The Use of Disease-Modifying Therapies in Multiple Sclerosis:

Principles and Current Evidence
SUMMARY

A Consensus Paper by the Multiple Sclerosis Coalition

MS Coalition®

Updated March 2017

Original July 2014

Accelerated Cure project for multiple sclerosis

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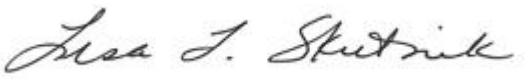
A Letter from the MS Coalition

The treatment of multiple sclerosis (MS) requires comprehensive management strategies. One important component is modifying the disease course. When deciding on a disease-modifying therapy for MS, you and your healthcare team must consider many factors. What does the research say about medications for someone with your disease course? How is the treatment administered? What are the potential side effects? Further complicating matters may be issues of access to care. Will your insurance provider pay for the medication? Will you be required to demonstrate that other medications have failed to benefit you first?

To help the MS community (people with MS and their family members, healthcare providers and insurers) navigate the existing information on the available treatments for MS, the member organizations of the Multiple Sclerosis Coalition* developed a consensus document to describe our current knowledge of disease modification in MS and provide support for broad access to U.S. Food and Drug Administration (FDA)- approved MS disease-modifying therapies. The paper was written by a team representing the MS Coalition member organizations and reviewed by a panel of expert MS clinicians to ensure the content was accurate, complete and unbiased.

This version of the document provides a summary of each section of the consensus paper. You can refer to the corresponding sections in the full consensus paper for more details and the related journal citations. We hope that you will benefit from reading this document and share the information, as you feel appropriate, with your friends and family members, healthcare providers and insurance companies.

Sincerely,



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*The Multiple Sclerosis Coalition, which was founded in 2005 to increase opportunities for cooperation and provide greater opportunity to leverage the effective use of resources for the benefit of the MS community, includes Accelerated Cure Project for Multiple Sclerosis, Can Do Multiple Sclerosis, Consortium of Multiple Sclerosis Centers, International Organization of Multiple Sclerosis Nurses, Multiple Sclerosis Association of America, Multiple Sclerosis Foundation, National Multiple Sclerosis Society, MS News and Views (since 2015), and United Spinal Association.

HOW TO USE THIS PAPER

For making treatment decisions with your healthcare professional:

This summary and the full consensus version can be found at: [http://ms-coalition.org/cms/images/stories/dmt_consensus_ms_coalition042017.pdf] containing links to all cited references, summarizes the findings from the initial (pivotal) clinical trials of the disease-modifying therapies, as well as other studies demonstrating the importance of early and ongoing treatment.

Whichever version you prefer to read, be sure to share the fully-referenced document with your healthcare providers.
[http://ms-coalition.org/cms/images/stories/dmt_consensus_ms_coalition042017.pdf]

For self-advocacy with your insurance provider:

- Both versions of this document are designed as education and advocacy tools to support the effective use of the available FDA-approved disease-modifying therapies to manage your MS. When advocating with your insurance company, provide the fully referenced version of the paper so that the individuals involved in making decisions about your coverage have access to the evidence they need to make the most informed decisions.

- The findings reported in this paper clearly demonstrate the importance of early and ongoing treatment with a disease-modifying therapy. They also demonstrate the importance of being able to try different medications – with different mechanisms of action or a different route of delivery or side effect profile – if your initial treatment is not providing sufficient benefit, has intolerable side effects or potential health risks, or poses other challenges that make it difficult for you to adhere to the treatment plan that you and your healthcare provider have devised. A medication, no matter how effective it has been shown to be in clinical trials, cannot work effectively for you if you are unable to take it consistently in the manner it has been prescribed for you.

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KEY CONSIDERATIONS REGARDING DISEASE-MODIFYING THERAPY IN MS

The following treatment and access considerations are based on the findings reported in the remainder of this paper.

Treatment Considerations

- **Starting treatment with an FDA-approved disease-modifying therapy as soon as possible is recommended:**
  - When a person has been diagnosed with relapsing or primary progressive MS, regardless of age.
  - When a person has had a first episode of neurologic symptoms as well as MRI findings consistent with MS, and other possible causes have been ruled out.
- **Treatment with any disease-modifying therapy should be continued indefinitely, unless any of the following occur (in which case an alternate disease-modifying therapy should be considered):**
  - The individual and his or her healthcare professional determine that the treatment is failing to adequately control the disease.
  - The side effects are intolerable.
  - Signs of a severe adverse event, such as progressive multifocal leukoencephalopathy (PML) become evident.
  - A person is unable to follow the recommended treatment regimen.
  - A more appropriate treatment becomes available.
- Movement from one disease-modifying therapy to another should only occur for medically appropriate reasons.
- When evidence suggests that a medication is not providing adequate benefit, another treatment that works differently on the disease process (has a different mechanism of action) should be considered.
- The factors affecting choice of treatment at any point in the disease course are complex and most appropriately analyzed and addressed collaboratively by the person with MS and his or her healthcare professional.

