelerated atrophy.

Symptom burden worsens as damage to the brain accumulates

The brain appears to have an inbuilt neurological reserve – a finite capacity to retain function by remodelling itself to compensate for loss of nerve cells, loss of nerve fibres and atrophy. It does this partly by rerouting signals via undamaged areas or adapting undamaged areas to take on new functions.38,39 This ability is present in addition to the mechanisms that exist to repair physical damage to the CNS. Neurological reserve and repair mechanisms explain why MS-related brain damage may go undetected during the early phase of the disease – and therefore why MS may be undiagnosed and untreated for a long time. There is evidence that cognitive impairment is present in a significant proportion of people before the clinical symptoms of MS appear – sometimes years before.40 It is therefore important to diagnose MS as early as possible (Section 2), before neurological reserve is exhausted and the progressive stage of the disease begins (Figure 2b).

Usually, damage to the CNS is first detected when clinical symptoms appear. Symptoms may take the form of an attack (known as a relapse, or bout), when a lesion develops in a location that noticeably disrupts nerve function, although most lesions (~90%) do not directly lead to relapses (Figure 2c, 2d).41,42 Clinically evident progression of symptoms can also occur from the onset if neurological reserve is exhausted before a relapse occurs; however, progressive disease most often manifests after a period of relapses and remissions. Occasionally, lesions are detected before any clinical symptoms appear, on a brain scan43 that is conducted for another purpose (for example, headaches).

The range of symptoms experienced by a person with MS (Figure 3)44–47 can depend on the locations of lesions in the CNS. The most common clinical symptoms reported when first

First-person account46

The fine motor coordination in my left hand was affected, at times my speech was slurred, and the stiffness in my legs made walking extremely tiring and difficult ... I had gone from a very healthy and physically active person to a very handicapped one. My whole life had changed.

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Brain health: time matters in multiple sclerosis

Figure 2. The damage caused by MS typically leads to relapses followed by progressive disease.

**a.** The brains of people with MS shrink (atrophy) more rapidly than usual as a result of damage caused by the disease. 
**b.** The brain can use its neurological reserve to compensate for damage by remodelling itself. However, when neurological reserve is used up, the clinical symptoms of the disease may progress. 
**c.** MS causes lesions – acute areas of damage to the brain and spinal cord that accumulate over time. If a lesion noticeably disrupts nerve function, it leads to a relapse (an attack of clinical symptoms). 
**d.** A typical MS disease course involves relapses, followed by progressive disease. 
**e.** A person with MS may have a variety of diagnoses over time (see text for details), but disease-modifying therapies are effective only in the early stages when relapses are still present.

CIS, clinically isolated syndrome; NRSPMS, non-relapsing secondary progressive multiple sclerosis; RIS, radiologically isolated syndrome; RRMS, relapsing–remitting multiple sclerosis; RSPMS, relapsing secondary progressive multiple sclerosis.
1. Raise awareness of the global burden of multiple sclerosis

visiting a healthcare professional are sensory (40% of people with MS; numbness, tingling, burning pain), motor (39% of people with MS; weakness, stiffness, clumsiness, difficulty with walking), visual (30%) and fatigue (30%; a feeling of lacking physical or mental energy that interferes with usual or desired activities).1

Multiple sclerosis typically involves relapses and progression
People with brain lesions who have not yet had any clinical symptoms are said to have radiologically isolated syndrome (RIS) (Figure 2d, 2e). About one-third of people with RIS will go on to experience at least one attack of clinical symptoms within 5 years.48 An initial attack of symptoms is known as a clinically isolated syndrome (CIS) (Figure 2d, 2e).49 Many people (approximately 30–70%) with CIS will develop MS, even though they may not initially meet the full diagnostic criteria for the disease.49

About 80–90% of people with MS will initially have the relapsing–remitting form of the disease (RRMS) (Figure 2d, 2e).44,50 People with RRMS experience acute (sudden) attacks of symptoms (relapses). Usually, a relapse develops over a few days, before the symptoms plateau and ease off (remit) over the following few weeks or months;51 during this time CNS repair mechanisms operate and neurological reserve is ‘used up’ to remodel and compensate for the damage.38,39 Although complete physical recovery from a relapse often occurs (most likely early on),32 relapses can also be associated with

First-person account47

I always need help ... That really kills me. I've stopped going out because I'm afraid of doing it in my pants ... I’m always scared of sudden incontinence and creating a stink.

Figure 3. The symptoms of MS are distressing and exhausting.44–47
Brain health: time matters in multiple sclerosis

A sustained increase in disability,\textsuperscript{53,54} Incomplete recovery from relapses contributes to stepwise disability progression.\textsuperscript{51,52}

If and when neurological reserve and repair mechanisms are exhausted, and can no longer compensate for damage, a stage of progressive disability begins, called secondary progressive MS (SPMS).\textsuperscript{55} In SPMS, disability progressively worsens (with or without relapses),\textsuperscript{54,56,57} especially the ability to walk.\textsuperscript{58} Typically, there is an ‘overlap’ phase during which relapses still occur (relapsing SPMS, RSPMS), followed by progression with no relapses (non-relapsing SPMS, NRSPMS) (Figure 2d, 2e). If RRMS is left untreated, 50–60% of people develop SPMS within 15–20 years and it takes only 14 years on average for people to become unable to walk for 100 metres unaided.\textsuperscript{59} In addition, about 10–15% of people with MS have a progressive disease course from the outset, with a gradual progression of clinical symptoms in the absence of relapses (known as primary progressive MS; PPMS).\textsuperscript{60}

**Appropriate drug treatment can reduce disease activity**

The key therapeutic strategy in MS should be to minimize relapses, lesions and brain atrophy at all stages of the disease. This is especially important in early disease, when it is possible to reduce the number of new lesions and amount of brain inflammation, both of which lead to atrophy. This approach aims to maximize brain health, productivity and quality of life.

A number of disease-modifying therapies (DMTs) have been approved in various jurisdictions for treating CIS and relapsing forms of MS. These drugs can directly affect the disease course by reducing relapses, slowing disability progression, reducing the number of new lesions and slowing the rate of brain atrophy (Sections 3–5). To date, no DMTs have been approved for PPMS, and the only DMT to have been approved in a small number of jurisdictions for NRSPMS has since been removed from the market in the USA. Relapsing forms of MS are therefore the main focus of the DMT-related sections of this report.

**Multiple sclerosis affects all areas of life**

**Quality of life decreases as the disease advances**

Disability in MS is typically measured using the Kurtzke Expanded Disability Status Scale (EDSS), which allocates increasing numerical values to greater levels of physical disability (0.0, normal neurological functioning; 10.0, death).\textsuperscript{61} However many factors that affect quality of life, such as mental health, vitality,\textsuperscript{62} cognitive impairment\textsuperscript{63} and fatigue,\textsuperscript{64} are either not included or are poorly measured by the EDSS. Even in the early stages of MS, cognitive impairment may result in a lower quality of life,\textsuperscript{65} have a negative impact upon day-to-day activities\textsuperscript{66,67} and lead to a reduced ability to work.\textsuperscript{66,68} Persistent or sporadic fatigue also leads to a lower quality of life\textsuperscript{64} (see first-person account below) and affects about 75% of all people with MS.\textsuperscript{69}

When making decisions about how healthcare resources should be allocated, it is necessary to compare how different diseases affect health-related quality of life. In the cost-effectiveness analyses that drive such decisions, a person’s perspective on their state of health is measured using **utility**, a value between 1 (full health) and 0 (death). A number of studies have shown that people with MS report a lower utility than the

**First-person account\textsuperscript{70}**

What a silly word ‘fatigue’ is. It sounds like ‘I need to have a quick sit-down on this sofa’. In reality it’s more like ‘I can hardly move and my brain has shut down on me, I feel like I’ve just had a heavy bout of flu’.

It’s hard to predict when fatigue will strike. Sometimes I have to cancel meeting up with friends, or cut short a very happy outing when my energy slumps. I have to build in rest days to avoid a crash-and-burn episode of fatigue. These make my diary seem fuller than it really is. ‘No I can’t meet on Wednesday, it’s got to be a rest day’. I am lucky to have friends who are understanding of fatigue.

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1. Raise awareness of the global burden of multiple sclerosis

general population, even early in the disease when physical disability is minimal, and that they experience a rapid decrease in utility with increasing disability (Figure 4).62,63,71–73

Although advancing age can be expected to lead to a decrease in utility, people with MS in the 18–29-year age group already rate their own health status lower than those aged 80 years or older in the general population do. Also, when individuals in the same age group are compared, the average utility is about 0.2–0.3 points lower for people with MS compared with the general population (Figure 5).74

Many studies have shown that the worsening of symptoms that results from disability progression markedly affects day-to-day living and quality of life.62,76–79 The symptoms that emerge during relapses last for weeks to months and also lead to restricted mobility,80 a temporary worsening of pain,80 an increased risk of symptoms of depression,81 a lower quality of life and reduced function,62,82 these are on top of the significant symptom burden that may already have accumulated.

Multiple sclerosis often results in unemployment

Unemployment levels among people with MS are higher than those in the general population, even at low levels of physical disability (Figure 6).71,72,83 This suggests that the ability to work is affected early on; the most likely reasons for this are problems such as cognitive decline, fatigue, depression and anxiety, which are not fully captured by the EDSS. This observation is supported by real-world evidence (evidence obtained from outside the clinical trial setting), which indicates that cognitive impairment84,85 and fatigue, as well as problems with hand function and mobility,84 are associated with an increased likelihood of becoming unemployed.

**First-person account**75

My mother is 20 years older than I am and I can’t keep up with her. I do feel that I’ve been cheated. I have been made an old woman before my time.

**First-person account**75

One of the things that I found difficult was losing friendship because you are no longer in the workforce. It becomes a pretty lonely thing.
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Figure 5. People with MS report a lower average health status (mean utility) than those of a similar age in the general population.\textsuperscript{74}

EDSS, Kurtzke Expanded Disability Status Scale.
Reproduced and adapted with permission from Gisela Kobelt from Kobelt G, Kasteng F. Access to innovative treatments in multiple sclerosis in Europe. The European Federation of Pharmaceutical Industry Associations (EFPIA) 2009.\textsuperscript{74} © Gisela Kobelt 2009.

Figure 6. The proportion of people with MS who are in employment is greatly reduced even at low levels of physical disability, and decreases markedly as disability increases.\textsuperscript{71,72,83}

EDSS, Kurtzke Expanded Disability Status Scale.
The range (shaded areas) and median (dotted lines) of the proportion of the general population in employment are shown for the age groups stated for the countries listed. It should be noted that, in many of these countries, people retire at less than 65 years of age.
Reproduced and adapted from J Neurol Neurosurg Psychiatry, Kobelt G, Berg J, Lindgren P et al. 77, 918–26, © 2006 with permission from BMJ Publishing Group Ltd.
As physical disability progresses, the proportion of people with MS who are unemployed rises markedly (Figure 6). Case studies have shown, however, that the chances of people with MS remaining in the workforce can be improved by using approaches that focus on ability (rather than on disability), such as adapting working environments, working hours and job roles. Indeed, a Europe-wide campaign focusing on supporting sustainable employment was launched in March 2015 by the European Multiple Sclerosis Platform.

Being a caregiver can be a lifetime commitment
Despite the devastating impact of the disease, the life expectancy of people with MS is reduced by only 5–10 years; this indicates that many individuals live a long time with substantial disability. As a result, nearly one-third of people with MS need care, about 80% of which is provided ‘informally’ by unpaid caregivers such as relatives. As the disease progresses, the need for care gradually increases. A typical informal caregiver spends more than 4 hours per day on caring activities over many years, which is both physically and emotionally draining. Thus, the personal costs of disability progression fall not just on people with MS but also on their families.

Figure 7. The total societal costs of MS are borne mainly by health and social care services, people with MS and their families.
DMT, disease-modifying therapy; GP, general practitioner (family or primary care physician).

Caregiver account
My old life has vanished. It’s just me, my husband, and his disease. That’s all. The disease stands between me and my husband. I used to work, now my life is dedicated to him. This is all very depressing and I don’t know how long I can go on.
Costs of multiple sclerosis soar as the disease progresses

The total costs of MS to society include direct medical and non-medical costs, and indirect costs (Figure 7). In Europe, the overall annual cost of MS to society has been estimated at €15.5 billion. This represents an average annual cost of €37 000 per person with MS,74 comparable with averages of $52 000 (€39 000) in the USA75 and AUD 49 000 (€33 000) in Australia.93 (For ease of comparison, all monetary values in this section have been adjusted to 2010 values using the Consumer Price Index.)

This annual cost per person is greater than that for other long-term conditions such as asthma,94 chronic obstructive pulmonary disease (a collection of chronic lung problems)95,96 and diabetes.97 It is also greater than the annual cost per person of most other brain disorders considered by the European Brain Council in a series of economic cost estimates,98 apart from the neuromuscular condition Guillain–Barré syndrome (which costs approximately €54 000 per person,98 about 80% of whom do not have persistent neurological problems99 — unlike in MS where accumulated disability is mostly irreversible).98

Figure 8. As disability progresses, informal care (black) and indirect costs (dark orange) increase dramatically and greatly exceed the cost of pharmaceuticals (medicines; light orange).71

Average annual costs per person with MS a in the UK and b in Germany at EDSS scores 2.0 and 6.5, converted to 2010 euros. Examples of items in each cost category can be found in Figure 7. Percentages have been independently rounded. EDSS, Kurtzke Expanded Disability Status Scale.
As a person with MS becomes more disabled, total societal costs (detailed in Figure 7) increase significantly. In Europe, the mean annual cost per person with MS has been estimated at €23 000 for EDSS score 0.0–3.5, rising as disability increases to €46 000 for EDSS score 4.0–6.5 and €77 000 for EDSS score 7.0–9.5.\(^7^4\) **Indirect costs** (productivity losses associated with sick leave, incapacity to work and early retirement) – and especially **informal care costs** – increase dramatically with increasing disability (Figure 8).\(^7^1\) This additional cost burden falls largely outside of the healthcare and social care systems, and a lot of it is borne by people with MS and their families. Medicines (pharmaceuticals) comprise a relatively low proportion of total societal costs, especially at greater levels of disability (Figure 8).\(^7^1\)

Relapses also lead to additional costs, only about half of which are borne by the healthcare system (for example, inpatient, outpatient and professional care, consultations, tests and medicines).\(^1^0^0^–^1^0^4\) The cost per relapse was estimated at €3400–9600 in a series of recent European studies in people with RRMS and EDSS scores less than 5.0\(^1^0^0^–^1^0^7\) and at $10 100 (€7600) in members of a US patient support group with RRMS.\(^8^2\)

These data show that the bulk of the additional costs of disability progression and roughly half of the costs of relapses fall outside the healthcare and social care systems. However, in many countries these significant societal costs are not considered when treatments for MS are being assessed (Section 6).

The following sections of this report outline a therapeutic strategy that has the potential to improve outcomes for people with relapsing forms of MS by reducing relapses and disability progression. It could also lead to lower formal and informal care costs and indirect costs, which escalate at higher levels of disability.
2. Speed up referral and diagnosis

**Key points**
- The earlier that MS can be diagnosed, the sooner treatment can be initiated.
- Ideally, people with suspected MS should be referred for diagnosis to a neurologist with a special interest, and expertise, in MS and an experienced team and facilities at their disposal. Such specialists are best placed to diagnose, treat and manage MS.
- It is currently possible to diagnose MS earlier than ever before – 10 times more rapidly than in the 1980s – by using evidence from magnetic resonance imaging (MRI) brain scans in conjunction with clinical assessments.
- However, significant delays can still occur between noticing the first symptoms and receiving a diagnosis. Such delays could be reduced by improving awareness of MS among the general public and healthcare professionals who make referrals and by improving access to specialist MS healthcare professionals and diagnostic equipment.

