Malaysian Consensus for The Treatment of Multiple Sclerosis 2025

Malaysian Society of Neurosciences
Persatuan Neurosains Malaysia

Authors' Disclaimer

Multiple sclerosis and its related disorders are a heterogenous group of conditions. Evidence-based practices and knowledge about these conditions continue to evolve as new research and data emerge. This may require neurologists and physicians to change their diagnostic algorithms, treatment strategies, and management accordingly. It is the responsibility of everyone involved in the care of MS patients, especially healthcare providers, to equip themselves with the most up-to-date knowledge and clinical experiences in order to offer the best treatments for their patients.

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The authors would like to state that within this book, off-label use of certain drugs is described based on the best available evidence and, where evidence is limited, on clinical experience and real-world practice. This reflects clinical practice, and the treating neurologist or practitioner should always consult local and national prescription guidelines, seek pharmaceutical advice where needed, and adhere to safe and ethical prescribing practices before initiating any off-label treatment.

The MyMS Network contributors

2025

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Foreword

The Director-General of Health of Malaysia
Datuk Dr Mahathar Bin Abdul Wahab

It is with great honour that I present the *Malaysian Consensus Statement for the Treatment of Multiple Sclerosis 2025*, a much-anticipated update to our national clinical guidance for managing this complex and evolving neurological disorder. Since the publication of the last Clinical Practice Guideline for multiple sclerosis (MS) in 2015, the field has witnessed significant advances in diagnostics, neuroimmunology, imaging, and disease-modifying therapies. In light of these advancements, this updated consensus is both timely and imperative.

This document results from the concerted effort and close collaboration among a multidisciplinary team of experts, consisting of neurologists, neuroradiologists, neuropsychiatrists, ophthalmologists and pharmacists. They have come together to synthesise the best available evidence and translate it into practical recommendations tailored to the Malaysian healthcare context. I commend the commitment and dedication of this expert panel in ensuring that the updated consensus remains current, locally relevant, and aligned with international best practices.

MS is a chronic, often debilitating disease that affects individuals during the prime of their lives. The burden it places on patients, their families, and the healthcare system is substantial. Therefore, it is essential to equip healthcare providers with practical,

evidence-based guidance to support early diagnosis, optimise therapeutic strategies, and improve long-term outcomes for those living with MS.

The consensus statement places strong emphasis on timely initiation of DMTs, risk stratification to guide therapeutic escalation, and the individualised management of special populations, including pregnant women and those with cognitive impairment. It also provides updated recommendations on monitoring treatment response, addressing treatment failure, and promoting overall health and well-being. Notably, the guideline highlights the value of neuropsychiatric care and mental health as integral components of comprehensive MS management, an area that is often under-recognised yet crucial to enhancing quality of life.

I am particularly intrigued by the application of the modified Delphi methodology in developing this guideline. This approach ensures that the recommendations are firmly grounded in both best available evidence and expert consensus. It underscores the importance of structured consensus-building and peer validation in informing national health policy and guiding clinical decision-making.

As we advance efforts to strengthen neurology and neuroimmunology services across Malaysia, this document will serve as a foundational resource for clinicians, educators, policymakers, and trainees. It also embodies our broader commitment to ensuring that all Malaysians living with MS have access to high-quality, equitable, and contemporary care, whether they receive treatment in a tertiary centre in an urban area or a district hospital in a rural setting.

On behalf of the Ministry of Health Malaysia, I extend my sincere gratitude to all the contributors, including the Malaysian Society of Neurosciences, the Multiple Sclerosis Society Malaysia, frontline clinicians and patient reviewers, who played a vital role in shaping this consensus. It is my hope that this guideline will inspire and unify our collective efforts to achieve excellence in MS care across the nation.

Director-General of Health

Ministry of Health Malaysia

2025

Message from the Director of Kuala Lumpur Hospital, Malaysia
Dato' Dr Harikrishna A/L K. Ragavan Nair

It is with great pleasure that I write this foreword on behalf of Hospital Kuala Lumpur (HKL) for the Malaysian Consensus Statement for the Treatment of Multiple Sclerosis 2025. This important document marks a significant step forward in our collective mission to enhance the quality, consistency, and effectiveness of care for individuals living with Multiple Sclerosis (MS) in Malaysia.