Access Considerations

- Because MS varies from person to person, an individual and his or her healthcare provider need access to a full range of treatment options for the following reasons:
  - Access to medications with different mechanisms of action allows for treatment change if and when the current treatment is not providing sufficient benefit.
  - Pre-existing medical conditions or current medication(s) may interact with the prescribed DMT.
  - People with MS, their family members and their healthcare professionals may differ significantly in their tolerance for risks associated with the disease-modifying therapies. A medication's method of delivery and/or side effects may affect a person's

quality of life and ability to adhere to the treatment plan. A person who is unable to tolerate a medication or take it on a regular basis may need access to different medications in the same class (for example, an alternative beta interferon medication).

- Access to treatment should not be limited by frequency of relapses, level of disability, or personal characteristics such as age, gender or ethnicity.
- Absence of relapses while on treatment should not be considered a justification for discontinuing the treatment, since the absence of relapses may indicate that the treatment is working.
- Treatment should not be discontinued to allow for determination of coverage by an insurance company as this puts the individual at risk for an increase in disease activity.

OVERVIEW OF MS

Important points to understand about the nature of the disease include:

- MS is the most common non-traumatic, disabling neurologic disorder of young adults.
- Early in their disease course, most people with MS experience relapses and remissions of neurological symptoms – these clinical events are usually associated with areas of inflammation in the central nervous system (CNS – which includes the brain and spinal cord).
- Gradual worsening (known as disease progression) with or without relapses may take place early in the disease but generally increases over time.
- While traditionally viewed as a disease of only the white matter in the CNS, advanced MRI techniques have also shown significant early and ongoing damage in the gray matter of the CNS.
- Annual direct healthcare costs for people with MS are on average $24,327 higher than the general population. Those with MS are also significantly more likely to be unemployed.

Epidemiology, Demographics, Disease Course

Key points about the demographics of the disease include the following:

- MS is believed to affect more than two million people worldwide.
- Women are diagnosed at least two to three times more frequently than men.
- The disease is more common in Caucasians than in other racial groups.

Some demographics may be changing:

- Recent research has shown that African-American women appear to have a higher than previously reported risk of MS.

- People closer to the equator, previously believed to be at lower risk, are being diagnosed more frequently, which may suggest a change in regional risks.

Regarding the course of the disease, it differs from one individual to another and even varies within groups of individuals who have been diagnosed with the same disease course. However:

- 85-90 percent of people have a relapsing-remitting pattern (RRMS) at disease onset.
- Over time, RRMS transitions in the majority of people to a pattern of progressive worsening with few or no relapses (secondary-progressive MS – SPMS).
- Approximately 10-15 percent of those diagnosed with MS have a primary-progressive disease course (PPMS) and never experience clinical relapses. Instead, they demonstrate a steady progression of symptoms from the time of diagnosis onward.
- PPMS is generally diagnosed at an older age and is distributed more equally in men and women.

For more information about MS disease courses, refer to Appendix A in the full paper.

Inflammation and Damage in the Central Nervous System

It is important to understand the process by which MS appears to cause damage. The process appears to be immune-mediated, with the immune system attacking cells within the CNS. This attack on cells causes inflammation that damages the protective insulation of the nerve fibers (myelin), the cells that create this insulation (oligodendrocytes) and the nerve fibers that the insulation protects (axons).

Many different cells participate in the inflammatory response and they are the targets for the disease- modifying treatments that are currently available, as well as many of those in the research pipeline.

Key points to remember:

- Damage to the central nervous system occurs early in MS and continues throughout a lifetime with the condition.
- While MRI shows areas of damage (lesions) in the CNS, research has shown that MS affects the entire central nervous system, not merely where lesions are seen.
- Early and ongoing treatment with disease-modifying therapies is important to lessen the damage from inflammation.

OVERVIEW OF APPROVED DISEASE-MODIFYING THERAPIES IN MS

Fifteen disease-modifying therapies are approved by the U.S. Food and Drug Administration (FDA) (as of March 2017):

Self-injected agents:

- daclizumab (Zinbryta®)
- glatiramer acetate (Copaxone® and Glatopa®)
- interferon beta 1-a, subcutaneous (Rebif®)
- interferon beta 1-a, intramuscular (Avonex®)
- interferon beta 1-b (Betaseron® and Extavia®)
- pegylated interferon beta-1 a (Plegridy®)

Oral agents:

- dimethyl fumarate (Tecfidera®)
- fingolimod (Gilenya®)
- teriflunomide (Aubagio®)

Intravenous agents:

- ocrelizumab (Ocrevus™)
- alemtuzumab (Lemtrada®)
- mitoxantrone (Novantrone®)
- natalizumab (Tysabri®)

Detailed information about each of the medications is available in Table 1 in the consensus paper.