**Time is critical to preserving brain volume and physical function**

As discussed in Section 1, many people with CIS and early MS already experience brain atrophy more rapidly than the general population (Figure 1). This loss of brain tissue is often subclinical (not accompanied by clinical symptoms), owing to repair mechanisms in the CNS and neurological reserve that enable the brain to reorganize itself and reroute pathways to avoid damaged areas, even when repair is incomplete. If the brain were not so flexible, clinical symptoms of MS would become apparent sooner; this remarkable ability to compensate means that ongoing damage may go unrecognized until neurological reserve has deteriorated significantly.

In the absence of a cure for MS, the aim of starting treatment with a DMT should be to reduce subclinical disease activity, preserve brain volume and slow or prevent disability progression. Early diagnosis means that early DMT initiation can be accompanied by other appropriate steps to preserve brain tissue and optimize brain health (for example, exercise, smoking cessation, weight loss and control of comorbidities [other diseases present alongside MS] such as high blood pressure). This approach maximizes the chances of altering the disease course before further relapses or disability progression occur (Section 3).

**Early referral to a neurologist is essential**

Generally, a person experiencing symptoms compatible with early MS will go initially to their family doctor or primary care physician or to a hospital. From there, they should be referred urgently to a neurologist – a doctor who specializes in diseases of the nervous system.

**First-person account**

I started getting a lot of pain in my legs and lower back. Along with the pain, I was getting weird nerve sensations in my legs and my legs felt as though they were getting weaker and weaker. This continued from 2003 to this day. I saw orthopaedic specialists on nine occasions and they put the problems down to the sciatic nerve. In 2010 ... I registered with a new doctor ... . He told me he was referring me to a neurosurgeon [sic] to get this checked out properly. In early 2011, I was sent for full body MRI scans and lumbar punctures ... finally ... [in] February 2012, I was diagnosed with primary progressive MS ... . I have fought for 9 years to try and work out what was going on in my legs.

With permission from the Multiple Sclerosis Trust
Neurology is a wide-ranging discipline that has grown in complexity over the years, resulting in sub-specialization. For example, a world-leading neurology department of a large hospital may offer specialist clinics in the areas of epilepsy, headache, motor neurone disease, movement disorders (such as Parkinson’s disease), peripheral nerve disorders, and MS (sometimes combined with other autoimmune disorders under the term ‘neuroimmunology’).111

**Referral to an MS neurologist is desirable**

MS is a complex disease, and neurologists who specialize in MS (MS neurologists),112 together with their multidisciplinary teams (Table 1), are best placed to provide routine diagnosis and an

<table>
<thead>
<tr>
<th>Specialist aspect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS neurologists have access to specialist equipment and personnel</td>
<td>MS neurologists have direct access to specialist diagnostic and monitoring equipment (for example, MRI scanners) and often work with experienced and MS-specialized staff, including nurses, physiotherapists, psychologists and others</td>
</tr>
<tr>
<td>MS neurologists have knowledge of rapidly evolving treatment options</td>
<td>MS neurologists have in-depth knowledge of the latest techniques and treatment options. In the last 5 years alone, five new DMTs were approved for use in the USA113–117 and Europe;118–122 the situation is similar in other geographical regions</td>
</tr>
<tr>
<td>MS specialist nurses can implement programmes and support people with MS</td>
<td>MS specialist nurses are the key staff members in many MS clinical services. Their varied roles include implementation of DMT safety and effectiveness monitoring programmes, support and counselling, case management, symptom screening and management, and provision of education about MS disease and DMTs. There is evidence that MS specialist nurses are highly valued by people with MS,126 can provide emotional support123 and can improve their knowledge, confidence and ability to cope124</td>
</tr>
<tr>
<td>Involving MS specialist nurses can save money</td>
<td>The potential for economic savings has been illustrated in a number of case studies when MS specialist nurses were involved in ongoing care, through reduced numbers of hospital admissions and neurologist appointments125</td>
</tr>
<tr>
<td>Specialist clinics enable rapid diagnosis</td>
<td>Diagnosis of MS and CIS was more rapid at a specialist clinic compared with non-specialist options for those suspected of having demyelinating diseases (that is, diseases in which the sheath surrounding the nerves is damaged)126</td>
</tr>
<tr>
<td>Access to MS healthcare professionals increases the likelihood of people with MS taking a DMT</td>
<td>People with MS were more than twice as likely to be taking a DMT if they had access to an MS neurologist or specialist nurse, according to a 2013 UK survey. In Northern Ireland, a region where people with MS are invited to see a neurologist or MS specialist nurse for a twice-yearly review (unlike in the rest of the UK), 70% more people with MS eligible to receive a DMT were taking one compared with the national average127</td>
</tr>
<tr>
<td>A multidisciplinary team offers an integrated approach to care where different aspects of the disease are managed by specialists</td>
<td>Team members may include: MS neurologist, MS specialist nurse, physiotherapist, ophthalmologist, pharmacist, clinical psychologist, psychiatrist, occupational therapist, speech therapist, pain management specialist, chiropodist/podiatrist, urologist, continence advisor, social worker, dietician1</td>
</tr>
</tbody>
</table>

**Table 1.** Neurologists with a special interest in MS (described above as MS neurologists) and their multidisciplinary teams have extensive experience, knowledge and facilities at their disposal.

CIS, clinically isolated syndrome; DMT, disease-modifying therapy; MRI, magnetic resonance imaging.
Brain health: time matters in multiple sclerosis

integrated approach to specialist care and management.1,13–127 MS neurologists have broad experience of the long-term management of MS and the fast pace of changes in understanding of the disease, diagnostic criteria, treatment options and monitoring processes.

However, access to MS healthcare professionals, specialist teams and diagnostic facilities varies widely across the globe. There are about 120 times more MRI scanners and neurologists per capita in high-income countries than in low-income countries – and the numbers per capita vary considerably even within high-income countries – according to a 2013 survey.1 In addition, the existence of multidisciplinary hospital-based teams was reported by respondents from 36 of the 52 countries for which the survey question was completed.1 These data indicate that the existence of specialist personnel or facilities does not necessarily imply that they are readily accessible in practice.

Modern technology can be used to address some of the inequalities in access to diagnostic services and ongoing specialist care for people with MS, as indicated by a number of pilot studies in the field of telemedicine (remote diagnosis, treatment or ongoing management using telecommunications technology) (Table 2).129–136 Although telemedicine has proved to be extremely useful for servicing remote populations, it does not solve the problem of a low density of services per capita.

Technology can also provide greater access to specialist training for MS healthcare professionals. For example, 2379 nurses from 30 countries across the globe137 have registered for the MS Nurse Professional course, led by the European Multiple Sclerosis Platform in collaboration with the International Organization of Multiple Sclerosis Nurses and Rehabilitation in MS,138 in the 2 years to March 2015.

<table>
<thead>
<tr>
<th>Type of telemedicine resource</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis of lesions on MRI scans using software that runs in a web browser</td>
<td>Similar results to those obtained using conventional software129</td>
</tr>
<tr>
<td>Remote assessment of disability</td>
<td>Clinically valid information and similar total EDSS scores compared with ‘in-person assessments’ using a videoconference link130 or low-cost webcam131</td>
</tr>
<tr>
<td>Home-based rehabilitation programmes</td>
<td>Improvements in function, such as walking, balance132 and postural control133</td>
</tr>
<tr>
<td></td>
<td>Low-level evidence for reduction in impairments (such as fatigue, pain and insomnia) and improvement in functional activities and participation, based on a systematic review of nine randomized controlled trials134</td>
</tr>
<tr>
<td>Brief telecounselling sessions and home monitoring</td>
<td>Better adherence to medication than that found for people who did not receive these services135</td>
</tr>
<tr>
<td>Home monitoring</td>
<td>Less severe symptoms than in those who did not receive the service; additionally, two-thirds of those in the telecare home-monitoring group had a decrease in medical costs of at least 35%136</td>
</tr>
</tbody>
</table>

Table 2. Telemedicine can help to improve access to diagnostic services and ongoing specialist care by extending services to remote populations, as indicated by the results of several pilot studies.

EDSS, Kurtzke Expanded Disability Status Scale; MRI, magnetic resonance imaging.
Delays in the referral pathway are common

Delays between the onset of symptoms and MS diagnosis can occur at two key points. Delays between the onset of symptoms and an initial consultation with a healthcare professional are common\textsuperscript{126,139} and can last more than 1 year.\textsuperscript{139} This indicates the need to raise awareness of the symptoms of MS among the general population.\textsuperscript{139}

Further delays may then occur before eventual diagnosis by a specialist healthcare professional (neurologist or MS neurologist). In addition to waiting lists that inevitably occur when the numbers of neurologists per capita are low, such delays can also result from non-availability of diagnostic tools such as MRI scanners and lumbar puncture, from administrative issues (for example, long waiting lists for neurology services after referral)\textsuperscript{140} and from lack of awareness among family or primary care physicians (Figure 9).\textsuperscript{126,139,140}

There is evidence of a relationship between delays in referral to an MS neurologist and disability level at the time of the first visit: the longer the delay, the greater the initial disability level at that time.\textsuperscript{141} The effects of delays between diagnosis and treatment initiation are described in Section 3.

Magnetic resonance imaging evidence assists early diagnosis

Symptoms similar to those of MS appear in many other conditions.\textsuperscript{142} Therefore when making a diagnosis, clear differentiation between these other conditions and MS is crucial. Being diagnosed with a chronic, unpredictable, progressive incurable disease such as MS has huge personal implications, including reduced employability, increased anxiety and mental distress, and years of taking medicines.\textsuperscript{143}

Early diagnostic criteria required two or more acute clinical relapses

Historically, it was difficult to diagnose MS because lesions in the CNS could only be observed directly on autopsy. The early diagnostic criteria for MS (the Schumacher\textsuperscript{144}
and Poser criteria, published in 1965 and 1983, respectively) therefore relied on directly observable events: a diagnosis of clinically definite MS required at least two acute clinical relapses. The Poser criteria also incorporated evidence from electrical measurements of brain activity when certain nerves are stimulated (‘evoked potentials’) and lumbar puncture to help to support the clinical diagnosis.145

Evidence from brain scans now allows faster and more accurate diagnosis With the advent of MRI it became possible to classify lesion patterns in the CNS that are suggestive of MS. As understanding of MRI improved, the McDonald diagnostic criteria were introduced in 2001146 and further refined in 2005147,148 and 2010.149 The McDonald criteria allow a diagnosis of MS to be made in a person who has had just one relapse, by incorporating evidence from MRI scans. The criteria recognize that diagnostic certainty can be increased when lesions are observed in typical locations and when they can be shown to have appeared over a period of time (rather than all at once).150

As a result of incorporation of MRI evidence into the diagnostic criteria, people with MS can have their condition diagnosed more rapidly than was previously possible and in a more sensitive and consistent way.151 The number of people whose MS is accurately diagnosed within 1 year of their first relapse more than doubles152 or triples153 using the original McDonald criteria compared with the Poser criteria. In addition, a diagnosis can be established from the earliest MRI scans in about one in five people who have experienced a single relapse using the 2010 McDonald criteria.154 It should be noted, however, that the McDonald criteria are not always used consistently in clinical practice.155

Greater diagnostic certainty enables earlier treatment The McDonald criteria are now widely accepted and used to establish a diagnosis of MS. Of the 105 countries for which data were provided in a 2013 global survey, a version of the McDonald criteria was reported as being used in 92%.156 Real-world evidence from the USA shows that the average delay from symptom onset to diagnosis has fallen 10-fold, from 7.2 years in 1980–1984 to 0.63 years in 2000–2004 (Table 3).157 In the same time period, the proportion of people who had moderate or severe disability (as opposed to mild disability) on their initial visit to a healthcare professional fell from over 50% to about 25%.157 Early diagnosis means that early treatment is possible – which will improve the long-term prognosis for people with MS by reducing subsequent damage to the CNS and preventing further unnecessary clinical relapses or disability progression (Section 3).

Table 3. There has been a 10-fold decrease in the delay between the onset of MS symptoms and diagnosis since 1980 in the USA.157 SD, standard deviation.

<table>
<thead>
<tr>
<th>Onset of symptoms</th>
<th>Mean (SD) delay (years) from onset of symptoms to diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980–1984</td>
<td>7.2 (5.7)</td>
</tr>
<tr>
<td>1985–1989</td>
<td>5.3 (4.4)</td>
</tr>
<tr>
<td>1990–1994</td>
<td>3.7 (3.2)</td>
</tr>
<tr>
<td>1995–1999</td>
<td>1.8 (1.7)</td>
</tr>
<tr>
<td>2000–2004</td>
<td>0.63 (0.8)</td>
</tr>
</tbody>
</table>

The evolution and subsequent implementation of MS diagnostic criteria is an excellent example of the use of an evidence base to improve clinical practice and outcomes for people with MS. Despite clear diagnostic evidence, however, the prescribing guidelines for MS issued by national healthcare authorities in some countries still require a person to experience two clinical relapses, and in some cases disabling relapses, before a DMT can be initiated (Section 3). This means that further irreversible damage to the CNS can occur, both during the time spent waiting for a second relapse and as a result of the relapse itself.
2. Speed up referral and diagnosis

**Recommendations**

Delays in the diagnosis of MS should be minimized as these can result in irreversible disability progression.

- **Educate the general public to take prompt action if early symptoms of MS develop, by visiting a healthcare professional.** Awareness campaigns that highlight the typical initial symptoms, the negative impact of delaying treatment and the personal and societal costs of the disease would support this.

- **Educate family and primary care physicians about the importance of promptly referring people with suspected MS to a neurologist,** and ultimately to a specialist clinic, to speed up diagnosis and treatment initiation.

- **Recommend that general neurologists refer people suspected of having the disease to specialist MS neurologists.**

- **Improve access to specialist care for MS:** make diagnostic and monitoring procedures more widely accessible, increase the numbers of healthcare professionals who specialize in the management of MS, and ensure that these specialists provide prompt diagnostic and support services for people with suspected MS and those who have been newly diagnosed with the disease.

- **Adopt the latest accepted diagnostic criteria,** in order to diagnose MS as early as possible.
3. Intervene early to maximize lifelong brain health

Key points

- The goal of treating MS should be to preserve brain tissue and maximize lifelong brain health by reducing disease activity.
- There is a lot of evidence to support the therapeutic strategy of early intervention with a DMT. This should accompany measures to encourage a ‘brain-healthy’ lifestyle as part of a comprehensive approach to treatment.
- However, initiating treatment with a DMT is often delayed and subject to restrictions in licensing, prescribing guidelines and reimbursement policies.
- Treatment options are rapidly evolving and many DMTs are now available. They are not all equally effective in all people with MS, and they have a variety of side-effect profiles.
- The choice to initiate treatment should be an informed, shared decision between the person with MS and their clinician, and should consider all appropriate DMTs. The disease course, values, needs, limitations and lifestyle of the person with MS should all be assessed in parallel with the potential benefits and risks of specific DMTs.