As the nation's largest quaternary referral hospital, HKL has long been at the forefront of complex neurological care. Our clinicians have witnessed firsthand the evolving clinical challenges and therapeutic possibilities in managing MS. Over the past decade, the emergence of new disease-modifying therapies (DMTs), improved diagnostic criteria, and a deeper understanding of neuroimmunological mechanisms have transformed how MS is diagnosed, monitored, and treated.

Yet, until now, our national clinical guidance has not kept pace with these developments. The last Malaysian CPG on MS was published in 2015, and its revision was long overdue. This updated consensus, therefore, is not just a reflection of medical progress—it is a practical and strategic tool for improving patient outcomes. Developed through the collective expertise of neurologists, neuroradiologists, neuropsychiatrists, ophthalmologist and pharmacist from across the country—including several from HKL—it provides updated, evidence-based recommendations tailored to the Malaysian healthcare system. I am proud that Hospital Kuala Lumpur has played a central role in this initiative, both in terms of clinical leadership and service delivery.

This consensus document covers a broad range of relevant topics, including early initiation of therapy, individualised risk stratification, management of progressive MS, cognitive impairment, pregnancy-related considerations, and the role of mental health and well-being in overall care. These are not theoretical issues—they are realities faced daily by our clinicians and patients. By outlining clear, practical pathways and treatment algorithms, this guideline empowers clinicians at all levels to make timely and informed decisions.

What is particularly commendable is the document's multidisciplinary approach. The inclusion of neuropsychiatric perspectives, imaging protocols, and monitoring strategies recognises that MS is not a condition confined to neurology alone. It impacts the whole person—physically, cognitively, and emotionally—and demands an equally comprehensive response.

At Hospital Kuala Lumpur, we are committed to embedding these recommendations into clinical practice. We will continue to invest in multidisciplinary MS care, facilitate access to high-efficacy therapies, and support our clinicians through ongoing training, audit, and quality improvement initiatives. This guideline will serve as a blueprint not only for best practice but also for equitable care across regions and facilities.

I would like to extend my appreciation to the working group members and contributors, many of whom are from HKL, for their dedication and vision. This document is a testament to what can be achieved through collaboration, clinical integrity, and a shared purpose. I am confident it will elevate the standard of MS care not only at our institution but across the country.

Dato' Dr Harikrishna A/L K. Ragavan Nair

Director

Kuala Lumpur Hospital, Malaysia

2025

Introductory Statement by MyMS Network MOH-MOE Steering Committee Chair

Professor Dr. Suhailah Binti Abdullah

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system that results in neurological impairment and disability, which continue to represent a significant healthcare challenge. Traditionally viewed as a two-phase disease consisting of early predominantly inflammatory stage and a later more progressive neurodegenerative phase, the discovery of disease progression independent of relapse activity (PIRA) even in the earliest stage of disease support MS phenotypes as a disease continuum. Over the last decade, there has been a rapid expansion in the number of disease-modifying therapies (DMT) that substantially improve clinical outcomes, as well as adding complexity in treatment options and associated safety considerations.

With reference to the first Malaysian clinical practice guidelines (CPG) on the management of MS issued in 2015, the rapid evolution in the field of immunopathology and treatment landscape urges the need for an update to provide a framework in clinical decision-making.

The aim of this 2025 consensus statements is to provide an updated evidence-based recommendations for the management of MS in Malaysia, focusing on the aspect of treatment and monitoring of treatment response inclusive of specific circumstances such as pregnancy and breastfeeding. The developing committee is constituted by clinical experts in the field of neurology, ophthalmology, neuropsychiatry and pharmacy from

Ministry of health (MOH), Ministry of education (MOE) and private hospitals in Malaysia, to advocate diversity and inclusivity.

Despite the benefit of early initiation of high-efficacy therapies, we acknowledge the importance of individualised treatment strategy, shared decision-making and patient involvement in the treatment plan.

I would like to take this opportunity to express my gratitude to all committee members, individuals and organizations involved in developing this consensus. Your contribution, diligence and perseverance are instrumental in making this consensus a success. We hope that this consensus statement can facilitate the standardization of care and consistency in MS management, as well as to serve as a resource for healthcare professionals to provide optimal care for patients with MS.

Professor Dr. Suhailah Binti Abdullah

Consultant Neurologist,

University Malaya Medical Centre.