This information includes:

- Dosing schedule
- How the medication is given
- Pregnancy information
- Mechanism of action (how the medication is thought to work)
- Side effects
- Warnings and precautions

It is important for people with MS and their healthcare professionals to consider the full FDA prescribing information for these medications when making decisions about treatment.

DISEASE-MODIFYING THERAPY CONSIDERATIONS

MS varies greatly from person to person; the prognosis (expected outcome) for any single individual remains unpredictable. Yet, several important themes have emerged from the research that conducted in MS treatments:

- Early, effective control of the disease appears to play a key role in preventing increases in disability, thus prolonging the ability to remain active and engaged, and protecting quality of life.
- Physical limitations are only one aspect of disability that can result from early disease activity and disease progression; less visible symptoms such as fatigue and changes in cognition and mood contribute to disability as well.
- The ability to take a disease-modifying therapy as prescribed, over a long period of time, is essential to the effectiveness of the treatment. Because the ability to take a medication on a regular basis may be impacted by a wide range of factors, every effort must be made to identify and address and modify those factors promptly.

Disease Factors Highlighting the Importance of Early Treatment

The goal: To reduce early disease activity – both the clinical symptoms of which you and your doctor are fully aware, and the underlying changes in the CNS that may not be readily apparent.

The benefit: Reducing your early disease activity may lessen your long-term disability.

Evidence for the following points highlight the importance of early treatment:

- **Inflammation and damage to the CNS (neurodegeneration) occur early in MS.**
  - Early in the disease, new areas of inflammation occur much more frequently than the appearance of new symptoms, indicating that the disease is active even when a person is not experiencing a new attack or new symptoms. Damage to white and gray matter in the CNS is known to be present early in the disease process.
  - A loss of brain tissue (atrophy) occurs in the very earliest stages of the disease process. Once a certain level of damage has occurred in the CNS, disability progression continues at a rate that is unrelated to a person's prior history of relapses. Early treatment may delay the point at which a person reaches that level of damage.
  - Inflammatory activity is known to occur in both in relapsing and progressive forms of MS.

- **People who experience a first clinical event and have MRI findings that are typical of MS, and who do not receive treatment, are likely to experience further disease activity.**

The criteria for diagnosing MS traditionally required two distinct clinical episodes (relapses) before a definite diagnosis can be made. The term "clinically-isolated syndrome" (CIS) described a first, single episode of neurologic symptoms that lasts at least 24 hours and is caused by inflammation and demyelination in one or more areas of the CNS. More recently, diagnostic criteria allow for a diagnosis of MS on the basis of a single attack, if MRI findings show what appears to be disease activity over time. While this adjustment has made CIS a nearly obsolete diagnosis, we learn something significant from the CIS research that can be applied to those with clinically definite MS.

- In four studies on people who had experienced CIS, 80% of those in the placebo groups (receiving no active treatment) were later diagnosed with MS.
- Those people with a high number of lesions at the time of their first clinical event are likely to have more disability after 20 years than those with a small number of lesions on their initial MRI scan.
- The injectable disease-modifying therapies have been tested and found to be effective in CIS. Their use can delay the next relapse and reduce new areas of damage that can be seen on the MRI.
- MRI findings in people with CIS are often consistent with those seen in MS and they can be helpful in predicting disease progression. Based on the data from the published trials in people with CIS, treatment for individuals with early relapsing MS is essential in order to achieve the best possible short- and long-term outcomes.

- **Individuals with radiographically isolated syndrome (RIS) are at a significant risk for early damage and subsequent disease activity. An individual is diagnosed with RIS when, in the absence of symptoms, MRI demonstrates findings consistent with MS. In the most recent revision of the types of MS, this little-understood diagnosis was not included. However, research is ongoing and the following findings strongly suggest that early treatment of MS, whether clinically definite or probable, is important.**
  - Within 5 years, 30% of people with RIS will experience MS symptoms.
  - Within 5 years, two-thirds of people with RIS will develop new lesions on MRI.
  - 10 percent of people with RIS were found to have a progressive course of MS.
  - 20-30 percent of RIS patients develop cognitive changes similar to those with RRMS.
- **Early disease activity and disease course appear to impact long-term disability.**
  - Natural history studies of people diagnosed with MS who have received no disease-modifying therapy suggest that relapses in the first two years lead to earlier disease progression.
  - A study following individuals diagnosed with CIS found that the amount of lesion area that was visible on MRI in the first five years of the disease correlated with the degree of long- term disability.
- Earlier onset of secondary-progressive MS – in which inflammatory attacks decrease and progression becomes the hallmark of the disease – is typically associated with greater long-

term disability. **Cognitive changes, depression and fatigue may occur very early in the disease process.**