Intervention should aim to maximize brain health and physical function

Early intervention is key

MS causes irreversible damage to the brain and spinal cord. Although repair mechanisms and remodelling of the CNS can partially compensate for a while, these mechanisms eventually fail to keep up with the damage caused by inflammatory disease activity. Ultimately neurological reserve – the capacity that the CNS has to compensate for injury by remodelling itself – is exhausted (Figure 2b). The clinical consequences of MS then become clear – steady increases in physical and mental disability without remissions, as seen in people who have transitioned to SPMS.

Following this transition, the opportunity to change the course of the disease is diminished. No DMTs have been approved worldwide for NRSPMS, and – even if treatment were possible – reversal of persistent disability is highly unlikely. Additionally, the depletion of neurological reserve means that fewer resources remain to combat the cognitive and physical effects of normal age-related brain atrophy. Effective DMT and lifestyle interventions must, therefore, be initiated as soon as the disease is diagnosed in order to protect neurological reserve and maximize lifelong brain health. This approach is in line with the principles on brain health established by the World Federation of Neurology and promoted across a number of brain and mental health disease areas by the World Brain Alliance.

Treating and managing multiple sclerosis requires a comprehensive approach

Maximizing lifelong brain health is equivalent to preserving neurological reserve. The results of recent research imply that neurological reserve has two components: brain reserve (brain volume) and cognitive reserve (see Box opposite). Preserving brain volume and cognitive reserve protects against disability progression, and these two factors independently protect against disease-related cognitive decline. The therapeutic strategy in MS should aim to preserve as much brain reserve and cognitive reserve as possible by using DMTs to slow down the disease course and by adopting a ‘brain-healthy’ lifestyle.

Cardiovascular fitness correlates with brain volume and cognitive reserve (processing speed) in people with MS, and improving it...
3. Intervene early to maximize lifelong brain health

Aerobic exercise should be part of managing MS. Avoidance of smoking should be another component of a ‘brain-healthy’ lifestyle. Cigarette smoking is associated with decreased brain volume in people with MS, as well as with higher relapse rates, increased disability progression, increased cognitive impairment and reduced survival compared with not smoking. Additionally, smokers with CIS are nearly twice as likely as non-smokers with CIS to develop further inflammatory lesions and, thus, MS. Limiting the use of alcohol is also important, because there is evidence that unsafe levels of drinking (currently or in the past) lead to reduced survival in people with MS.

Activities that enhance cognitive reserve by being intellectually enriching (such as education, reading, hobbies and creative expression) have been shown to protect against cognitive impairment in MS when pursued over a lifetime and should be prioritized day-to-day.

Minimizing comorbidities (other diseases present alongside MS) will help to reduce their negative effect on the MS disease course and to limit the potential for disability unrelated to MS, which can add to the overall impairment burden.

- In people with MS, high blood pressure and heart disease are both associated with lower brain volume, and obesity is associated with higher lesion numbers.
- High blood pressure, type 2 diabetes, dyslipidaemia (high levels of cholesterol and/or fat in the blood) and peripheral artery disease (narrowing of the arteries outside of the heart and brain) are all associated with greater disability progression if they co-exist at any time in the MS disease course; so too are vascular diseases in general (those affecting the blood vessel system).

Heart disease, influenza, pneumonia, urinary tract infections and cancer are all predictors of reduced survival among people with MS.

To summarize, maximizing lifelong brain health in MS involves a comprehensive approach that incorporates lifestyle measures such as aerobic exercise, avoidance of smoking and excessive alcohol consumption, activities that enhance cognitive reserve, and steps to minimize comorbidities, in addition to intervention with a DMT (the focus of the remainder of this section).

A lot of evidence supports early intervention with a DMT

Long-term studies clearly show that early intervention with a DMT is more likely than late intervention to lead to a better outcome in people with CIS and RRMS (Figure 10). There are three main components to the body of evidence supporting this.

- In people with a diagnosis of CIS, treatment with a DMT increases the time to a second relapse (that is, conversion to RRMS under any diagnostic criteria) and improves MRI outcomes, including brain atrophy rate (Appendix 1a).
- In people with a diagnosis of CIS, initiating treatment with a DMT early in the disease course is associated with better long-term outcomes than delaying treatment (Appendix 1b).
In people with a diagnosis of RRMS, initiating treatment with a DMT early in the disease course is associated with better long-term outcomes than delaying treatment ([Appendix 1c]).198–209

It is important to note that, nowadays, many of the participants in the CIS trials summarized in [Appendix 1a and 1b] would have been diagnosed with RRMS according to the 2010 revision of the McDonald diagnostic criteria.210 Therefore, this evidence also supports early treatment in RRMS.

In the majority of studies summarized in [Appendix 1b and 1c], participants were randomly chosen to receive either a DMT or placebo (a ‘dummy’ treatment with no therapeutic effect) for an initial period, followed by a DMT for an extended period. These ‘placebo-switch’ studies therefore show the difference between initiating a DMT early in the disease course and later.

Further evidence that DMTs are most effective early in the disease course is provided by a recent meta-analysis of published randomized clinical trials in RRMS. This showed that DMTs are more effective at slowing disability progression from MS in younger people than in older people; they also reduce the relapse rate most effectively in younger people (rather than older people), in patients with low EDSS scores (rather than high scores) and in those with active lesions (i.e. lesions that are currently inflamed) rather than no active lesions.211

Support for early treatment in RRMS is also provided by real-world evidence from databases and registries ([Appendix 1c]).208,209 In addition, for people with CIS, an analysis of data from an international registry shows that the greater the length of time spent taking a DMT within 12 months of onset, the lower the risk of a sustained increase of at least 1 point on the EDSS in the same time period.212 Furthermore, data from the Swedish registry indicate that earlier treatment with a DMT is associated with slower disability progression (from diagnosis of MS to EDSS score ≥ 4.0) than later treatment.213

Initiating treatment with a DMT “as early as possible in eligible patients” is also recommended in the 2015 guidelines from the Association of British Neurologists (ABN).112 Once a transition from RRMS to SPMS has occurred, however, DMTs become ineffective at preventing disability progression,214–216 although some clinical trials have demonstrated significant effects on the relapse rate,214,215 number of new lesions215–217 and total lesion volume on MRI.216,217 To date, no DMTs have been approved for PPMS, and the only DMT to have been approved in a small number of

**Figure 10.** Early intervention with a DMT in MS and CIS is thought to give the best long-term prognosis. CIS, clinically isolated syndrome; DMT, disease-modifying therapy.
3. Intervene early to maximize lifelong brain health

Jurisdictions for NRSPMS has since been removed from the market in the USA.

**Disease-modifying therapies are not all equally effective**

During the 1990s, several DMTs were approved for relapsing forms of MS; in this report these are collectively referred to as ‘established DMTs’. Real-world evidence of their long-term effectiveness is mixed; some studies report that a particular class of established DMT can slow (but not prevent) disability progression and conversion to SPMS, but others report no effect on disability progression or on the risk of developing SPMS. The results of these studies indicate that established DMTs are, at best, modestly effective in altering the natural disease course of MS.

From the 2000s onwards, several ‘newer DMTs’ have been developed and approved. A number of these have been shown to be more effective at reducing disability progression, relapse rate and/or burden of lesions when compared head-to-head with established DMTs in clinical trials. (It should be noted that many participants in clinical trials are newly diagnosed with MS and are therefore starting treatment with a newer DMT.) Some newer DMTs that have been approved for clinical use have not been subject to head-to-head trials but have instead been compared with placebo or tested in a study that was set up to include an established DMT as a ‘reference arm’ (see Glossary) rather than a direct comparator. Furthermore, a number of other DMTs are in various stages of development – a fact that highlights the increasing complexity of MS management and the need for early specialist referral.

Each of the newer DMTs is associated with a particular set of benefits and risks (e.g. possible side effects) and sits in a unique class of drugs. They also have a variety of mechanisms of action (the biochemical interactions through which drugs mediate their effects), formulations (ways in which the active drug is combined with other ingredients to make the final product) and routes of delivery (for example, pills, injections, infusions). It is therefore not always straightforward to choose the DMT that is most appropriate to the disease course, values, needs, limitations and lifestyle of each person with MS (see later in this section).

**Disease-modifying therapy is often started late, with restricted choice**

**Treatment initiation criteria may lag behind diagnostic criteria**

The revised McDonald (2010) diagnostic criteria enable an MS diagnosis to be made on the basis of one attack (relapse) and MRI evidence from a baseline scan (Section 2). However, in a 2013 global survey of 106 countries, responders from 14 of the 27 countries for which data were provided on criteria for initiating DMT in people diagnosed with RRMS reported that these included the requirement for at least two clinically significant relapses within 2 years. This reflects the Poser diagnostic criteria, which have been obsolete for over a decade since the widespread adoption of the McDonald criteria.

Prescribing guidelines governing DMT initiation should evolve in parallel with diagnostic criteria in order to prevent unnecessary loss of cognitive reserve, loss of brain tissue, deterioration in brain health and disability progression as a result of waiting for further relapses to occur before starting treatment.

**Initial treatment options may be restricted**

Once the decision has been made to initiate treatment, the choice of initial DMT is influenced by several factors, including DMT licensing, prescribing guidelines, reimbursement, the disease course and the personal attitudes, knowledge and life choices of people with MS and their clinicians (Table 4). Even if several initial DMT options have been approved by regulatory authorities, national/local prescribing guidelines and reimbursement policies may curtail genuine choice. Some regulators and insurers impose treatment sequence restrictions, only allowing people with MS access to some DMTs after they have first experienced treatment failure on an established DMT. This means that a particular DMT may be available for initial use according to its licence, but not be accessible in practice – as illustrated in the following examples.

- In the USA, some insurance companies require a person with MS to experience treatment failure on a DMT from their ‘preferred formulary’ (typically a less-expensive established DMT) before they will reimburse the cost of a different DMT.
In Spain and Italy, prescribing guidelines and formularies operate at a regional level, and the DMTs available for initial use may differ from the list of nationally reimbursed DMTs.\textsuperscript{230,231}

National reimbursement guidelines in a number of European countries place greater restrictions on the circumstance under which a particular newer DMT will be funded than the licence issued by the European Medicines Agency (EMA) (Section 6).\textsuperscript{231}

In some countries, no DMT costs are reimbursed by the government or insurance companies, and in others, only established DMTs are funded.\textsuperscript{235–238} This is discussed further in Section 6.
3. Intervene early to maximize lifelong brain health

How is treatment initiated in clinical practice?

MS is a rapidly evolving specialty, and the publication dates of studies that investigate how treatment is initiated lag behind the available DMT options. According to the results of a number of studies, the most recent of which includes data from 2011, many people with MS do not start treatment with a DMT (Table 5), and most of those who do so receive an established DMT (Table 6). Although these results probably reflect clinical practice at the time, a number of newer DMTs have been approved since these studies were conducted; some of these DMTs have an evidence base that supports superior efficacy to that of established DMTs. Indeed, recently published data from Australia show newer DMT use rising from 8% of total DMT use in 2011 to 33% in 2013. This study did not differentiate between DMT initiation, continuation and switching, but the results indicate a rapid change of attitude in a country where there are fewer obstacles than in other parts of the world and where treatment can be initiated with any approved therapy.

<table>
<thead>
<tr>
<th>Country</th>
<th>Data source</th>
<th>Date/individuals included</th>
<th>Finding</th>
</tr>
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<tbody>
<tr>
<td>Australia</td>
<td>Registry (1113 people)</td>
<td>People diagnosed with RRMS in 1998–2010</td>
<td>18% did not start a DMT during a median follow-up period of 2 years</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Survey (1572 people, 89% response rate)</td>
<td>People with MS in 2011</td>
<td>31% had never received a DMT. Reasons given included concern about side effects, uncertainty about the effectiveness of DMTs, disease course (mild or progressive) and advice received from neurologists</td>
</tr>
<tr>
<td>USA</td>
<td>Insurance claims database (11 061 people)</td>
<td>People diagnosed with MS in 2001–2007</td>
<td>57% did not start a DMT over an average follow-up period of 3 years</td>
</tr>
<tr>
<td>USA</td>
<td>Insurance claims database (7993 people)</td>
<td>People diagnosed with MS in 2008–2011</td>
<td>28% did not start a DMT within 6 months of diagnosis</td>
</tr>
</tbody>
</table>

Table 5. Many people with MS do not start treatment with a DMT.

*Reasons for not starting treatment were not included in the data set.

DMT, disease-modifying therapy; RRMS, relapsing–remitting multiple sclerosis.

Choice of therapy should be an informed, shared decision

Following a diagnosis of MS, the objective should be to initiate, and continue, treatment with the DMT that is most appropriate to the disease course, values, needs, limitations and lifestyle of the individual. A 2014 consensus paper by the Multiple Sclerosis Coalition in the USA recommends that the complex factors surrounding DMT choice should be discussed collaboratively by the person with MS and their treating MS healthcare professional. A 2015 position statement by the American Academy of Neurology (AAN) concurs that individualized treatment decisions should be made by people with MS in conjunction with their treatment team. Guidelines from the ABN, published in 2015, similarly recommend that risks, benefits and personal factors are discussed, and that the views of people with MS should be taken into account when choosing a DMT.

There is evidence that such dialogue is important to people with MS, and is already happening in practice. A 2014 survey of 105 people with MS in the UK showed that 84%...
wanted to be part of the decision-making process. In a 2015 survey of about 5000 people with MS in the USA, 43% reported sharing responsibility for treatment decisions with their healthcare professional and a further 42% reported that they made the final decision after hearing their doctor’s opinion.

Our recommendation is that MS healthcare professionals should have the time to help people with MS understand the following so that they can make a fully informed choice of initial DMT:

- the possible outcomes of their disease with no, inadequate or suboptimal treatment
- the benefits of early treatment
- the goal of minimizing disease activity while optimizing safety
- the potential benefits and risks of DMTs
- the role they can play in managing their disease by living a ‘brain-healthy’ lifestyle and making informed, shared decisions about treatment
- any limitations in the current understanding of MS and DMTs.

People with MS need to be fully aware that they have an irreversible disease and that brain atrophy and deterioration in cognitive reserve may not manifest as clinical symptoms until later. Informing people with MS about their disease has been shown to increase disease-related knowledge, with no negative effect. Indeed, a recent UK survey found that 59% of people who felt adequately informed about treatments for MS were taking a DMT compared with only 27% of those who did not feel adequately informed.

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<tr>
<th>Country/region</th>
<th>Data source</th>
<th>Date/individuals included</th>
<th>Finding</th>
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</thead>
<tbody>
<tr>
<td>Australia</td>
<td>Registry (771 people)</td>
<td>People diagnosed with RRMS between 1998 and 2010 who commenced treatment with a DMT</td>
<td>Almost 99% of those who commenced treatment started with an established DMT. However, a newer DMT became available only during the final 24 months of the study</td>
</tr>
<tr>
<td>Europe</td>
<td>EMA</td>
<td>As at September 2015</td>
<td>The EMA has excluded some newer DMTs from initial use in most people with RRMS</td>
</tr>
<tr>
<td>USA</td>
<td>Survey (75 people)</td>
<td>Neurologists from MS treatment centres, 2010</td>
<td>All recommended initiating a DMT for a young adult with mild RRMS; 90–98% recommended an established DMT, depending on other risk factors</td>
</tr>
<tr>
<td>USA</td>
<td>Insurance claims database (6181 people)</td>
<td>People with MS who commenced treatment with a DMT between January 2007 and September 2009</td>
<td>93% commenced treatment with an established DMT</td>
</tr>
<tr>
<td>USA</td>
<td>FDA</td>
<td>As at September 2015</td>
<td>There is discrepancy between the USA and Europe in the licensed indications for the use of a particular DMT in people with active RRMS</td>
</tr>
</tbody>
</table>

Table 6. Most people with MS who receive a DMT will start with an established treatment.