Message from the President of the Malaysian Society of Neurosciences (MSN)

Dr Ahmad Shahir Mawardi

The journey toward this updated Malaysian Consensus Statement for the Treatment of Multiple Sclerosis 2025 is a testament to the strength and unity of Malaysia's neuroscience community. As President of the Malaysian Society of Neurosciences (MSN), I take immense pride in witnessing this milestone, which reflects not only scientific progress but also the enduring collaboration between clinicians, researchers, and allied professionals nationwide.

Multiple sclerosis, a condition once poorly understood and under-recognised in our region, has now entered an era of rapid clinical and therapeutic evolution. As the spectrum of diagnostic and treatment options expands, so too does the responsibility of the medical community to ensure that our practices are consistent, evidence-based, and accessible.

This consensus document reflects that responsibility in action. Developed through meaningful dialogue and shared expertise, it brings together neurologists, neuropsychiatrists, neuroradiologists, ophthalmologists, pharmacists, and others who have contributed diverse insights into a unified framework for care. Their collective work ensures that the recommendations are not only clinically sound, but also relevant across various practice settings in Malaysia.

MSN's role in this process has been to foster this spirit of inclusivity and scientific rigor. We believe that guidelines such as this serve not just to inform practice, but to elevate standards, strengthen inter-professional ties, and ultimately, improve the lives of people living with MS.

To all contributors - thank you for helping turn shared expertise into shared progress.

Dr Ahmad Shahir Mawardi
President
Malaysian Society of Neurosciences
2025

Message from the Scientific Committee Co-chairs

Dr Shanthi Viswanathan
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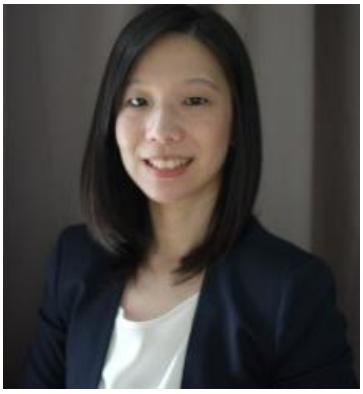

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Multiple sclerosis (MS) and its related disorders has a growing importance within multicultural Malaysia. According to the Atlas of MS the prevalence of MS has increased to 6 per 100,000 population in 2024. Though previously considered a rare disease, the improved awareness and ability to diagnose this condition in Malaysia has led to an urgent to better manage this disease. The last clinical practice guidelines on multiple sclerosis were published in 2015. It has been 10 years since its publication.

Within this time, many new developments have occurred in MS care. Among them, the 2024 revisions to the McDonald diagnostic criteria for MS, development of new knowledge about the pathobiology of MS, and the expansion of the spectrum of MS to include radiologically isolated syndrome (RIS) and clinically isolated syndrome (CIS).

Aside from this, advances in biological and neuroimaging biomarkers, as well as the exponential increase in the number of medications available for the management of MS have spurred the need for this revision. Currently, 27 different disease modifying treatments (DMTs) are approved for MS. Latest evidence suggests that early treatment of MS benefits patients by preventing long term disability and disease progression. Given these developments, this consensus statement is timely in guiding all those involved in the management of people with MS (pwMS). Many new concepts such as RIS and the use of newer high-efficacy DMTs, its pre-screening and monitoring, and special

considerations such as pregnancy, vaccination and breastfeeding pose challenges to both patients and their physicians.

The coming together of a group of subject matter experts (SME) from a wide range of specialities who are truly representative of the Ministry of Health, Ministry of Education, private sector, patient groups, pharmacists and other key opinion leaders, through the MyMS Network is a momentous occasion in the development of this consensus statement. The MyMS Network MOE-MOH steering committee has worked hard to develop a comprehensive yet pragmatic document organised into easy to read recommendation boxes utilising a rigorous Delphi method that analysed the latest available data on MS management over the last 30 years.

As a disclaimer, this document is not meant to replace good clinical judgement and critical thinking, as the management of MS should be individualised and not take on a one size fits all approach. Shared decision making and personalised treatment plans are important. This document will be revised as needed in the future with the evolution and acquisition of new data.

We, the Scientific Chairs would like to take this opportunity to thank all members of the development group from the MyMS Network as well as the wonderful support from the Hospital Director and the Director General of Health Malaysia, the Department of Neurology Kuala Lumpur Hospital, Health Technology Assessment division of the Ministry of Health, and everyone who contributed to this documents in whatever way. We would finally also like to acknowledge Novartis for their secretarial support, particularly Ms Emily Teng and Dr. Priveena Nair.