Research has shown that approximately 60 percent of people with MS will experience changes in their thinking or memory (cognition); 36-54 percent will experience depression; and up to 92 percent will experience significant fatigue. All of these factors contribute to increased disability and diminished quality of life.

- A growing body of evidence indicates that approximately 20-30 percent of people have already experienced cognitive changes at the time of the first clinical event (CIS) that suggests MS.
- 20-30 percent of RIS patients develop cognitive changes similar to those with RRMS.
- Some studies indicate cognitive changes may appear as much as 1.2 years before MS onset.
- Early cognitive changes continue to progress, even in people who experience few or no physical changes.
- Approximately 30 percent of children and teens with MS have some cognitive changes.
- Depression and fatigue may accompany cognitive deficits in early MS, with each having a significant impact on quality of life, employment and other important activities of daily life.

- **So-called "benign MS" may not be benign for many people.**

  The term "benign MS" has been used to describe individuals who have minimal physical disability (as defined by the Expanded Disability Status Scale - EDSS) 10 years after their diagnosis. However this definition of benign disease does not take into account the less visible symptoms of MS such as mood changes, cognitive changes, and fatigue.

  - In one study, cognitive, psychological and social changes and challenges were found in a group of individuals with "benign MS."
  - In another group of people with "benign MS" who were followed for 10.9 additional years, many became increasingly physically disabled in addition to experiencing cognitive changes, pain and depression. This group also developed more lesion activity as shown on MRI.
  - In a third group of people with "benign MS" that was studied after 20 years, only 51 percent of the group maintained their benign status. Others in the group had progressed to needing a mobility aid and/or developed secondary-progressive MS. The authors of this study concluded that appropriate criteria for determining which individuals will have a truly benign course of the disease have not yet been identified.

In summary, early and ongoing treatment helps to minimize the inflammation, damage to nerve fibers (axons), and loss of brain tissue that take place early in the disease course. This damage can occur even in the absence of symptoms. These findings indicate that the best chance for reducing long-term disability is during the early relapsing phase of the disease. Given the medications that

are currently available – all of which primarily target inflammation – early treatment is key, with the goal being to slow the accumulation of lesions, decrease the number of relapses, and prevent disease progression.

Evidence Demonstrating the Impact of Treatment Following a First Clinical Event

Published results in CIS, all of which were done with the injectable disease-modifying therapies, demonstrated that early treatment successfully delayed conversion to clinically definite MS.

Evidence Demonstrating the Impact of Treatment on Relapsing MS

Although none of the available disease-modifying therapies are fully effective in controlling the disease, each has been shown in one or more controlled clinical trials to provide significant benefits in relapsing forms of MS.

- **Impact on relapse rate and MRI activity**
  - Each of the approved disease-modifying therapies has demonstrated a decrease in relapse rate and reduction in disability progression.
  - Each of the treatments demonstrated either a reduction in the number of gadolinium-enhancing lesions or a decrease in the number of new or enlarging lesions, or both.
  - Later studies demonstrated an impact of treatment on the development of "black holes" (persistent T1 hypointensities on MRI, which are thought to be indicative of tissue damage) and on brain tissue loss (atrophy).
  - Clinical trial data may not be directly compared from one medication to another because of differences in the populations that were studied and in the clinical trial designs that were used.

Details about the disease-modifying therapies are available in Tables 2 - 4 of the full consensus document.

Evidence Demonstrating the Impact of Treatment on Progressive MS

Many treatments have been investigated for use in secondary progressive or primary progressive MS. In secondary progressive MS, only mitoxantrone is approved for use by the FDA. However, it is seldom used in the United States because of its high-risk profile. In primary progressive MS, only ocrelizumab has received FDA approval. The data from the ocrelizumab clinical trial suggested greater benefit in patients of younger age with more recent progression, recent relapse(s) and/or MRI activity.

- **Impact of treatment on long-term clinical outcomes**
  - Most extension studies following CIS and the pivotal trials of the disease-modifying therapies found that treatment may delay conversion from CIS to clinically definite MS, decrease relapse rates and delay disease progression.