DMT, disease-modifying therapy; EMA, European Medicines Agency (the European regulatory authority); FDA, Food and Drug Administration (the US regulatory authority); RRMS, relapsing–remitting multiple sclerosis.
Adherence to prescribed DMTs is associated with fewer relapses that require hospitalization and lower medical costs than non-adherence— but adherence to established DMTs is incomplete and variable in practice, ranging from 88% to a worryingly low 41% in various studies. However, when people with MS report that they are well informed about their disease and its treatment, and have good, open, trust-based relationships with healthcare professionals, their adherence improves. As discussed in Section 2, MS specialist nurses play a key role in many MS clinical services. As the staff members who often have the closest connection to people with MS, they are well placed to encourage adherence by establishing trust and rapport, and providing education, emotional support and reassurance.

The benefits of DMTs most desired by people with MS are symptom control and prevention of disability progression. Although neurologists and people with MS generally agree that the ability to perform work and other day-to-day activities is the most important component of health status, neurologists tend to identify physical functioning as being key, while people with MS place a strong emphasis on emotional well-being (feeling peaceful, happy and calm). This highlights the importance of good dialogue between MS healthcare professionals and people with MS.

When people with MS were offered a theoretical choice of DMTs with no worse than mild side effects, the most important factors they identified were route of administration (for example, a pill, an injection or an infusion) and frequency of administration. However, a 1% risk of a serious side effect can reduce patient preference for a particular DMT by fivefold. This reluctance among people with MS to use DMTs with a greater potential for serious side effects highlights the need for a shared, informed exploration of the choices available because the attitudes of people with MS towards potential benefits and risks of DMTs may be affected by the options offered by neurologists and how these options are presented.

To summarize, for a person with MS who has the option of receiving a DMT, and has more than one choice of DMT, treatment and management decisions rely on how well they understand their disease, the extent to which they are risk averse, the experiences of others they know, the pros and cons of the available treatments and their neurologist’s willingness to prescribe a newer DMT.

First-person account

I only have one appointment a year and don’t feel this is enough. I would like to be informed about new research and clinical trials. I am extremely interested in this but have to find this information for myself.
Brain health: time matters in multiple sclerosis

Recommendations

Early intervention in MS is vital and needs to involve people with MS proactively in shared decision-making and the management of their disease.

- **Align prescribing guidelines with the latest accepted diagnostic criteria** to give people with MS the opportunity to start treatment and receive support promptly, as soon as diagnosis is confirmed.

- **Ensure that MS healthcare professionals can take the time to educate people with MS about strategies to manage their disease.** Emphasize the importance of a ‘brain-healthy’ lifestyle, the benefits of early treatment with therapies that can modify the disease course, the likely consequences of inadequate or suboptimal treatment and the goal of minimizing disease activity while optimizing safety.

- **Implement a shared decision-making process** that embodies dialogue between people with MS and healthcare professionals. A well-informed and proactive collaboration between people with MS and their healthcare team is vital to successful management of the disease.

- **Make the full range of disease-modifying therapies available** to people with active relapsing forms of MS, regardless of their treatment history, to speed up adoption of the most appropriate treatment strategy that optimizes effectiveness and safety for each individual.

- **Seek regulatory and health technology assessment approvals** to implement these recommendations.
4. Monitor disease activity and treat to a target

**Key points**

- The practice of monitoring to ensure that disease activity remains below a target level is routine in many areas of medicine.
- In MS, all parameters that predict future relapses and disability progression should be included in the definition of disease activity. This definition should evolve as further evidence becomes available.
- Regular clinical and radiological monitoring of disease activity and recording this information formally need to become commonplace in managing MS in order to identify suboptimal disease control and inform treatment decisions.

**Monitoring disease activity enables individualized treatment**

There are two primary reasons for monitoring: to evaluate treatment effectiveness and to evaluate safety. The monitoring of parameters that indicate disease activity allows the effectiveness of a DMT for each individual person with MS to be assessed and enables swift action to be taken in the case of treatment failure (Figure 11) — that is, when disease activity has not been minimized in response to treatment (Section 5). The monitoring process should also incorporate safety and tolerability parameters, individualized for each DMT, to ensure that people with MS are not exposed to unnecessary risk or side effects from their medication.112

Monitoring can be either routine or driven by clinical events such as relapses or side effects of medication. Parameters that can be monitored may be measured clinically (for example, disability progression and relapses), radiologically (using MRI) or in a laboratory (for example, from a blood sample), or they may be reported by the person with MS (patient-reported outcomes; for example, activity limitations, cognitive status and level of fatigue). Parameters that cannot be measured or observed during a clinical examination are known as subclinical parameters.

The practice of monitoring to ensure that disease activity remains below a target level is routine for several conditions that can cause irreversible damage to major organs.

- In people with diabetes, blood glucose concentrations are routinely monitored, with the aim of maintaining them within the normal range to reduce long-term damage to multiple organ systems, including the heart, eyes, nerves and kidneys.260–262

- In people with cardiovascular disease (diseases relating to the heart and blood vessels), blood pressure and cholesterol levels are monitored and treatment is tailored in order to bring them into the normal range. This is done to reduce the risk of cardiovascular events that could damage organs such as the heart (from a heart attack, for example) or the brain (from a stroke).263

- In people with rheumatoid arthritis, treatment based on monthly monitoring has been shown to improve physical function and quality of life compared with routine care, at no additional cost (routine care here comprised quarterly appointments with specialists, but without a formal composite measure of disease activity). Monitoring the number of swollen joints, joint tenderness, inflammatory markers in the blood and patient-reported measures of disease activity provided the basis for treatment decisions that reduce damage to joints.264 Subsequently, an international task force recommended a ‘treat-to-target’ strategy...
based on regular monitoring of composite measures of disease activity with the aim of achieving clinical remission – in this case the absence of significant inflammatory disease activity.265

Although MS and rheumatoid arthritis cause irreversible damage to different body systems, they have several features in common. Both are degenerative, autoimmune, inflammatory conditions that affect physical function, and both are treated with DMTs that target the respective inflammatory processes. However, in one crucial aspect the management of MS lags behind that of rheumatoid arthritis – in MS, the ‘treat-to-target’ approach has not yet been adopted in routine clinical practice. Regular monitoring of clinical and subclinical disease activity needs to become central to the management of MS (Figure 11).259

There is also evidence that monitoring can improve adherence to prescribed DMTs (which is associated with fewer serious relapses and lower medical costs than non-adherence250) and that data from monitoring can be used to encourage conversations and collaboration between people with MS and their healthcare professionals.266 Increased engagement of people with MS in shared treatment decisions, as recommended in this report, is more likely to take place if the routine monitoring of disease activity and safety parameters becomes commonplace.

**Figure 11.** Monitoring is crucial to identifying treatment failure and enabling timely switching to a different DMT.259


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**First-person account**

After receiving a diagnosis of MS in 2005, I began treatment with a DMT. Over the next 5 or 6 years I tried three different treatments but continued to have relapses, so I asked my consultant to prescribe a different drug for me. I really wanted to see my MRI scans to know what was happening inside my brain, but my neurologist was reluctant to show me these.

I had to be very proactive, push for my case and fight to have my opinion heard. Eventually I was switched to a newer treatment. I then realized that this was far more effective than previous drugs had been. I stopped experiencing relapses, and I felt less fatigue and that the ‘brain fog’ had lifted, which really improved my quality of life. I now visit a different MS neurologist who shares the results of my MRI scans with me. I could see for myself that I had no new MRI lesions while taking this new DMT.

I am happy to make my views clear to neurologists, but not everyone is so comfortable doing this. However, I would encourage others with MS to have an active involvement in all the decisions about their treatment. Some neurologists are more ‘conservative’ than others and may be reluctant to try new treatments. As the person most affected, though, I appreciate being part of the discussion.
The remainder of this section presents the evidence for the inclusion of candidate parameters in the overall definition of disease activity.

**Clinical and subclinical indicators of disease activity should be monitored**

Historically, the treatment target for MS was to prevent or reduce clinical disease activity – relapses and, especially, disability progression. The need to prevent disability progression is underscored by real-world evidence from a large international database of people with MS, which indicates that the EDSS score 5 years after the onset of MS predicts disability progression, and that once disability has progressed, it worsens more rapidly from EDSS score 4.0 onwards than from EDSS score 2.0 onwards.

However, neurological reserve is affected by damage to the CNS even when it does not lead directly to disability progression or a relapse (Section 1); therefore, it makes sense to consider all indicators of disease activity, not just the clinical symptoms at the ‘tip of the iceberg’. The remainder of this section discusses the clinical and subclinical parameters illustrated in Figure 12, with the greatest focus on the subclinical parameters with the most substantial evidence base (MRI lesions and brain atrophy).

![Figure 12](image-url) Monitoring disability progression and relapses can be supplemented by other measures of disease activity. MRI, magnetic resonance imaging.

Relapses indicate disease activity and predict disability progression

Studies consistently show a correlation between relapses in the first few years of the disease and later levels of disability. The passage of a short time from the first to the second relapse appears to be a particularly strong predictor of disability progression. In addition, meta-analyses and real-world evidence indicate that correlations exist between the effects of DMT on relapses and disability progression, and that relapses predict disability progression. There is therefore a robust rationale for including relapses in the definition of disease activity.

However, relapses are not the only factor implicated in future disability progression, and there are other problems with simply using the recorded ‘relapse rate’. Many relapses go unreported – nearly half of people with MS who responded to a recent UK survey indicated that they had failed to report a relapse to a healthcare professional, and over one-quarter said that they had not reported their most recent relapse. In turn, whether or not a relapse is reported can depend on how frequently a person with MS sees a neurologist.

MRI lesions indicate disease activity, and predict relapses and disability progression

Lesions detectable by MRI scans are already used as evidence of disease activity in the diagnosis of MS (Section 2) and in clinical trials and as a basis for initiating a DMT in many countries. Additionally, the EMA recently stated that MS may be defined as ‘active’ based on clinical and/or MRI evidence. There is strong evidence for using MRI lesions as a predictor of relapses and disability progression from analyses and meta-analyses of data from clinical trials and real-world sources involving tens of thousands of people with MS (Table 7). The evidence from each of the studies listed in the table is presented in greater detail in Appendix 2a.

With the increasing availability of MRI scanners, the prospect of routinely monitoring brain lesion activity has become viable in many countries. This increases the likelihood of detecting disease activity before irreversible damage to brain tissue and loss of neurological reserve have occurred. Thus, MRI evidence of subclinical disease activity can help to guide treatment decisions in a more timely manner than clinical evidence of disease activity (relapses and disease progression) alone. However, despite the major role that MRI plays in the diagnosis of MS and the decision to initiate DMT, many people with MS are switched to a different DMT only if they experience new clinical symptoms, and not solely on the basis of MRI evidence of new lesions (Section 5). Moreover, MRI monitoring is not routinely carried out in clinical practice everywhere. The ABN, in their 2015 guidelines, suggest incorporating MRI scanning into a routine

<table>
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<tr>
<th>Correlations exist between the effects of DMTs and:</th>
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<tr>
<td>- relapses and disability progression</td>
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<tr>
<td>- MRI lesions and disability progression</td>
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<tr>
<td>- MRI lesions and relapses</td>
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In people with CIS, the number of new lesions predicts the risk of a second relapse (that is, conversion to RRMS by any diagnostic criteria)

The short-term (6–9 months) treatment effect on MRI lesions predicts the medium-term (12–24 months) treatment effect on relapses

Changes in total lesion load (total volume of lesions visible on MRI) during the first 1–2 years of treatment predict long-term (10 years) disability progression

The initial treatment effect on MRI lesions predicts the long-term (up to 16 years) treatment effect on relapses and disability progression

Table 7. MRI lesions predict relapses and disability progression.

CIS, clinically isolated syndrome; DMT, disease-modifying therapy; MRI, magnetic resonance imaging; RRMS, relapsing-remitting multiple sclerosis.
annual review process. However, a 2014 survey of 108 UK neurologists with an interest in MS revealed that although 59% of respondents used MRI to monitor treatment response, only 9% did so routinely.282

**Brain atrophy indicates disease activity and predicts disability progression**

The central theme of this report is that the goal of treating MS should be to preserve brain tissue and by doing so optimize lifelong brain health. Brain atrophy occurs as a result of damage that takes place via a number of different mechanisms. This implies that brain volume should be monitored in addition to active and total numbers of lesions, which represent only one kind of damage. In addition, brain volume is a measurable indicator of brain reserve, and rates of brain atrophy higher than those in the general population indicate MS disease activity.

Evidence from studies suggesting that brain atrophy should be included in the definition of disease activity as a predictor of clinical symptoms of MS are summarized below. Further details of each study are presented in Appendix 2b.159–163

- Meta-analyses of clinical trial data show a correlation between the effects of treatment on brain atrophy and disability progression.159,160 This is independent of the correlation between the effects of treatment on MRI lesions and disability progression159 because brain atrophy results from diffuse damage and lesions that are difficult to observe, as well as from lesions observable using MRI scans.29

- Studies in people with CIS receiving a DMT have shown that those with a greater rate of brain atrophy are more likely to be diagnosed with MS within 2 years,163 and are more likely to experience a second relapse within 4 years,162 than those who experience less brain atrophy.

- Long-term (10 years) disability progression can be predicted by the rate of brain atrophy during the first 1–2 years of treatment.161

The importance of measuring brain atrophy is already recognized. In a survey of UK neurologists with a special interest in MS, over half of the 56 respondents believed that brain atrophy was a relevant parameter to measure.282 However, the MRI technology required to measure brain atrophy is not yet widely available in clinical practice.

**Other candidate parameters indicating disease activity are not yet validated**

The evidence base for the other potential markers of disease activity included in Figure 12 (lesions in the grey matter of the brain, spinal fluid neurofilament levels and patient-reported outcomes) is growing, but is not yet sufficiently strong to support their incorporation into the routine clinical monitoring of disease activity in people with MS. In general, we recommend that evidence-based treatment targets should evolve as further evidence becomes available.

The MRI techniques used in current clinical practice can detect lesions in the white matter of the brain (which consists mainly of nerve axons that transmit signals between different parts of the brain), but MS also affects the grey matter (the part of the brain mainly responsible for cognition and processing information). New MRI protocols have been developed to detect lesions in the grey matter,283 but the technology and evidence base do not yet exist for adding grey matter lesions to the current definition of disease activity.

Neurofilaments are the protein ‘scaffolding’ of nerve fibres and are released when damage occurs. In a recent study in which people with RRMS received one of the newer DMTs for 1 year, reductions in the levels of a particular neurofilament in cerebrospinal fluid correlated with lower numbers of relapses and fewer new lesions during the same time period.284 In addition, a recent study in people with CIS has shown that levels of the same neurofilament in the blood are high compared with those in healthy people, and that higher levels in individuals with CIS were associated with higher disability scores, numbers of lesions and numbers of active lesions.285 Furthermore, higher levels of another neurofilament in the blood have been shown to be associated with greater numbers of lesions and higher disability scores than lower levels in people with MS.286 If results such as these are confirmed by further studies, blood neurofilament levels
have the potential for adoption as an indicator of subclinical disease activity that is accessible even in countries where there are few MRI scanners.