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Abbreviations

9-HPT: 9-hole peg test
AAN: American Academy of Neurology
ACTH: adrenocorticotrophic hormones
ALC: absolute lymphocyte count
ART: assisted reproductive technology
CDMS: clinically definite multiple sclerosis
CDP: confirmed disability progression
CIS: clinically isolated syndrome
CNS: central nervous system
CSF: cerebrospinal fluid
DCA: Drug Control Authority
DMF: dimethyl fumarate
DMT: disease modifying treatments
EAN: European Academy of Neurology
ECTRIMS: European Committee for Treatment and Research in Multiple sclerosis
EDSS: Expanded Disability Status Scale
EML: Essential Medicines List
FBC: full blood count
FDA: Food and Drug Administration
GA: glatiramer acetate
GFAP: glial fibrillary acidic protein
HAMS: highly active multiple sclerosis
HBV: hepatitis B virus
HCP: healthcare providers
HET: high-efficacy therapy
HSV: herpes simplex virus
HTA: Health Technology Assessment
IFNB: interferon beta
Ig: immunoglobulin
IV: Intravenous
JCV: John Cunningham virus
kFLC: kappa free light chains

LFT: liver function test
MET: modest-efficacy therapy
MOE: Ministry of Education
MOH: Ministry of Health of Malaysia
MP: methylprednisolone
MRI: magnetic resonance imaging
MS: multiple sclerosis
MSSM: Multiple Sclerosis Society of Malaysia
NfL: neurofilament light chains
NPRA: National Pharmaceutical Regulatory Agency
OCB: oligoclonal bands
ON: optic nerve
PIRA: progression independent of relapse activity
PML: progressive multifocal leukoencephalopathy
PO: per oral
PPMS: primary progressive multiple sclerosis
pwMS: people with multiple sclerosis
RAW: relapse-associated worsening
RIS: radiologically isolated syndrome
RRMS: relapsing remitting multiple sclerosis
RTX: rituximab
S1P: sphingosine-1-phosphate
SC: subcutaneous
SDMT: single digit modality test
SME: subject matter experts
SPMS: secondary progressive multiple sclerosis
T25FW: timed 25-foot walk
TB: tuberculosis
TER: teriflunomide
VHET: very high-efficacy therapy
VZV: varicella zoster virus
WHO: World Health Organization

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The Scientific Committee extends its sincere gratitude to the expert reviewers for generously contributing their time, expertise, and thoughtful insights to the development of this consensus.

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Introduction

Over the past few years, there has been a marked increase in the number of disease modifying treatments (DMTs) available for the treatment of Multiple Sclerosis (MS)[1]. The management of MS remains challenging due to evolving phenotypic descriptions, diverse disease types, varying expectations and treatment responses, as well as ongoing developments in our understanding of its pathobiology, diagnosis, classification, investigations and management[1-5].

The diagnosis of MS has historically relied on the demonstration of both dissemination in space (DIS) and dissemination in time (DIT), which refer to the presence of demyelinating lesions in at least two distinct CNS regions and evidence that lesions have occurred at more than one time point, respectively[6]. The recent 2024 revision of the McDonald criteria[7] allows DIS and DIT to be demonstrated using MRI, laboratory biomarkers, or clinical events, with the addition of the optic nerve as a fifth lesion site, kappa free light chains as a CSF biomarker to fulfill intrathecal immunoglobulin synthesis, and advanced MRI biomarkers for improved sensitivity and specificity for typical MS presentations (see Appendix 3). This revision promotes an earlier and more accurate diagnosis of MS, including in those who were previously classified as clinically isolated syndrome (CIS) or radiologically isolated syndrome (RIS).

As such, periodic reviews of the latest literature are essential to guide the optimal use of DMTs, particularly when tailoring recommendations to local healthcare settings. Recent studies suggest that early use of DMTs, especially high-efficacy therapies (HETs), improves the long-term outcomes in patients with MS (pwMS) in terms of relapse rates and disability progression[3, 4, 8-11].