- These studies also indicated that disease-modifying therapies may delay the conversion from relapsing to progressive MS (which generally occurs in about 90 percent of untreated individuals with relapsing-remitting MS after 20-25 years). Some extension study data have also suggested that early treatment helps to preserve cognitive function compared to delayed treatment.
- Extension study data also suggest that early treatment helps to preserve cognitive function.
- One study demonstrated decreased mortality in patients treated early in the course of their disease compared with those treated somewhat later. This is a finding that requires more studies with more recently available disease modifying therapies.

- **Impact on quality of life**
  Neither an MRI nor a clinical examination can demonstrate the impact of MS on a person's quality of life. Several studies looking at the impact of disease-modifying therapies have demonstrated a positive impact, particularly on the ability to carry out activities of daily living.

- **Benefits gained through early treatment may never be equaled in those whose treatment is delayed**
  While some conflicting data exist, several studies suggest that benefits gained through early treatment – including delayed conversion to clinically definite MS (CDMS) and reduced relapse rates and disability – may not be equaled in those who start treatment later in the disease course.

Evidence Supporting the Need for Treatment to Be Ongoing

The evidence suggests that treatment needs to be ongoing for benefits to persist. Stopping treatment has been shown to have a negative impact, which may include an increase in the frequency and severity of relapses, worsening symptoms, or the appearance of new or worsening lesions on MRI.

Regardless of the reason for stopping treatment – whether a decision by the person with MS or clinician, issues of cost, access, or insurance coverage – research shows that discontinuing or interrupting treatment may provoke a return of disease activity.

Use of Disease-Modifying Therapies in Pediatric MS

Studies have estimated the incidence of MS in children and teens under the age of 18 to be between 0.18 and 0.51/100,000 children per year. This roughly translates to between two and five youngsters diagnosed with MS per every million children each year. Additionally, 3 percent of adult patients report a possible first attack prior to age 18. More than 97 percent of children and adolescents experience a relapsing-remitting disease course.

While none of the available disease-modifying therapies are specifically FDA approved for use in children or teens, these medications are often prescribed to slow disease activity in these age groups. The injectable disease-modifying therapies for MS (Avonex, Betaseron, Copaxone, Extavia, Glatopa, Rebif) are generally considered to be the initial treatment options. As in adults, however, evidence of ongoing relapses, MRI activity and increasing disability indicate the need to change treatment. Some children and teens experience particularly active disease that does not respond to the first treatment used or even to other medications that are prescribed.

Important findings related to pediatric MS include:

- Children experience annual relapse rates that are two-to-three times higher than the relapse rates of adults during the first three years of the disease.
- In addition to physical symptoms, 30 to 40 percent of children with MS demonstrate cognitive impairment early in the disease course.
- One study found that only slightly more than half of children were successfully treated with the first medication they were given. Regarding those who needed to try other treatments, 25.2 percent of children were switched once; 11.2 percent were switched twice; and 7.8 percent required three changes in medication.
- Several analyses that looked back at how well children and teens tolerated treatment with natalizumab (Tysabri), as well as the safety of this medication for them, concluded that this medication is an appropriate treatment option for children and teens with very active disease.

Pediatric clinical trials of all new medications are now required by the FDA – a requirement that will pave the way for approved treatment options for children and teens. Several trials (fingolimod, teriflunomide, dimethyl fumarate) are underway, but enrolling participants has proven challenging, since pediatric MS is relatively rare.

Treatment Considerations in Women and Men in Their Reproductive Years

None of the FDA-approved disease-modifying therapies have received FDA approval for use during pregnancy or breastfeeding. The current standard of care is to avoid the use of disease-modifying therapies during pregnancy and breastfeeding. The risks and benefits of continuing therapy during pregnancy require careful discussion, taking into account the level of disease activity, personal preferences and the patient's and doctor's risk tolerance. For further information about specific risks related to each therapy, see the full consensus paper.

Rationale for Access to Full Range of Treatment Options

Although all of the disease-modifying therapies have been proven effective, none of these medications are completely effective. Moreover, the efficacy of a treatment may vary greatly from person to another and for each individual over time.

For all of the following reasons, access to the full range of options is essential:

- **If a person does not get sufficient benefit from one medication, access to other options is essential.**
  The goal of treatment is to control disease activity as quickly and effectively as possible and to prevent irreversible damage in the CNS. If the medication does not adequately control the disease, alternative options should be available.

- **If a person develops neutralizing antibodies (Nabs) while being treated with interferon beta, access to a non-interferon medication is essential.**
  Trials of the interferons have demonstrated that many people taking these medications Develop NAbs that appear to reduce the effectiveness of the medication they are taking. A person who has persistent disease activity while taking an interferon beta medication, regardless of whether this is due to NAbs or not, needs access to non-interferon treatment options.