In 2015, a panel of MS experts proposed the inclusion of measures of cognition, fatigue and depression in the definition of disease activity, as these patient-reported outcomes contribute substantially towards quality of life in people with MS.267

Regular monitoring provides a strong basis for treatment decisions

A proactive approach to monitoring, with a clear treatment target, should be adopted as a core principle of MS management, and people with MS should be encouraged to request this from their clinicians. The proposal of detailed clinical guidelines is beyond the scope of this report, but we recommend that any treatment target should be evidence based, and should evolve as further evidence becomes available.

The evidence base presented in this section indicates that MRI evidence of disease activity (or inactivity) complements clinical measurements of disease progression and can help to guide treatment decisions in a timely manner. Given the strong association between inflammatory lesions and subsequent clinical relapses and disability progression, the appearance of new lesions should be prospectively and accurately monitored by MRI brain scans performed at predefined intervals. Indeed, recent international57 and Canadian287 consensus papers have recommended that disease activity should be assessed at least annually using MRI.

Ideally, brain volume should also be monitored, because it is a measurable indicator of brain reserve and because high rates of brain atrophy in some people with MS are likely to predict poor outcome. We acknowledge that routine brain volume monitoring will rely on the incorporation of measurement techniques for this parameter into radiological practice, and that the technology required to do this is not yet widely available. However, quality monitoring of lesion development (counting new lesions) in MRI brain scans is currently feasible and should be routinely carried out in people with MS.

Recording the results of monitoring in a database or registry, accessed via a clinical management tool, can facilitate decisions about lifelong care and treatment for each person with MS because it allows MS healthcare professionals to view their full history of disease activity and treatment in one place. Systematically monitoring clinical and subclinical indicators of disease activity can help to identify treatment failure (suboptimal response to the current DMT). This, in turn, enables prompt switching to an alternative DMT to be considered; the evidence that outcomes can be improved by such a switch is presented in Section 5. Data from registries can also be analysed in order to generate a real-world evidence base that may be used to inform future clinical and regulatory practice and demonstrate value to payers;288,289 this is further discussed in Section 6.
4. Monitor disease activity and treat to a target

Recommendations

Regular clinical and radiological monitoring of disease activity and recording this information formally are key to the therapeutic strategy recommended in this report.

- Include evidence from monitoring via regular clinical evaluation and scheduled/unscheduled MRI brain scans in any definitions of disease activity or suboptimal response, in order to assist in the rapid identification of treatment failure and the decision to switch treatment.

- Ensure that MS healthcare professionals can take the time to monitor disease activity in people with MS.

- Agree and implement standardized data collection techniques, protocols and data sets, nationally and internationally, to track clinical and subclinical events in routine practice. **Incorporate these into a clinical management tool** to facilitate individualized practice.
5. Act swiftly on the evidence of disease activity

Key points

- When the results of monitoring indicate suboptimal disease control, swift action should be taken to consider switching the person with MS to a different DMT.
- The traditional approach towards switching has been to increase the dose or injection frequency or to try another DMT with the same mechanism of action (MoA).
- A number of newer DMTs are now available, with different MoAs, and some of these have an evidence base supporting superior efficacy to that of an established DMT.
- Many people with MS may benefit from switching to one of these newer DMTs, as shown by a growing evidence base from clinical trials and real-world studies.

Early detection of a suboptimal response to treatment is crucial

MS is a highly variable disease. No single DMT has yet been shown to be effective in all people with MS, and the likelihood that a particular individual will be a responder or a non-responder to any given DMT cannot be predicted at present. Consequently, many people with MS may need to try several different DMTs before optimal control of disease activity is achieved. Studies have shown that disease activity during treatment with a DMT is predictive of a poor prognosis. Prompt detection of disease activity that indicates a suboptimal response to a DMT is therefore very important, so that switching to an alternative agent can be considered.

No consensus exists on the definition of ‘suboptimal response’

There is currently no widely agreed definition of a suboptimal response to DMT, nor are there universally followed guidelines for managing MS in people who are non-responders. A number of authorities have issued guidance, but no single consensus exists.

A treatment target of ‘no evidence of disease activity’ (NEDA) has been adopted in the management of other chronic progressive diseases, such as rheumatoid arthritis, spondyloarthritis, lupus and cancer. Similarly, NEDA has been proposed as a treatment target in MS by a panel of experts, and has been defined as no relapses, no increase in disability and no MRI activity (no new or newly enlarged lesions or active lesions). These experts suggest that people with MS should be offered the opportunity to switch to an alternative DMT when there is evidence of disease activity according to these criteria. The predictive power of the NEDA measure is illustrated by a recent study of 219 people with CIS or RRMS. This showed that if NEDA was reached in an individual after 2 years of treatment with a DMT, there was an almost 80% chance that their disability would not have progressed 7 years later (by more than 0.5 EDSS points).

Attaining and maintaining NEDA may not be possible for every person with MS. In the same study, a state of NEDA was reached in 27.5% of participants after 2 years and in only 7.9% after 7 years. However, most of the participants took established DMTs (as they were enrolled in the study before any newer DMTs became available), and the numbers included were too low for the relative merits of treatment switching strategies to be evaluated. A similar issue surrounds an analysis of four clinical trials of newer DMTs (with an evidence base supporting superior efficacy to that of an established DMT), the results of which indicated that NEDA was reached in only 32–39% of participants after 2 years of treatment – there was no option for participants who remained in...
these trials to switch to a different DMT if they experienced a suboptimal response. There is not yet an evidence base that indicates what proportion of people with MS may be expected to reach NEDA if all DMTs were available and if MRI indicators of disease activity were routinely monitored to enable timely switching.

Recently, it has been suggested that brain atrophy rate should be included in the definition of NEDA,299 this would shift the focus of MS treatment to preventing organ damage and promoting brain health. In addition, a panel of MS experts has proposed the inclusion of measures of cognitive function in the NEDA definition because cognition, fatigue and depression contribute substantially towards quality of life in people with MS.267 Furthermore, a measure based on the number of new MRI lesions and relapses during the first year of treatment (the ‘modified Rio score’) has been shown to predict a poor response to a particular class of established DMT over the course of 3 years300 and 5 years.301

Demonstrable disease activity should raise questions about treatment strategy

Complete freedom from disease activity detectable by MRI is unlikely to be possible for all people with MS using current DMTs; however, neurologists should be mindful of the principle and at least aim for the lowest level of subclinical disease activity that is not predictive of further suboptimal response. The Canadian MS Working Group, in a 2013 paper, recommends managing the treatment of people with MS by monitoring three domains: relapses, disability progression and MRI activity (new lesions). A change in management would be warranted by high, medium or low levels of concern in one, two or three of these domains, respectively.232 The Multiple Sclerosis Coalition in the USA, in a 2014 consensus paper, recommends considering switching DMT if there is additional clinical or MRI disease activity; this means that a decision to switch treatment could be based on MRI evidence alone. The paper also recommends that suboptimal response should be “determined by the individual and his or her treating physician”.210 The ABN, in its 2015 guidelines, notes that “new MRI lesions are a more sensitive index of inflammatory disease activity than clinical relapses.”112

However, in practice, switching tends to be based on clinical evidence alone. Regulatory authorities guide the circumstances under which a named DMT can be initiated, but they do not define suboptimal response and seldom provide guidance on when to switch from one DMT to another. Currently, some neurologists will not switch a person with MS to a different DMT without clinical evidence of disease activity (relapses or disability progression), even when clear MRI evidence of disease activity is available.244,302 In a survey of MS specialist nurses in the UK, conducted in January 2014, 72% of respondents reported that they would wait for two or more relapses before referring a person with MS for a review of their DMT. In addition, most neurologists in the USA recommend a minimum treatment duration of 6–12 months before switching to another DMT for reasons of inadequate disease control,244 as treatment can take some time to take effect.

The development of a clinical guideline is outside the scope of this report, but we recommend that treatment targets and definitions of ‘disease activity’ and ‘suboptimal response’ should be evidence based, should evolve as further evidence becomes available and should aim to maximize lifelong brain health.

What happens in current clinical practice?

Switching among established therapies is common

The majority of people with relapsing forms of MS start treatment with an established DMT that was approved during the 1990s (Section 3). Within 2 years of starting an established DMT, about one-third to two-thirds of people with MS are classified as ‘non-responders’ or ‘suboptimal responders’, as defined by a variety of different clinical measures involving relapses and/or disability progression.303,304 This proportion could be higher if the description of disease activity included MRI measures.41

Among the established DMTs, there are only two MoAs. Owing to the limited options available, a traditional strategy for treatment switching was to increase the dose or injection frequency, or to try another DMT with the same MoA. In a US study involving 6181 people with MS who initiated treatment with a DMT in
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2007–2009, 79% of those who switched from an initial established DMT did so to another established DMT; the rest switched to a newer DMT. Of those who switched for a second time, about two-thirds received yet another established DMT. Of those who switched for a second time, about two-thirds received yet another established DMT. This approach could indicate a reluctance to prescribe more recently approved DMTs until options involving established DMTs have been exhausted. Now that several newer DMTs with a range of MoAs are available, however, a 2014 consensus paper by the Multiple Sclerosis Coalition recommends that non-responders consider switching to a different DMT regimen, for example to one with a different MoA.210

Attitudes towards newer therapies vary

The decision to prescribe a newer DMT might be influenced by prescribing guidelines, drug reimbursement policies, insurance company rules at the local, regional or national level, patient choice and concerns regarding potential side effects (Table 4 in Section 3). Furthermore, some neurologists may be wary of the need to change routine clinical practice in order to meet the monitoring requirements of some newer DMTs. Neurologists are familiar with managing the side effects of established treatments; however, newer DMTs have different safety profiles from those of established DMTs and some require a greater degree of monitoring.109,305 Therefore, people with MS and their treating healthcare professionals need to balance the potentially higher efficacy levels of some newer DMTs against their individual risk profiles.109,305

The varying attitudes towards innovation among professionals in specialist fields, such as neurology, should not be underestimated; they can result in geographical differences in the approach to disease management or the speed of adoption of newer treatments. This sociological phenomenon is known as the ‘diffusion of innovation’306 and, alongside factors such as a lack of up-to-date information, it may account for differences in overall practice patterns.

The proportion of people receiving treatment for MS who were given a newer DMT varied widely between countries in 2013 (Figure 13)8,231,246,307,308 and even within countries. For example, data from Australia show that newer DMT use rose from 8% to 33% of total DMT use in 2011 and 2013, respectively. When the figures for newer DMT use in 2013 are broken down according to states and territories within the country, they range from 17% to 40% of total DMT use.246

Combination therapy (i.e. using more than one drug at the same time) has been successfully employed to treat certain types of cancer,309 a complex disease in which drugs with different MoAs can have an additive effect. Such an approach is also being investigated for people with MS whose disease is inadequately controlled, but clinical experience is currently limited.232

Discontinuation and treatment gaps are common

Gaps in the treatment of people with active MS are thought to be equivalent to, or worse than, periods of non-adherence, and hence treatment gaps will have a negative impact on the disease course. When switching treatment, 30% of people with MS have gaps in their therapy exceeding 30 days, and almost 20% have gaps in excess of 60 days.241 Some regulatory authorities recommend treatment gaps when switching between certain DMTs to avoid the risk of unwanted effects on the immune system that might increase the likelihood of serious infections.122,243 Real-world evidence indicates that such gaps can increase the risk of a relapse; this evidence could be used as a basis for updating recommendations about the maximum length of treatment gaps.310

Choice of therapy should be an evidence-based decision

Delivering treatment switching, or excluding the use of newer DMTs, may be detrimental to establishing rapid control of the disease before further relapses or disability progression occur. Indeed, a recent position paper by the AAN recommends that people with MS should be able to access all DMTs “when they have the potential to provide clinical benefit” and that any treatment sequences imposed by payers or insurance carriers should be driven by evidence-based data and not DMT costs.247

There is increasing evidence that people with MS whose disease is inadequately controlled by an established DMT will benefit from receiving an appropriate newer DMT. Several studies have shown that people with MS who switch from an established DMT to a newer DMT (with an evidence base supporting superior efficacy to that
5. Act swiftly on the evidence of disease activity

of an established DMT) are more likely to be free from relapses, disability progression and new MRI activity – and can even experience improvements in their disability status – compared with switching to another established DMT. A number of other studies have demonstrated that improvements in disability, quality of life measures, and cognition are also possible when people with MS receive a newer DMT (with an evidence base supporting superior efficacy to that of an established DMT; Appendix 3). As adequate control of disease activity will not always be achieved in all people with MS taking any one DMT, regular monitoring should be the cornerstone of any treatment strategy (Section 4).

The favourable results obtained in the studies that compared treatment switching indicate that neurologists should consider evidence-based approaches to using newer DMTs in people with relapsing forms of MS and suboptimally controlled disease activity. As with treatment initiation (Section 3), the full range of DMTs should be considered when switches are made, to enable people with MS and their treating healthcare professionals to make fully informed, shared decisions.

Figure 13. The proportion of people with all forms of MS receiving a newer DMT in 2013 varied considerably between countries.

*All newer DMTs available at the time that these studies were conducted have an evidence base supporting superior efficacy to that of an established DMT. The data were generated from DMT sales figures as described in the original sources, and therefore potentially include people with all forms of MS (relapsing or progressive), and do not differentiate between treatment initiation and treatment switching. All DMTs for Australia: calculation based on sales figures, population and number of people with MS. DMT, disease-modifying therapy.
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Recommendations

Rapid switching to another DMT if monitoring reveals a suboptimal response will maximize the chance of achieving the best possible outcome for every person with MS who would be at risk of inflammatory disease activity if they were not receiving treatment.

- **Ensure that MS healthcare professionals can take the time to educate people with MS about strategies to manage their disease.** Emphasize the importance of a ‘brain-healthy’ lifestyle, the benefits of early treatment with therapies that can modify the disease course, the likely consequences of inadequate or suboptimal treatment and the goal of minimizing disease activity while optimizing safety.

- **Implement a shared decision-making process** that embodies dialogue between people with MS and healthcare professionals. A well-informed and proactive collaboration between people with MS and their healthcare team is vital to successful management of the disease.

- **Make the full range of disease-modifying therapies available** to people with active relapsing forms of MS, regardless of their treatment history, to speed up adoption of the most appropriate treatment strategy that optimizes effectiveness and safety for each individual.

- **Maintain treatment with a disease-modifying therapy** for as long as a person with MS would be at risk of inflammatory disease activity if they were not receiving treatment; in the case of a suboptimal response, make a prompt decision about whether or not to switch therapy.

- **Seek regulatory and health technology assessment approvals** to implement these recommendations.
6. Take a comprehensive economic approach to evaluating treatment cost-effectiveness

Key points

- As a person with MS becomes more disabled, costs outside the healthcare system markedly increase until they comprise about two-thirds of all costs.

- The treatment strategy outlined in this report, of early intervention, regular monitoring and timely switching of therapy to maximize lifelong brain health, has the potential to reduce disability progression and therefore to avoid some of these long-term costs.