According to the Atlas of MS 2020, the prevalence of MS in Malaysia has risen to 6 per 100,000 population[12]. Patients, caregivers and healthcare professionals in Malaysia face several challenges, including barriers to timely diagnosis, inconsistencies in disease management, and limited access to treatment. Recent regional and a Malaysian publication highlighted these concerns, specifically in relation to initiating appropriate DMTs, access to HETs, managing the burden of pre-treatment screening and ongoing monitoring, and making decisions about switching therapies in cases of inadequate response or adverse effects[12-15].

Resource-limited countries face a unique challenge in balancing the ethical imperative to provide treatment with the economic constraints of healthcare delivery[12-15]. Additional concerns include the absence of reliable efficacy biomarkers, delays in detecting disease progression and cognitive impairment in people with multiple

sclerosis (pwMS), and the lack of clear guidance for managing pwMS in special situations such as pregnancy, breastfeeding, contraceptive use, and vaccination[13-19].

The Malaysian Clinical Practice Guideline (Version 1, 2015) aimed to address this by providing guidance for all healthcare professionals involved in MS care, including MS-trained neurologists, general neurologists, and pwMS themselves[17]. Although it remains widely used and disseminated as of 2025, ten years have passed since its publication. An unpublished survey conducted amongst Ministry of Health (MOH) neurologists in 2019 at Kuala Lumpur Hospital revealed that 100% of respondents concurred with the need for a revised evidence-based guide and consensus statement to make the best risk-benefit treatment decision for pwMS[18]. All agreed on the need for education, updated information and improved access to MS treatment.

As of June 2025, there are eight MS drugs registered with the Drug Control Authority (DCA) of Malaysia and are available for use within the country[19]. Among these, only interferon beta, teriflunomide, fingolimod and recently ofatumumab are listed in the MOH's Drug Formulary [19]. With the exception of ofatumumab, these drugs are currently included in the formularies of most public hospitals[19].

Oral dimethyl fumarate, cladribine, natalizumab, ocrelizumab and alemtuzumab are all approved for use in Malaysia but are not listed in the MOH's Drug Formulary[19, 20]. These drugs can only be accessed on a named patient basis with special approval from the MOH, or purchased by patients themselves from private pharmacies or private hospitals. The cost of these on-label treatments ranges from RM 3,300 to RM 5,800 per month, or RM 3,400 to RM 45,000 per dose, depending on the prescribed dosage and frequency of administration[19, 20].

In contrast, off-label rituximab, which is available as both originator and biosimilars, is more accessible locally[19, 20]. Many pwMS choose intravenous biosimilar rituximab, which costs RM 2200 per vial, typically administered as an induction dose of 1 g (2 vials) followed by 500 mg (1 vial) every six months. However, off-label rituximab is still subject to purchase limits in public hospitals[14].

In 2023, interferon beta, teriflunomide and off-label rituximab were added to Malaysia's Essential Medicines List (EML) [21], and in July 2023, the World Health Organization (WHO) added rituximab to its Model List of Essential Medicines for MS[22], benefiting Malaysian pwMS. Despite these developments, newer sphingosine-1-phosphate (S1P) modulators, diroximel and monomethyl fumarate, pegylated interferon beta, depot glatiramer acetate, and subcutaneous ocrelizumab are still unavailable in Malaysia.

To address this, a multidisciplinary steering committee was formed comprising clinical neurologists, neuroradiologists, ophthalmologists, neuropsychiatrists,

pharmacists and patient representatives from the MS society of Malaysia (MSSM)[23]. Members were chosen from the MOH hospitals, the Ministry of Education (MOE) hospitals, private hospitals, and MSSM. The committee systematically reviewed existing literature to develop consensus recommendations on MS management in Malaysia, factoring in the economic challenges and barriers to treatment faced by pwMS here.

Objectives

General Objectives

The overall aim of this document is to establish a consensus by experts and to provide an evidence-based updated set of recommendations for the management of MS in Malaysia, addressing issues related to its treatment and monitoring of treatment response, including MS in special situations such as pregnancy and breastfeeding.

Specific Objectives

To review current evidence and provide recommendations on:

1. Treatment options across the clinical spectrum of MS including clinically isolated syndrome (CIS), relapsing and progressive MS and radiologically isolated syndrome (RIS)
2. Development of a standardised method for monitoring treatment response to DMTs
3. Switching or discontinuation of DMTs
4. Management of pwMS in special situations such as MS dyscognition, pregnancy, and lactation

The management of pwMS in Malaysia needs to be comprehensive and pragmatic. The recommendations are not intended to replace clinical judgement or individualised treatment decisions and the need for holistic patient care. It aims to amalgamate evolving diagnostic and prognostic concepts, and the latest United States (US) Food and Drug Administration FDA)-approved therapies for practical application within the Malaysian healthcare context.