- **If a person is not able to use specific medications because of pre-existing conditions or allergies, access to suitable options is essential.**
  For a variety of reasons cited as "contraindications" in a medication's prescribing information, or due to allergies, a person may not be a suitable candidate for one or another of the available disease- modifying treatments. In addition to these contraindications, data collected since Avonex, Betaseron, Extavia and Rebif were approved have led many healthcare providers to avoid the use of these medications in people who are depressed or have a history of significant depression. Though several studies have found no relationship between these medications and depression in people with MS, the prescribing information for each of these medications includes a warning regarding this risk.

- **Individuals at a high-risk for PML need access to other options.**
  People who are or become JC antibody-positive need access to treatments that do not put them at risk for PML
  - Tysabri, Gilenya, Tecfidera, and Ocrevus all contain warnings about the risks of developing PML.

- **Because disease severity varies at onset from one person to another, access to the full range of disease-modifying therapy options is necessary.**
  - Some adults have very active disease from onset.
  - African-Americans appear to experience a more active disease course than Caucasians.
  - Some children may experience very active disease that does not respond to the medications generally considered first-line treatment options for pediatric MS.

- **If an individual is not able to adhere to a treatment regime for one reason or another, access to other options is essential.**
  Helping people adhere to their treatment plan begins with identifying those who are having difficulty and addressing whatever factors may be preventing them from taking their medication as prescribed. It may be necessary to switch to a different medication in order to improve their ability to adhere to treatment.

- For all the same reasons that clinicians and their patients need access to the full range of approved disease-modifying therapies, they may also need to turn to non-approved options that have demonstrated efficacy in people with MS (See Appendix B for further information about those off-label options).

CONCLUSIONS

This document provides a review of the current scientific literature about the role of disease-modifying therapy in MS treatment. Additional details and journal references for the points made in this summary, as well as a list of the content reviewers, can be found in the full consensus paper [http://ms-coalition.org/cms/images/stories//dmt_consensus_ms_coalition092016.pdf]. We anticipate that you will use these companion papers for discussion with your healthcare professional(s) and with your healthcare insurance company and pharmacy benefit managers.

GLOSSARY

Adaptive immune system – A sub-system of the immune system that is called into action against any disease- producing agents (pathogens) such as viruses or bacteria that are able to evade or overcome the first-line defenses of the innate immune system.

Adherence – The extent to which an individual takes a medication as collaboratively agreed upon with his or her healthcare provider (dose, frequency, length of time).

Annualized relapse rate – An outcome measurement in clinical trials that describes the number of relapses that have occurred per year of the trial. It is often used to compare the treated group to the placebo group.

Antigen – Any substance that triggers the immune system to produce an antibody; generally refers to infectious or toxic substances.

Axon – The nerve fiber that extends out from the nerve cell and conducts impulses to other nerve cells or muscles.

B-cell – A type of lymphocyte (white blood cell) manufactured in the bone marrow that makes antibodies.

Black hole – An area of tissue damage that appears dark on T1-weighted MRI imaging (also referred to as a T1 hypointense lesion). The darkening can be temporary due to new inflammation and swelling or permanent due to damage to the nerve fibers (axons).

Brain atrophy – A loss of brain tissue caused by destruction of nerve cells and the connections between them.

Central nervous system (CNS) – The part of the nervous system that includes the brain and spinal cord.

Clinically isolated syndrome (CIS) – A first clinical episode of neurological symptoms with features suggestive of MS. A CIS is often accompanied by one or more lesions on MRI that are typical of MS.

Clinical disease activity – Evidence of disease activity that is apparent to the patient (e.g. symptoms, relapses) or to the healthcare provider during the neurologic exam.

Cognitive impairment – Changes in mental function caused by trauma or disease process. Some degree of cognitive impairment occurs in approximately 50–60 percent of people with MS, with information processing, memory and executive functions being the most commonly affected functions.

Expanded Disability Status Scale (EDSS) – A part of the Minimal Record of Disability that summarizes the neurologic examination and provides a measure of overall disability. The EDSS is a 20-point non-linear scale, ranging from 0 (normal examination) to 10 (death due to MS) in half-point increments. A person with a score of 4.5 can walk three blocks without stopping; a score of 6.0 means that unilateral walking aide such as a cane or a crutch is needed to walk about 330 feet; a score of 6.5 means a person needs bilateral assistance (two canes, two crutches or a walker) to walk about 65 feet without stopping; a score of 7.5 indicates that a person cannot take more than a few steps, even with crutches or help from another person.