- However, most health technology assessment (HTA) bodies and reimbursement agencies consider only the costs borne by healthcare and social services. This leads to suboptimal decisions, where DMTs that have the potential to provide an economic benefit to society as a whole may not be considered cost effective.

- The global prices of DMTs – as for other pharmaceutical products – are generally set based on the conditions in high-income countries, and other countries may have difficulties in granting access to these therapies.

- Current financing models focus on the prices of individual DMTs; however, this effectively incentivizes the rationing of individual drugs instead of focusing on finding the optimal therapy for each person with MS. Alternative financing models should, therefore, be investigated.

- For people with MS in low-income countries, access to DMTs can be improved by developing financial support programmes and less-expensive DMTs.

- Recording the results of monitoring in databases or registries will generate real-world evidence of the effectiveness and safety of individual DMTs and therapeutic strategies. This can be used to inform future clinical and regulatory practice.

All benefits and costs should be included in economic evaluations

Costs outside the healthcare system increase as disability progresses

As a person with MS becomes more disabled, costs outside the healthcare system, such as informal care and production losses due to incapacity to work, markedly increase until they comprise about two-thirds of all costs (Figure 8 in Section 1). Diagnosing and treating MS early needs to be coupled with a management strategy based on monitoring, and with increased payer flexibility to switch among all DMTs at the first sign of disease activity; this will help to preserve brain tissue, maximize lifelong brain health and reduce the likelihood of relapses and disability progression (Sections 2–5). Although the immediate direct costs of DMTs and the demands on healthcare resources (such as MRI) are likely to increase with this approach, the high costs occurring in the later stages of MS will be reduced if unnecessary disability progression can be avoided.

National health technology assessments evaluate what to fund from the public budget

When a treatment has been approved by the relevant regulatory authority, a national HTA body will generally assess its value – the health benefits in relation to costs – to decide whether it will be funded from the public budget. A
formal economic evaluation of health outcomes and costs is used to support this decision in most countries.\textsuperscript{324}

Health outcomes are commonly measured using quality-adjusted life-years (QALYs). These measure the effect of a treatment on length and quality of life and can be compared across diseases.\textsuperscript{325} A treatment that reduces the likelihood of a person dying early, or improves health-related quality of life, will have a positive impact on QALYs. Some economic evaluations also consider the impact that informal caregiving has on the health of family members. This is highly applicable to MS – indeed, the results of a recent survey indicate that caregivers’ health-related quality of life deteriorates as the person with the disease becomes more disabled.\textsuperscript{326}

Costs of informal care and incapacity to work are not always considered

It is widely accepted that economic evaluations of health outcomes should include all potential health benefits to all parties. It is logical, therefore, that economic evaluations should also consider the potential costs to all parties;\textsuperscript{327} in other words, they should take a societal perspective. However, most HTA bodies and reimbursement agencies have adopted a payer perspective, where only the costs borne by healthcare and social services are considered. The costs to wider society, such as informal care and incapacity to work, are often considered only in a secondary analysis – or not at all.

Direct costs commonly accrue in one part of society and benefits in another

Adopting a payer perspective (narrow cost model) leads to suboptimal decisions, with the result that treatments with the potential to provide an economic benefit to society (other than savings to healthcare services) may not be considered to be cost effective.\textsuperscript{327} It is quite normal for direct costs to accrue in one part of society and benefits in another. As the health-related benefits of treatment are enjoyed by people with the disease and their families, it is only fair to factor in also the burden of informal care and indirect costs that would otherwise be borne by these parties to a large extent. In the case of MS in particular – a chronic, progressive disease that starts at a young age – taking a societal viewpoint is crucial when evaluating the potential for the long-term health benefits of early treatment with a DMT to outweigh the costs. Our recommendation is that economic evaluations should be carried out from a societal perspective; in other words, that they should consider health benefits and costs to all parties.

Access to disease-modifying therapies should be improved

Access to DMTs varies widely

Access to DMTs depends not only on clinical effectiveness and the decisions of regulatory authorities (Section 3) but also on affordability. In the USA, prices have increased five to seven times more rapidly than prescription drug inflation, and currently no DMTs cost less than US$50 000 (€37 500) per year for an individual person with MS. These US costs are two to three times higher than those in Australia, Canada or the UK.\textsuperscript{328} As global prices for DMTs are generally set based on the conditions in high-income countries, healthcare providers in some other countries may have difficulties in granting wide access to them. Compared with a more wealthy nation, healthcare expenditure in a low-income country will not only be less in absolute terms but will also constitute a lower proportion of total expenditure as health care competes with other basic necessities. As a consequence, reimbursement of the costs of DMTs in different countries varies from no funding at all, particularly for newer therapies, to full reimbursement (Figure 14).\textsuperscript{235–238,329}

Policy makers could encourage the pharmaceutical industry to expand the scope of existing financial support programmes, so as to improve access where it is currently limited. Offering discounts in this way, however, could create the problem of parallel trade (the import of DMTs purchased elsewhere at a lower price), which would need to be controlled – a topic that is beyond the scope of this report. The development and use of less-expensive DMTs (for example, generic versions) could also help to make these drugs more accessible to people with MS in low-income countries.

Access to newer DMTs varies widely

Even in high-income and upper-middle-income countries where the costs of newer DMTs are fully reimbursed, access to these therapies varies widely. Given that newer DMTs tend to be more expensive than established DMTs,\textsuperscript{328}
6. Take a comprehensive economic approach to evaluating treatment cost-effectiveness

much of this difference appears related to affordability. A correlation exists between the proportion of people with MS who are on treatment and receiving a newer DMT and the per capita spending on health care (Figure 15).\textsuperscript{231,246,329}

Sometimes, additional administrative restrictions are put in place to limit the number of people with MS who can receive treatment and, thus, limit the budget that can be spent on DMTs. In some Eastern European countries, affordability has historically led to waiting lists or limits on the length of time for which a person with MS can be prescribed a DMT.\textsuperscript{231}

HTA bodies have restricted reimbursement to a narrower group of people with MS than that specified by the EMA in some high-income countries. For example, the EMA indicates that a particular newer DMT can be used in (a) people with RRMS whose disease has failed to respond to at least 1 year of treatment with an established DMT, or (b) those with rapidly evolving, severe RRMS.\textsuperscript{243} In the Netherlands, however, reimbursement is restricted to people in group (a), while in England reimbursement is restricted to those in group (b). In Italy, the restrictions for group (a) regarding recent relapses are tighter than the EMA indication, while in Belgium the DMT costs will only be reimbursed for people below a certain disability level on the EDSS.\textsuperscript{231}

Alternative financing models should continue to be investigated

Our recommendation is that the full range of DMTs should be available to people with active relapsing forms of MS, regardless of their disease history, so that they and their treating healthcare professionals can make shared, informed decisions about treatment. Established DMTs feature prominently in budgets set aside for specialty drugs that are used in all disease areas.\textsuperscript{330} In order to provide greater access to newer DMTs, investigations into alternative financing models should be continued.

Current payment systems tend to focus on the cost per pack/vial of medicine, which was an important factor in the 1990s, when fewer DMTs were available than today. In this context, the advent of biosimilar drugs (generic versions of biological drugs that can be marketed once the original patent has expired) and the approval of further newer DMTs is likely to drive an overall focus on reducing the cost per pack/vial of DMT. Improved outcomes for people with MS, however, are seldom the consequence of

Figure 14. The costs of DMTs, especially newer DMTs, are more likely to be reimbursed in higher-income countries than in lower-income countries.\textsuperscript{235–238,329}

*aBy the government and/or by health insurance.
Income brackets are defined in the Glossary. DMT, disease-modifying therapy.
treatment with just one DMT. Rather, they result from a therapeutic strategy that aims to find the most appropriate DMT for each individual by switching treatment if there is evidence of disease activity. It is not logical from a societal perspective, therefore, for payment systems to focus on the costs of individual DMTs rather than the optimal treatment for each person with MS.

One possible solution is a capitation, or ‘payment per patient per month’, scheme in which a fixed payment is made in return for a negotiated range of services. Such payments may be combined with additional payments that are conditional on meeting selected quality or outcome standards. This could help to incentivize keeping each person with MS as well as possible, and it may promote an integrated approach to care, with optimized procedures for diagnosis, monitoring and treatment switching.

Real-world evidence should drive regulatory and funding decisions

The therapeutic strategy of early treatment, monitoring and switching, with the full range of DMTs available, will change the economic picture of MS and has the potential to reduce the long-term costs of the disease significantly. Regulatory authorities and payers, however, make initial decisions about DMTs based on their efficacy and safety in short-term clinical trials – an environment in which it is not possible to switch to a different DMT if disease activity is inadequately controlled. Consideration of real-world evidence from registries and databases of the long-term effectiveness and safety of DMTs and therapeutic strategies will help regulatory authorities, HTA bodies and payers to ensure that these decisions do not become out of date or rigid, denying people with MS the flexibility to benefit from the most recent evidence.

The registries that currently exist, however, have been set up independently of one another, for different reasons, and they cover different kinds of patient populations. As a result, the parameters collected, and the data collection techniques and protocols that are followed, are often not standardized. In this context, two international data sets that have overcome some of these hurdles are worthy of note:

- MSBase is an online registry that individual MS clinics can choose to sign up to. As of
July 2015, it contains over 35,000 patient records from 199 clinics in 69 counties, and it has led to the publication of a number of papers, including several presenting real-world evidence of the effectiveness of DMTs (Section 5). The European Register for Multiple Sclerosis (EUReMS) aims to unite existing national MS registries around a core data set. To date, data have been provided from 13 registries, although only three participating national registries contain the parameters necessary for inclusion in a study assessing the effectiveness and accessibility of DMTs.

The routine monitoring of people with MS with an agreed minimum data set has not yet been widely adopted, although we earlier recommended standardizing and recording the results of treatment and routine monitoring in the context of a clinical management tool to facilitate individualized practice (Section 4). Additionally, we recommend incorporating such results into national and international MS registries and databases in order to generate real-world evidence of the long-term effectiveness and safety of individual DMTs. This would also enable the effectiveness of overarching therapeutic strategies to be evaluated, for example the predictive power of NEDA (by any definition covered by the data set) on clinical outcomes or the effect of variations in practice patterns on disease activity and health outcomes for people with MS. For this to be possible, we further recommend that the curators of databases and registries should ensure accessibility of data to those performing HTAs and economic evaluations.

### Recommendations

The therapeutic strategy of early treatment, monitoring, and switching, with the full range of DMTs available, will change the economic picture of MS and has the potential to reduce the long-term costs of the disease significantly.

- **Carry out economic evaluations of therapies and other healthcare interventions from a societal perspective**, considering the health benefits and costs to all parties, to improve assessments of true cost-effectiveness.

- **Encourage the continuing investigation, development, and use of cost-effective therapeutic strategies**, of approaches that reduce the costs of managing MS and of alternative financing models, to improve access to treatment.

- **Agree and implement standardized data collection techniques, protocols, and data sets**, nationally and internationally, to track clinical and subclinical events in routine practice. **Incorporate these into national and international MS registries and databases** to generate real-world evidence of the long-term effectiveness and safety of therapeutic strategies; such evidence can be used by regulatory bodies and payers, and will enable differences in practice patterns to be assessed and addressed.

- **Ensure that access to multiple sclerosis registries and databases is available** for those carrying out health technology assessments and economic evaluations.
## Appendix 1. Evidence supports the benefit of early treatment

Results from clinical trials and real-world studies support early intervention with a DMT in CIS and RRMS.

a. In people with a diagnosis of CIS, treatment with a DMT increases the time to a second relapse and improves MRI outcomes in randomized controlled trials.

<table>
<thead>
<tr>
<th>Length of time taking DMT or placebo</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 years</td>
<td>DMT vs placebo</td>
</tr>
<tr>
<td></td>
<td>▪ Reduced risk of second relapse&lt;sup&gt;b&lt;/sup&gt;&lt;sup&gt;187,188&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>▪ Fewer new lesions&lt;sup&gt;187&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>▪ Fewer active lesions at 18 months&lt;sup&gt;187&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>▪ Lower total volume of lesions&lt;sup&gt;187&lt;/sup&gt;</td>
</tr>
<tr>
<td>2 years</td>
<td>DMT vs placebo</td>
</tr>
<tr>
<td></td>
<td>▪ Reduced risk of second relapse&lt;sup&gt;189&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>▪ Increased time to second relapse&lt;sup&gt;189&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>▪ Lower relapse rate&lt;sup&gt;189&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>▪ Fewer new lesions&lt;sup&gt;189&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>▪ Lower total volume of lesions&lt;sup&gt;189&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>▪ Reduced rate of brain atrophy&lt;sup&gt;190&lt;/sup&gt;</td>
</tr>
<tr>
<td>2 years</td>
<td>DMT vs placebo&lt;sup&gt;191&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>▪ Increased time to second relapse</td>
</tr>
<tr>
<td>3 years</td>
<td>DMT vs placebo&lt;sup&gt;192&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>▪ Reduced risk of second relapse</td>
</tr>
<tr>
<td></td>
<td>▪ Increased time to second relapse</td>
</tr>
<tr>
<td>2 years</td>
<td>DMT vs placebo&lt;sup&gt;193&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>▪ Reduced risk of second relapse</td>
</tr>
<tr>
<td>2 years</td>
<td>DMT vs placebo&lt;sup&gt;194&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>▪ Reduced risk of second relapse</td>
</tr>
<tr>
<td></td>
<td>▪ Reduced risk of new lesions</td>
</tr>
</tbody>
</table>

Participants in all studies had been diagnosed with CIS and had clinically silent MRI lesions. All positive outcomes shown were statistically significant.

*aOr until a second relapse.

<sup>b</sup>Both in the main trial and in a *post hoc* analysis of a subgroup with at least one active lesion.

CIS, clinically isolated syndrome; DMT, disease-modifying therapy; MRI, magnetic resonance imaging.
b. In people with a diagnosis of CIS, starting treatment early in the disease course is associated with better long-term outcomes than delaying treatment in randomized controlled trials with subsequent extension studies.

<table>
<thead>
<tr>
<th>Length of time taking DMT or placebo*</th>
<th>Subsequent length of time taking DMT</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 years</td>
<td>2 years</td>
<td>Early DMT vs later DMT&lt;sup&gt;195&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Reduced risk of second relapse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Increased time to second relapse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Less brain atrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Fewer new lesions per year</td>
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<tr>
<td></td>
<td></td>
<td>- Lower total lesion volume</td>
</tr>
<tr>
<td>3 years</td>
<td>10 years</td>
<td>Early DMT vs later DMT&lt;sup&gt;196&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Reduced risk of second relapse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Lower relapse rate between years 5 and 10 of extension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- No effect on disability progression, new lesions or proportion of people developing progressive MS</td>
</tr>
<tr>
<td>2 years</td>
<td>11 years</td>
<td>Early DMT vs later DMT&lt;sup&gt;197&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Increased time to second relapse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Lower relapse rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- No effect on disability progression</td>
</tr>
</tbody>
</table>

Participants in all studies had been diagnosed with CIS and had clinically silent MRI lesions. All positive outcomes shown were statistically significant.

*Or until a second relapse.

CIS, clinically isolated syndrome; DMT, disease-modifying therapy.
Appendix 1. Evidence supports the benefit of early treatment

c. In people with a diagnosis of RRMS, starting treatment early in the disease course is associated with better long-term outcomes than delaying treatment.