Methods

Study Design

The full methodology is detailed in a recent publication[23]. We employed a two-stage modified Delphi process (Appendix 1) to achieve expert consensus on recommendations for the use of DMTs in MS. The Delphi panel comprised of 14 subject-matter experts (SMEs). The SMEs met and engaged via email and face-to-face discussions. The first stage involved formulating the clinical questions that would guide the development of the recommendations. In the second stage, the SMEs independently evaluated draft recommendations developed in response to the finalised clinical questions (Appendix 2). Each recommendation was subjected to iterative rounds of anonymous scoring and comments using a 10-point Likert scale (1 = strong disagreement; 10 = strong agreement). Consensus was reached if at least 85% of SMEs rated the corresponding statement as 8 or higher.

This method aligns with established approaches for health policy and guideline development[24-29]. The guidance was then reviewed by relevant stakeholders and further revised, with the final version endorsed by the MOH-MOE steering committee.

Data Sources and Selection Criteria

Relevant literature was identified through a search of databases including Pubmed, Cochrane, EMBASE, MEDLINE, and drug regulatory databases. Only studies published in peer-reviewed journals, including randomised controlled trials, meta-analysis, systematic reviews, pivotal consensus guidelines, and real-world data that the panel considered of high quality were considered for this consensus. Where evidence was lacking, peer-reviewed expert opinion and the committee's learned, real world experience, were taken into account. Current prescribing information of the relevant drugs were obtained from package inserts and included where appropriate.

Results

The following are the final recommendations following three iterative sequential Delphi rounds. Consensus was reached on 15 recommendations.

Q1a. Early treatment: Should MS patients be treated as early as possible?

Natural history studies have shown that 50-60% of patients who initially have a relapsing-remitting course will eventually progress to a secondary progressive disease with gradual accumulation of disability within 10-15 years [30, 31]. MS is increasingly recognised as a disease continuum [32-34], whereby inflammation and neurodegeneration occur from onset, with inflammatory processes predominantly in the early stages and smouldering disease activity later on. Disability results from both relapse associated worsening (RAW) and progression independent of relapse activity (PIRA)[32, 34, 35].

Evidence supports early initiation of DMTs, especially within the first two years of diagnosis. Starting DMTs early is associated with delayed progression of Expanded Disability Status Scale (EDSS) and reduction in PIRA [35-40]. A real world registry-based retrospective study by Chalmer et al (2018) [36], showed that early treatment delayed time to EDSS 6.0 and time to death.

International guidelines such as the American Academy of Neurology (AAN)[39], the European Committee for Treatment and Research in Multiple sclerosis - European Academy of Neurology (ECTRIMS-EAN)[41], real world data, and the MS Brain Health consensus [42] also support earlier treatment initiation after diagnosis to improve long-term outcomes.

Table 4a and Table 4b list the DMTs currently available in Malaysia.

Recommendation 1a: Early initiation of DMT (Achieved 93.3% agreement based on the Likert Scale thresholds)

i.	All patients with relapsing MS should be offered early treatment with DMTs as soon as a clear diagnosis is made*[9, 11, 38, 39, 41, 43]
ii.	Prior to initiation of treatment, pwMS should be given sufficient information about the type of MS disease state (i.e., CIS, RRMS, SPMS or PPMS), the severity of their disease activity (i.e., active, inactive, highly active or aggressive), and the risks for future disability[32] (See Table 1 and Table 2).
iii.	Patients with highly active or aggressive disease activity should be advised to start treatment as soon as possible[9, 11]
iv.	PwMS should be advised about the types of DMTs currently available, goals of treatments, required pre-treatment screenings and monitoring, and possible adverse events[1, 39] (See Table 5).
v.	PwMS and their caregivers should be given **enough time to make an informed** decision at that visit or on subsequent visits.
vi.	Discussions should also include information on social or employment adjustments as well as reproduction, contraceptives and immunisation.
vii.	All eligible and agreeable MS patients who pass the pre-screening should be started on MS **DMTs within 2 months of diagnosis***[44].