Extension study – An unblinded phase of a clinical trial in which all participants receive the active drug. This type of study often follows the placebo-controlled portion of the trial and is conducted to gather more information about safety and tolerability of the drug.

Gadolinium – A chemical compound that is given intravenously (into a vein) during an MRI to identify new or re- activated areas of inflammation.

Gadolinium (Gd)-enhancing lesion – A lesion appearing bright white on magnetic resonance imaging following injection of the chemical compound gadolinium. A Gd-enhancing lesion reveals a breakdown in the blood-brain barrier, which is indicative of either a newly active lesion or an previous lesion that has become reactivated.

Gray matter – A major component of the CNS that contains nerve cell bodies and appears gray, in contrast to the areas of the brain that contain myelinated nerve fibers and appear white (white matter).

Immune-mediated disease – A disease in which components of the immune system – t cells, antibodies, and others – are responsible for the disease either directly (as occurs in autoimmunity) or indirectly (for example, when damage to the body occurs secondary to an immune assault on a foreign antigen such as a bacteria or virus).

Immune system – A collection of cells, tissues and molecules that act as the body's defense against disease-producing agents (pathogens) such as viruses and bacteria.

Innate immune system – A sub-system of the immune system consisting of cells and proteins that are always present and ready to mobilize and fight disease-producing agents (pathogens) such as viruses or bacteria.

Lesion – An abnormal area seen on MRI that may represent inflammation, demyelination, and/or axonal damage. A lesion (or plaque), which can vary from a few millimeters to a few centimeters in diameter, generally contains inflammatory cells (white blood cells) and other cells that contribute to brain inflammations and damage.

Lymphocyte – A type of white blood cell that is part of the immune system. Lymphocytes can be subdivided into two main groups: B-lymphocytes, which originate in the bone marrow and produce antibodies; T-lymphocytes, which are produced in the bone marrow and mature in the thymus. Helper T-lymphocytes heighten the production of antibodies by B-lymphocytes; suppressor T-lymphocytes suppress B-lymphocyte activity and seem to be in short supply during an MS exacerbation.

Magnetic resonance imaging (MRI) – A diagnostic procedure that produces visual images of different body parts without the use of X-rays. Nuclei of atoms are influenced by a high frequency electromagnetic impulse inside a strong magnetic field. The nuclei then give off resonating signals that can produce pictures of parts of the body. An important diagnostic tool in MS, MRI makes it possible to visualize and count lesions in the white matter of the brain and spinal cord.

Mechanism of action – The way in which a medication works in the body to achieve the desired outcome. Among the FDA-approved medications to treat MS, there are thought to be seven different mechanisms of action.

NARCOMS (North American Research Committee on Multiple Sclerosis) – A research program that allows people with MS to facilitate MS research by sharing information about their diagnosis, symptoms, disease course and treatments.

Natural history study – A study that follows a group of people over time who have or are at risk of developing a certain medical condition or disease. Natural history studies in MS studied the course and progression of the disease before the disease-modifying therapies became available.

Neurodegeneration – The progressive loss of nerves and nerve function, a consequence of the MS disease process.

Neuroinflammation – Inflammation of nervous system tissue caused by an immune response to trauma, toxins or the invasion of disease-producing agents such as viruses or bacteria into the CNS.

Neutralizing antibody – Antibodies are proteins of the immune system that are produced in response to foreign substances, including viruses and bacteria. Neutralizing antibodies can develop in response to a component of a medication and can interfere with the action of the medication, even rendering it ineffective. A small percentage people with MS who receive interferons or natalizumab treatment develop neutralizing antibodies and will require treatment with an alternate MS medication.

Non-responder – An individual who does not receive the expected or desired results from a particular treatment.

Oligodendrocyte – A type of cell in the central nervous system that is responsible for making and supporting myelin.

Opticospinal MS – A diagnostic term – based on the predominance of symptoms involving vision and mobility – that was originally used to describe common symptoms of MS in the Asian population.

Pivotal trial – A large, placebo-controlled and double-blinded clinical study (in which neither the participant nor researcher knows who is receiving drug or placebo) that is designed to demonstrate the safety and effectiveness of a new drug. The data from the trial are presented to a regulatory agency (e.g., the FDA) that will decide if the drug should be approved for human use.

Placebo – An inactive, non-drug compound that is designed to look just like the test drug. It is administered to control group subjects in double-blind clinical trials (in which neither the researchers nor the subjects know who is getting the drug and who is getting the placebo) as a means of assessing the benefits and liabilities of the test drug taken by experimental group subjects.