<table>
<thead>
<tr>
<th>Study type</th>
<th>Length of time taking DMT or placebo</th>
<th>Subsequent part of study: length of time and treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT, then open-label extension</td>
<td>2 years</td>
<td>2 years, DMT</td>
<td>Early DMT vs later DMT&lt;sup&gt;198&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Longer time to sustained disability progression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Fewer new lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Lower total brain lesion volume</td>
</tr>
<tr>
<td>RCT, then open-label extension</td>
<td>2 years</td>
<td>4 years, DMT</td>
<td>Early DMT vs later DMT&lt;sup&gt;199&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Less disability progression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Lower relapse rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Less brain atrophy</td>
</tr>
<tr>
<td>RCT, then open-label extension</td>
<td>2 years</td>
<td>5–6 years, DMT</td>
<td>Early DMT vs later DMT&lt;sup&gt;201&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Lower risk of disease progression</td>
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<td></td>
<td></td>
<td></td>
<td>- Lower relapse rate</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- Lower total brain lesion volume</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- No effect on brain atrophy</td>
</tr>
<tr>
<td>RCT, then open-label extension</td>
<td>9 months</td>
<td>6–7 years, DMT</td>
<td>Early DMT vs later DMT&lt;sup&gt;200&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Lower proportion of people requiring walking aids</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- No effect on total lesion volume, normalized brain volume or brain atrophy rate</td>
</tr>
<tr>
<td>RCT, then open-label extension</td>
<td>2.5 years</td>
<td>8 years, DMT</td>
<td>Early DMT vs later DMT&lt;sup&gt;202&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Higher proportion of people with stable or improved EDSS score (i.e. lower risk of disease progression)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- No effect on relapse rate</td>
</tr>
<tr>
<td>RCT, then treatment at discretion of physician</td>
<td>2 years</td>
<td>15 years, treatment at discretion of physician</td>
<td>Early DMT vs later treatment&lt;sup&gt;203&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- No statistically significant effect on disability progression</td>
</tr>
<tr>
<td>RCT, then treatment at discretion of physician</td>
<td>5 years</td>
<td>16 years, treatment at discretion of physician</td>
<td>Early DMT vs later treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Better survival rates: risk of death 47% lower&lt;sup&gt;204&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- 78% of deaths in delayed DMT group adjudicated to be from MS-related causes&lt;sup&gt;205&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- No effect on disability progression, relapse rate or MRI parameters&lt;sup&gt;206&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

continued …
Brain health: time matters in multiple sclerosis

continued …

<table>
<thead>
<tr>
<th>Study type</th>
<th>Length of time taking DMT or placebo</th>
<th>Subsequent part of study: length of time and treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Post hoc analysis of two RCTs</strong></td>
<td>1 year/2 years (depending on trial)</td>
<td>–</td>
<td>Time between onset of symptoms and treatment: &lt; 3 years vs ≥ 3 years&lt;sup&gt;207&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Greater reduction in relapse rate vs placebo and vs established DMT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Fewer new/newly enlarged lesions/year vs placebo and vs established DMT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Fewer active lesions vs placebo</td>
</tr>
<tr>
<td><strong>Real-world evidence from registry</strong></td>
<td>Treatment initiation occurred within 1–5 years of onset of MS</td>
<td>–</td>
<td>Early treatment (within 1 year of onset) vs later treatment&lt;sup&gt;208&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Reduced risk of disability progression (a 1-point increase in EDSS score)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Reduced risk of reaching EDSS score ≥ 4.0</td>
</tr>
<tr>
<td><strong>Real-world evidence from registry</strong></td>
<td>7 years (DMT or no DMT)</td>
<td>–</td>
<td>DMT vs no DMT&lt;sup&gt;209&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Reduced risk of transition to SPMS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Reduced risk of reaching EDSS score ≥ 4.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Increased time to reaching EDSS score ≥ 4.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Reduced risk of reaching EDSS score ≥ 6.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Increased time to reaching EDSS score ≥ 6.0</td>
</tr>
</tbody>
</table>

Participants in all studies had been diagnosed with RRMS. All positive outcomes shown were statistically significant.

DMT, disease-modifying therapy; EDSS, Kurtzke Expanded Disability Status Scale; MRI, magnetic resonance imaging; RCT, randomized controlled trial; RRMS, relapsing–remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.
Appendix 2. Relapses, lesions and brain atrophy indicate disease activity

**a.** Relapses predict disability progression; MRI lesions predict relapses and disability progression.

<table>
<thead>
<tr>
<th>Study description</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
</table>
| Systematic review and analysis of all clinical trials in CIS, RRMS and SPMS published between 1 January 1993 and 3 June 2013 (18,809 people) | Disability progression, Relapse rate, New lesions | Treatment effects on relapses and disability progression are correlated \( (R^2 = 0.75) \)  
| | | Treatment effects on new lesions and disability progression are correlated \( (R^2 = 0.64) \) |
| Meta-analysis of all clinical trials in RRMS published before 1 September 2008 (23 trials, 6,591 people) | Relapse rate, Active lesions | Treatment effects on active lesions and relapses are correlated \( (R^2 = 0.81) \) |
| Meta-analysis of all clinical trials in RRMS published between 1 September 2008 and 31 October 2012 (31 trials, 18,901 people) | Relapse rate, New or active lesions | Treatment effect on MRI lesions (after 6–9 months) predicts treatment effect on relapses (after 12–24 months)  
| | | Concurrent treatment effects on MRI lesions and relapses are correlated \( (R^2 = 0.71) \) |
| Meta-analysis of all published clinical trials in RRMS (19 trials, 10,009 people) | Disability progression, Relapse rate, MRI lesions | Treatment effects on relapses and disability progression are correlated \( (R^2 = 0.71) \)  
| | | Treatment effects on MRI lesions and disability progression are correlated \( (R^2 = 0.57) \) |
| Analysis of clinical trials of newer DMTs (three trials, 3,890 people) | Disability progression, Relapse rate, Active lesions | Treatment effect on active lesions predicts 92% of treatment effect on clinical outcomes (disability and relapse rate) |
| Meta-analysis of clinical trials of a particular established DMT class in CIS and RRMS published between 1 January 2000 and 21 May 2013 (11 trials, 2,171 people) | Disability progression, Relapses, Active lesions, New lesions | Initial poor response to DMT, as measured by active and new lesions, predicts clinical outcomes (relapses and disability progression) up to 16 years after treatment initiation |
| Retrospective analysis of MRI scans conducted in people with MS who also had 10-year follow-up disability data (166 people) | Disability progression (after 10 years), Total volume of lesions (change over 1–2 years), Brain atrophy (change over 1–2 years) | Changes in brain atrophy and lesion load both predict EDSS disability progression 10 years after the initial MRI scan in a ‘relapse onset’ subgroup containing people with CIS, RRMS and SPMS |

continued …
Brain health: time matters in multiple sclerosis

continued …

<table>
<thead>
<tr>
<th>Study description</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-year RCT in which people with RRMS received established DMT, followed by 15 years of treatment at discretion of physician (69 people)</td>
<td>Disability progression</td>
<td>Number of relapses, active lesions and new lesions during initial 2 years of observation predict disability progression 15 years later</td>
</tr>
<tr>
<td></td>
<td>Relapses</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Active lesions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>New lesions</td>
<td></td>
</tr>
<tr>
<td>Real-world study of people with CIS treated with an established DMT for 4 years (210 people)</td>
<td>Disability progression</td>
<td>Number of new lesions and brain atrophy predict a second relapse (that is, conversion to RRMS under any diagnostic criteria) within 4 years</td>
</tr>
<tr>
<td></td>
<td>Relapses</td>
<td></td>
</tr>
<tr>
<td></td>
<td>New lesions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brain atrophy</td>
<td></td>
</tr>
<tr>
<td>Real-world study of people with CIS treated with an established DMT for 2 years (220 people)</td>
<td>Disability progression</td>
<td>Number of lesions at baseline and rate of brain atrophy during first 6 months of observation predict conversion to RRMS</td>
</tr>
<tr>
<td></td>
<td>New lesions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brain atrophy</td>
<td></td>
</tr>
<tr>
<td>Real-world study of people with CIS (1989 people)</td>
<td>Disability progression</td>
<td>Time to disability progression is associated with relapse rate</td>
</tr>
<tr>
<td></td>
<td>Relapses</td>
<td></td>
</tr>
<tr>
<td>Real-world study of people with CIS (107 people)</td>
<td>Disability progression</td>
<td>Total volume of lesions and rate of change of lesion volume (especially during the first 5 years) both moderately predict disability progression 20 years later</td>
</tr>
<tr>
<td></td>
<td>MRI lesions</td>
<td></td>
</tr>
</tbody>
</table>

All results shown were statistically significant.

$R^2$ is a measure of how much of the variability in one item (e.g. disability progression) is shared with another item (e.g. new lesions). For example, $R^2 = 0.64$ means that 64% of the variation in one item is explained by variation in the other.

CIS, clinically isolated syndrome; DMT, disease-modifying therapy; EDSS, Kurtzke Expanded Disability Status Scale; MRI, magnetic resonance imaging; RCT, randomized controlled trial; RRMS, relapsing–remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.
Appendix 2. Relapses, lesions and brain atrophy indicate disease activity

### b. Brain atrophy predicts relapses and disability progression.

<table>
<thead>
<tr>
<th>Study description</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
</table>
| Meta-analysis of all published clinical trials in RRMS of at least 2 years in duration published before December 2012 (13 trials, > 13 500 people)\(^\text{159}\) | Disability progression New/enlarging lesions Brain atrophy | - Treatment effects on brain atrophy and disability progression are correlated ($R^2 = 0.48$)  
- Treatment effects on new/enlarging MRI lesions and disability progression are correlated ($R^2 = 0.61$)  
- The correlation with disability progression is greater when both of these MRI markers are combined ($R^2 = 0.75$) |
| Post hoc analysis of three published clinical trials of a newer DMT for which there is an evidence base supporting superior efficacy to that of an established DMT in RRMS (3635 people)\(^\text{160}\) | Disability progression Brain atrophy | - Rate of brain atrophy is associated with disability progression |
| Retrospective analysis of MRI scans conducted in people with MS who also had 10-year follow-up disability data (166 people)\(^\text{161}\) | Disability progression (after 10 years) Total volume of lesions visible on MRI (change over first 1–2 years) Brain atrophy (change over first 1–2 years) | - Brain atrophy and lesion volume both predict EDSS disability progression 10 years after the initial MRI scan in a ‘relapse onset’ subgroup containing people with CIS, RRMS and SPMS |
| Real-world study of people with CIS treated with an established DMT for 4 years (210 people)\(^\text{162}\) | Disability progression Relapses New lesions Brain atrophy | - Number of new lesions and brain atrophy predict a second relapse (that is, conversion to RRMS under any diagnostic criteria) within 4 years |
| Real-world study of people with CIS treated with an established DMT for 2 years (220 people)\(^\text{163}\) | Disability progression New lesions Brain atrophy | - Lesion volume at baseline and rate of brain atrophy during first 6 months of observation predict conversion to RRMS |

All results shown were statistically significant.

$R^2$ is a measure of how much of the variability in one item (e.g. disability progression) is shared with another item (e.g. new lesions). For example, $R^2 = 0.61$ means that 61% of the variation in one item is explained by variation in the other.

CIS, clinically isolated syndrome; DMT, disease-modifying therapy; EDSS, Kurtzke Expanded Disability Status Scale; MRI, magnetic resonance imaging; RRMS, relapsing–remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.
Appendix 3. Growing evidence supports the use of appropriate newer therapies

There is increasing evidence that people with MS whose disease is inadequately controlled by an established DMT will benefit from receiving an appropriate newer DMT.

<table>
<thead>
<tr>
<th>Study description</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT: 1 year of treatment with a newer or established DMT</td>
<td>Early newer DMT vs later newer DMT</td>
</tr>
<tr>
<td>Extension: 1 year of treatment with newer DMT (1027 people)</td>
<td>■ Lower relapse rate</td>
</tr>
<tr>
<td></td>
<td>■ Longer time to next relapse</td>
</tr>
<tr>
<td></td>
<td>■ Fewer new lesions</td>
</tr>
<tr>
<td></td>
<td>■ Fewer people with active lesions</td>
</tr>
<tr>
<td></td>
<td>■ No effect on disability progression</td>
</tr>
<tr>
<td>2 years of treatment with a newer or established DMT following treatment failure</td>
<td>Switch to newer DMT vs switch to established DMT</td>
</tr>
<tr>
<td>(RWE, matched groups, 1838 people)</td>
<td>■ Reduced disability progression over 2 years</td>
</tr>
<tr>
<td></td>
<td>■ Reduced relapse rate in year 1</td>
</tr>
<tr>
<td></td>
<td>■ Reduced risk of first on-treatment relapse in year 1</td>
</tr>
<tr>
<td></td>
<td>■ Reduced risk of disability progression in first 3 months</td>
</tr>
<tr>
<td>2 years of treatment with a newer or established DMT following treatment failure</td>
<td>Switch to newer DMT vs switch to established DMT</td>
</tr>
<tr>
<td>with an established DMT (RWE, 285 people)</td>
<td>■ Greater proportion of people with no relapses, no disability progression and no new MRI lesions after 2 years</td>
</tr>
<tr>
<td></td>
<td>■ No significant differences after 1 year</td>
</tr>
<tr>
<td>1 year (on average) of treatment with one of two newer or established DMTs</td>
<td>Both newer DMTs vs baseline (before starting treatment with newer DMT)</td>
</tr>
<tr>
<td>following treatment failure with an established DMT (RWE, matched groups, 578</td>
<td>■ Reduced relapse rate</td>
</tr>
<tr>
<td>people)</td>
<td>■ Greater improvements in disability (i.e. improved function)</td>
</tr>
<tr>
<td>3 months (at least) of treatment with a newer or established DMT following</td>
<td>Switch to newer DMT vs switch to established DMT</td>
</tr>
<tr>
<td>treatment failure up to 12 months previously with an established DMT</td>
<td>■ Reduced relapse rate</td>
</tr>
<tr>
<td>(RWE, matched groups, 527 people)</td>
<td>■ Reduced risk of a further relapse</td>
</tr>
<tr>
<td></td>
<td>■ Reduced risk of disability progression</td>
</tr>
<tr>
<td></td>
<td>■ Increased probability of improvements in disability (i.e. improved function)</td>
</tr>
<tr>
<td>Treatment with a newer or established DMT following switching from an established</td>
<td>Switch to newer DMT vs switch to established DMT</td>
</tr>
<tr>
<td>DMT (RWE, matched groups, 264 people)</td>
<td>■ Reduced relapse rate</td>
</tr>
<tr>
<td></td>
<td>■ Reduced probability of a further relapse</td>
</tr>
</tbody>
</table>

continued …
Appendix 3. Growing evidence supports the use of appropriate newer therapies

<table>
<thead>
<tr>
<th>Study description</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years of treatment with a newer DMT (clinical trial, 4821 people)</td>
<td>Newer DMT vs baseline (before starting treatment with newer DMT)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>No worsening in disability on average (unchanged mean EDSS scores)</td>
</tr>
<tr>
<td></td>
<td>Annual relapse rate fell between baseline and year 5</td>
</tr>
<tr>
<td>3 years of treatment with a newer DMT (RWE, 64 people)</td>
<td>Newer DMT vs baseline (before starting treatment with newer DMT)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Improvements in disability on average (i.e. improved function) during first year of treatment</td>
</tr>
<tr>
<td></td>
<td>No worsening in disability between baseline and year 3</td>
</tr>
<tr>
<td></td>
<td>Annual relapse rate fell between baseline and year 3</td>
</tr>
<tr>
<td>1 year of treatment with a newer DMT (clinical trial, 195 people)</td>
<td>Newer DMT vs baseline (before starting treatment with newer DMT)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Improvements in disability (i.e. improved function), walking speed, quality of life, cognition, fatigue, depression and sleepiness compared with baseline</td>
</tr>
<tr>
<td>6 months of treatment with a newer DMT in people with MS and disabling bladder dysfunction (clinical trial, 30 people)</td>
<td>Newer DMT vs baseline (before starting treatment with newer DMT)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Improvements in incontinence-related quality of life after 6 months compared with baseline</td>
</tr>
</tbody>
</table>

All results shown were statistically significant.