Post-marketing study – Following FDA approval of a new drug, the manufacturer of the drug is generally required by the FDA to conduct continuing studies of the drug to obtain more information about its safety. These studies track reports provided by patients and healthcare providers of events related to previously known risks of the approved drug or of events that may suggest a risk that had not been identified during the clinical trials. These reports of adverse events that occur after the drug has come to market are critically important for evaluating the long-term safety of a new medication.

Prevalence – The number of all new and old cases of a disease in a defined population at a particular point in time.

Primary-progressive MS (PPMS) – A disease course characterized by steadily worsening neurologic function from the beginning, without relapses or remissions.

Prospective study – A study in which participants are selected using predetermined criteria, then divided into a group that will receive the treatment and a group that will receive placebo. All

participants are followed over time using predetermined outcome measurements to determine the differences between the groups.

Radiographically isolated syndrome (RIS) – The identification of MRI abnormalities consistent with MS that are found incidentally on an MRI done for another reason (e.g. following a motor vehicle accident) in an individual who has no neurological signs or symptoms suggestive of MS and no past history of any neurological symptoms.

Relapse – The appearance of new symptoms or the aggravation of old ones, lasting at least 24hours (synonymous with exacerbation, attack, flare-up); usually associated with inflammation and demyelination in the brain or spinal cord.

Relapsing-remitting MS (RRMS) – The most common disease course at the time of diagnosis, characterized by clearly defined attacks of worsening neurologic function (also called relapses or exacerbations), which are followed by periods of partial or complete recovery (remissions).

Retrospective study – A study in which the outcome has already occurred, and the investigation looks backward in time to help identify some factors that might be associated with the outcome. For example, a medical chart review may be undertaken to determine the average number of times the individuals in the study changed their disease- modifying therapy over a given period of time, and the reasons why they changed.

Secondary-progressive MS (SPMS) – A disease course that follows relapsing-remitting MS (RRMS), in which the disease begins to progress more steadily, with or without relapses. Most people diagnosed with RRMS will transition to SPMS within 10-20 years.

Sub-clinical disease activity – Disease-related changes that are apparent on MRI but unaccompanied by symptoms or other physical evidence of disease activity.

Sub-optimal response – A person's response to treatment with a disease-modifying therapy that is less than expected from the published data for that therapy and provides insufficient control of disease activity and/or progression.

T1-weighted MRI scan – A basic type of MRI scan used in MS imaging in which white matter appears light gray, gray matter appears dark gray and spinal fluid appears very dark gray or black. MS lesions are not always evident on T1, but when present they appear dark gray and indicate either swelling or damage to the nerve fiber (axon).

T2-weighted MRI scan – A basic type of MRI scan used in MS imaging in which the white matter appears dark gray, the gray matter appears light gray and the spinal fluid appears bright white. MS lesions also appear very light or bright white. T2-weighted imaging reveals the sum of MS activity, including new and old lesions.

T-cell – A lymphocyte (white blood cell) that develops in the bone marrow, matures in the thymus, and works as part of the immune system in the body.

U.S. Food and Drug Administration (FDA) – The U.S. federal agency that is responsible for enforcing governmental regulations pertaining to the manufacture and sale of food, drugs and cosmetics. Its role is to prevent the sale of impure or dangerous substances. Any new drug that is proposed for the treatment of MS in the United States must be approved by the FDA.

Transverse myelitis – An episode of inflammation across both sides of one level or segment of the spinal cord that can damage or destroy the myelin coating around nerve fibers. This damage interrupts the communication between the nerves in the spinal cord and the rest of the body, resulting in temporary or permanent paralysis and numbness below the level of the inflammation.

White matter – The part of the brain that contains myelinated nerve fibers--and therefore appears white--in contrast to the cortex of the brain, which contains nerve cell bodies and appears gray.

SUMMARY

The Food and Drug Administration (FDA) is amending its regulations governing the content and format of the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the "Use in Specific Populations" section of the labeling for human prescription drug and biological products. The final rule requires the removal of the pregnancy categories A, B, C, D, and X from all human prescription drug and biological product labeling. For human prescription drug and biological products subject to the Agency's 2006 Physician Labeling Rule, the final rule requires that the labeling include a summary of the risks of using a drug during pregnancy and lactation, a discussion of the data supporting that summary, and relevant information to help health care providers make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation. The final rule eliminates the "Labor and delivery" subsection because information about labor and delivery is included in the "Pregnancy" subsection. The final rule requires that the labeling include relevant information about pregnancy testing, contraception, and infertility for health care providers prescribing for females and males of reproductive potential. The final rule creates a consistent format for providing information about the risks and benefits of prescription drug and/or biological product use during pregnancy and lactation and by females and males of reproductive potential. These revisions will facilitate prescriber counseling for these populations.