<sup>a</sup>Newer DMT with an evidence base supporting superior efficacy to that of an established DMT.

<sup>b</sup>Analysis carried out post hoc.

<sup>c</sup>Treatment failure was defined as “the occurrence of ≥ 2 relapses or 1 relapse with residual disability.”

DMT, disease-modifying therapy; EDSS, Kurtzke Expanded Disability Status Scale; MRI, magnetic resonance imaging; RCT, randomized controlled trial; RWE, real-world evidence.
References


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270. Giovannoni G. Biomarkers in MS. EFNS/ENS Joint Committee for Treatment and Research In Multiple Sclerosis (MENACTRIMS).


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Resources

Milestone diagnostic criteria for multiple sclerosis

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>Year</th>
<th>Link</th>
</tr>
</thead>
<tbody>
<tr>
<td>McDonald revised¹⁴⁹</td>
<td>2010</td>
<td><a href="http://doi.org/10.1002/ana.22366">http://doi.org/10.1002/ana.22366</a></td>
</tr>
<tr>
<td>McDonald revised¹⁴⁷</td>
<td>2005</td>
<td><a href="http://doi.org/10.1002/ana.20703">http://doi.org/10.1002/ana.20703</a></td>
</tr>
<tr>
<td>McDonald¹⁴⁶</td>
<td>2001</td>
<td><a href="http://doi.org/10.1002/ana.1032">http://doi.org/10.1002/ana.1032</a></td>
</tr>
<tr>
<td>Poser¹⁴⁵</td>
<td>1983</td>
<td><a href="http://doi.org/10.1002/ana.410130302">http://doi.org/10.1002/ana.410130302</a></td>
</tr>
</tbody>
</table>
Glossary

Active MS lesion
On an MRI scan, an area of brain or spinal cord damage due to MS that has appearances of being new or active because it 'enhances' (shows up) when gadolinium is used as a contrast agent.

Alzheimer’s disease
The most common form of dementia (a group of diseases characterized by cognitive impairment).

Atrophy
Decrease in volume.

Autopsy
An examination carried out after someone has died to determine the cause of death; also known as a post-mortem.

Axon
A nerve fibre, the part of a nerve cell that transmits signals.

Biosimilar drug
Generic version of a biological drug that can be manufactured once the original drug's patent has expired.

Brain atrophy
Loss of brain volume implying loss of brain tissue – may be focal or generalized.

Brain reserve
A component of neurological reserve; can be thought of as the physical quantity of brain tissue present (see page 31).

Cardiovascular
Relating to the heart and blood vessels.

Central nervous system
The brain, spinal cord and optic nerve.

Cerebrospinal fluid
The fluid that circulates around the brain and spinal cord.

Chronic obstructive pulmonary disease
A collection of chronic (long-term) lung problems (e.g. chronic bronchitis), the symptoms of which typically include breathlessness, coughing and chest infections.

Clinically isolated syndrome
A single, initial, episode of CNS inflammation.

Cognitive impairment
A reduction of mental abilities or processes.

Cognitive reserve
A component of neurological reserve; can be thought of as the ability of the brain to process tasks and actively compensate for physical damage (see page 31).

Comorbidities
Other diseases present alongside the disease under discussion.

Direct medical costs
Costs directly paid by healthcare providers (for example, the costs of medicines, consultations, tests, inpatient stays and formal home care).

Direct non-medical costs
Costs directly paid by non-healthcare providers (for example, the costs of wheelchairs, home adaptations and informal care by relatives).

Disease-modifying therapy
A medication that can alter the natural course (natural history) of a disease; in the case of MS, a drug that reduces the frequency of relapses, accumulation of disability or accumulation of MRI changes.

Economic evaluation
An analysis of the ‘value’ of interventions (such as therapies or devices), which is based on ‘cost per health outcome’ compared with relevant alternative interventions.

Effectiveness
A measure of how well an intervention (e.g. a drug or medical device) works, in terms of health outcomes, when used in a real-world situation.

Efficacy
A measure of how well an intervention (e.g. a drug or medical device) works, in terms of health outcomes, when used in the ‘ideal’ situation of a clinical trial or laboratory study.
Established DMT
In this report, the term refers to DMTs approved for relapsing forms of MS during the 1990s, and to reformulations and generic versions of these substances.

Evoked potentials
Measurements of brain activity when certain sensory nerves are stimulated, which can detect when electrical signals are travelling more slowly than usual as a result of damage to the CNS.

Extension study
A study that follows on from a clinical trial; typically, participants are given the opportunity to continue/commence taking the drug being studied in the trial in order to investigate its long-term efficacy and safety.

Fatigue
A subjective lack of physical or mental energy that interferes with usual or desired activities.

Formulation
The manner in which the active drug is combined with other ingredients to make the final medicinal product.

Grey matter
Grey-coloured tissue in the CNS that is mainly responsible for cognition and processing information.

Head-to-head trial
A clinical trial designed to provide a direct comparison between (at least) two different therapies.

Health-related quality of life
An assessment of well-being that includes physical, mental and social measures.

Health technology assessment
Evaluation of a treatment or device to determine its value (health benefits in relation to costs), usually to decide whether it will be funded from the public budget.

High-income country
Gross national income per capita ≥ $12,746 in 2013 (World Bank definition).

Indirect costs
Costs that are not directly paid for by any party but that can be assessed (for example, productivity losses due to sick leave, unemployment or early retirement).

Kurtzke Expanded Disability Status Scale
A measure of physical disability that is commonly used for assessing people with MS; the scale ranges from 0.0 (no disability) to 10.0 (death as a result of MS) in increments of 0.5.

Lesion
An area of acute damage to the CNS.

Longitudinal study
A study in which the same variable is measured, repeatedly, over a long period of time.

Lower-middle-income country
Gross national income per capita ≥ $1,045 and < $4,125 in 2013 (World Bank definition).

Low-income country
Gross national income per capita ≤ $1,045 in 2013 (World Bank definition).

Lumbar puncture
In MS, a procedure in which a sample of cerebrospinal fluid is taken.

Magnetic resonance imaging
An imaging technique that allows soft tissue to be visualized based on the fact that different tissue types contain different concentrations of water.

Matched groups
An experimental design in which the participants included in different groups have been matched for factors (such as age, sex and length of time since disease onset) that enable a fair comparison to be made.

McDonald diagnostic criteria
Diagnostic criteria for MS, introduced in 2001 and revised in 2005 and 2010; in some cases, they allow MS to be diagnosed based on one clinical relapse and MRI evidence.
**Mechanism of action**  
The biochemical interaction through which a drug mediates its effect.

**Meta-analysis**  
Statistical methods used to combine the results of different studies in order to increase the number of data points being considered and reveal overall trends that may not be statistically significant with smaller numbers of data points.

**Motor symptoms of MS**  
These can include weakness, stiffness, clumsiness and difficulties in walking.

**MS neurologist**  
A neurologist who has a special interest, and expertise, in the diagnosis and management of MS. A specialist MS neurologist will typically see and manage a larger number of patients with MS than a general neurologist.

**Multiple sclerosis**  
A progressive neurodegenerative disease that causes physical and mental disability as a result of damage to the CNS.

**Neurodegeneration**  
Deterioration in structure and/or loss of function of nerve cells.

**Neurological reserve**  
The capacity of the brain to retain function by remodelling itself to compensate for loss of nerve cells, loss of nerve fibres and atrophy (see page 31).

**Neurologist**  
A clinician specializing in diagnosing, treating and managing disorders of the nervous system; an MS neurologist has a sub-specialism in MS.

**Newer DMT**  
In this report, the term refers to DMTs approved for relapsing forms of MS after the 1990s that have different MoAs from those of established DMTs; some newer DMTs have an evidence base supporting superior efficacy to that of an established DMT, which may include head-to-head clinical trials or real-world evidence.

**Open label**  
Type of trial in which the clinician and participant both know which drug is being used for treatment.

**Optic nerve**  
Nerve that connects the eye to the brain; part of the CNS.

**Placebo**  
A ‘dummy’ treatment with no therapeutic effect.

**Poser diagnostic criteria**  
Diagnostic criteria for MS introduced in 1983; they require at least two clinical relapses for a diagnosis of clinically definite MS.

**Post hoc**  
Analysis of data after it has been generated, in a way that was not specified before the start of an experiment or trial.

**Post-mortem**  
After death (see autopsy).

**Primary progressive MS**  
Disease course in which clinical disability becomes gradually worse from the onset of symptoms, with an absence of relapses.

**Purchasing power parity**  
A method of comparing expenditure across different countries.

**Quality-adjusted life-year**  
A measure of the effect that a treatment has on length and quality of life, which can be compared across different diseases.

**R²**  
A measure of how much of the variability in one item (e.g. disability progression) is shared with another item (e.g. new lesions); for example, \( R^2 = 0.61 \) means that 61% of the variation in one item is explained by variation in the other.

**Radiologically isolated syndrome**  
Damage to the CNS with the absence of any clinical symptoms; usually detected as a result of an MRI scan conducted for another reason (e.g. headaches).
### Randomized controlled trial
A clinical trial design in which participants are randomly allocated to treatment groups to receive the drug being investigated or a control substance (placebo or another drug).

### Real-world evidence
Evidence obtained outside the clinical trial setting (for example, by analysing data from a patient registry or database).

### Reference arm
A group of participants in a clinical trial who receive a reference treatment (for example, an established therapy); this term is typically used when the trial has not been set up to provide statistically significant comparisons between the new drug and the reference treatment (i.e. it has not been set up as a head-to-head trial).

### Relapse
An acute attack of symptoms of MS; usually, a relapse develops over a few days, before the symptoms plateau and ease off.

### Relapsing–remitting MS
Disease course in which people experience acute attacks of symptoms (relapses) separated by periods of remission.

### Remission
The period in between relapses in an RRMS disease course.

### Secondary progressive MS
Disease course in which clinical disability becomes gradually worse, with an absence of relapses, following an initial relapsing–remitting disease course.

### Sensory symptoms of MS
These can include numbness, tingling and burning pain.

### Statistically significant
In this report, ‘statistically significant’ is used to mean that the probability that a result could have occurred by random chance is less than 5%.

### Subclinical parameter
Something that cannot be measured/observed during a clinical examination (for example, MRI lesions or brain atrophy).

### Telemedicine
Remote diagnosis, treatment or ongoing management using telecommunications technology.

### Tremor
Uncontrollable shaking of part(s) of the body, e.g. hands.

### Upper-middle-income country
Gross national income per capita ≥ $4125 and < $12 746 in 2013 (World Bank definition).

### Utility
A person’s perspective on their state of health, expressed as a value between 1 (full health) and 0 (death); typically used in the context of cost-effectiveness analyses carried out to decide how healthcare resources should be allocated.

### Vertigo
A spinning sensation.

### Visual symptoms of MS
These can include painful loss of vision, unstable vision and double vision.

### White matter
White-coloured tissue in the CNS that is mainly responsible for carrying signals between different parts of the brain and spinal cord.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAN</td>
<td>American Academy of Neurology</td>
</tr>
<tr>
<td>ABN</td>
<td>Association of British Neurologists</td>
</tr>
<tr>
<td>CIS</td>
<td>clinically isolated syndrome</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>DMT</td>
<td>disease-modifying therapy</td>
</tr>
<tr>
<td>EDSS</td>
<td>Kurtzke Expanded Disability Status Scale</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency (the European regulatory authority)</td>
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<tr>
<td>EUReMS</td>
<td>European Register for Multiple Sclerosis</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration (the US regulatory authority)</td>
</tr>
<tr>
<td>GP</td>
<td>general practitioner (family or primary care physician)</td>
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<tr>
<td>HTA</td>
<td>health technology assessment</td>
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<tr>
<td>MoA</td>
<td>mechanism of action</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>MS</td>
<td>multiple sclerosis</td>
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<tr>
<td>NEDA</td>
<td>no evidence of disease activity</td>
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<tr>
<td>NRSPMS</td>
<td>non-relapsing secondary progressive multiple sclerosis</td>
</tr>
<tr>
<td>PPMS</td>
<td>primary progressive multiple sclerosis</td>
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<tr>
<td>QALY</td>
<td>quality-adjusted life year</td>
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<tr>
<td>RICT</td>
<td>randomized controlled trial</td>
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<tr>
<td>RIS</td>
<td>radiologically isolated syndrome</td>
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<tr>
<td>RRMS</td>
<td>relapsing–remitting multiple sclerosis</td>
</tr>
<tr>
<td>RSPMS</td>
<td>relapsing secondary progressive multiple sclerosis</td>
</tr>
<tr>
<td>RWE</td>
<td>real-world evidence</td>
</tr>
<tr>
<td>SPMS</td>
<td>secondary progressive multiple sclerosis</td>
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</tbody>
</table>

## Currencies

<table>
<thead>
<tr>
<th>Currency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUD</td>
<td>Australian dollars</td>
</tr>
<tr>
<td>€</td>
<td>euros</td>
</tr>
<tr>
<td>US$</td>
<td>US dollars</td>
</tr>
</tbody>
</table>
“The MS Trust warmly welcomes this important report. It is a timely, well-considered and mature exploration of the clinical, service and policy issues that impact the treatment of people with relapsing forms of multiple sclerosis. The report is a call to arms for everyone committed to improving services. Early treatment, active management and information to help people make their treatment choices are the benchmark in this new era in MS care. We congratulate the authors and look forward to supporting the implementation of the findings here in the UK and beyond.”

Amy Bowen
Multiple Sclerosis Trust

“This is an easy to read, beautifully illustrated, well-updated document. We endorse it.”

Takahiko Saida, Pan-Asian Committee for Treatment and Research in Multiple Sclerosis

“This report is an outstanding milestone to guide clinicians to approach MS appropriately, according to the most recent scientific evidence. Therefore, BCTRIMS is proud to join the international scientific community to endorse it.”

Marco Aurélio Lana-Peixoto, Brazilian Committee for Treatment and Research in Multiple Sclerosis

“This is a timely, challenging report that sets out important policy recommendations with the potential to have a significant impact on the lives of hundreds of thousands of people affected worldwide by multiple sclerosis.”

Maggie Alexander, European Multiple Sclerosis Platform

“It is a great document. I am pleased that ECTRIMS will endorse it.”

Xavier Montalban, European Committee for Treatment and Research in Multiple Sclerosis