**Subject to availability and accessibility of treatment.*

Table 1: Phenotypes and clinical course of MS

MS Phenotype	Description
Relapsing remitting MS (RRMS)[32]	• Alternating episodes of new or worsening neurological symptoms (relapses/attacks) which either completely recover or recover partially, with or without new MRI disease activity.
Clinically isolated syndrome (CIS)[30-32]	• First clinical demyelinating episode occurring in individuals, some of whom are at high risk of developing MS in the absence of any other diagnosis • In most cases, patients present either with optic neuritis (20-25%), transverse myelitis (30-50%), brainstem, or cerebellar disease (25-30%) and rarely cerebral hemisphere syndromes (5%) • Natural history studies have shown the majority will develop clinically definite MS (CDMS)
Radiologically isolated syndrome (RIS)[45]	• Refers to the presence of asymptomatic, incidentally identified demyelinating-appearing white matter lesions in the CNS (brain and or spinal cord) within individuals lacking symptoms typical of MS • RIS can be diagnosed as MS if any of the following criteria are met (refer to Appendix 3 for the definitions): o DIS and DIT o DIS and CSF OCB/kFLC o DIS and $\geq$6 CVS
Active MS[46]	• Evidence of new clinical disease activity i.e., o relapses and/ or o new MRI disease activity as evidenced by new /enlarging T2 lesions, or o new gadolinium-enhancing lesions
Highly active RRMS (HAMS)[46]	• One relapse in the previous year or 2 relapses in the preceding 2 years and • MRI evidence of disease activity with at least one associated poor prognostic factor (Table 2)
Rapidly evolving /aggressive /fulminant RRMS[46]	• Two or more disabling relapses in previous one year with incomplete recovery, with: o 1 or more gadolinium-enhancing lesions on brain MRI or o a significant increase in T2 lesion load as compared to a recent MRI and o worsening of EDSS >1 compared to baseline
Progression independent of relapse activity (PIRA)[47]	• PIRA refers to significant disability worsening compared to the baseline (reset after each PIRA event, relapse and EDSS score improvement) in the absence of relapses (in the prior 30 days), since the last

	EDSS assessment, confirmed with EDSS scores that remained above the worsening threshold for at least 12 months. • It occurs in both relapsing and progressive forms of MS.
Relapse associated worsening (RAW)[2, 47]	• Refers to a clinical disease worsening as a result of a new attack/relapse.
Progressive MS (PMS)[32, 48]	Describes a disease course that is characterised by steadily increasing neurological dysfunction or disability independent of relapses. There may be periods of fluctuations and stability. Superimposed relapses and MRI activity can also occur. Secondary progressive multiple sclerosis (SPMS) • Refers to a gradual progression after an initial RRMS course. • This deterioration is independent of relapses occurring over ≥3 to 6 months following an initial relapsing-remitting course as measured by EDSS. • Both PIRA and RAW contribute to secondary progression. • Some individuals may still experience relapses (active SPMS or SPMS with relapses), placing them within the broader category of relapsing MS. Primary progressive multiple sclerosis (PPMS) • Characterised by a gradual progression of neurological disability from disease onset, occurring without relapses. • Diagnostic criteria require supporting paraclinical evidence of central nervous system demyelination (see Appendix 3), and with the exclusion of alternative diagnoses.
Relapse or attack[32, 48]	• A relapse or attack is defined as a sudden worsening or new appearance of neurological symptoms that lasts for at least 24 hours, in the absence of a fever or other infection.

CNS = central nervous system; CSF = cerebrospinal fluid; CVS = central vein sign; DIS = dissemination in space; DIT = dissemination in time; EDSS = expanded disability status scale; kFLC = kappa free light chains; OCB = oligoclonal band; PIRA = progression independent of relapse activity; RAW = relapse associated worsening; RIS = radiologically isolated syndrome; T2 = T2-weighted (MRI sequence)

Q1b. Early initiation of high-efficacy therapies: Should pwMS be treated early with HETs?

The window of opportunity for effective treatment in MS is in the early stage of the disease where the inflammatory process is prominent[49]. Hence, the general consensus is for early treatment initiation to reduce CNS inflammation that is translated into clinical relapses and new MRI lesions. Thus, preventing the long-term outcome of secondary progression[50]. Taking into account the risks and benefits, international guidelines, consensus, and literature reviews, we categorised the DMTs into modest-efficacy therapies (MET) and HET, and their position in the treatment of active and highly active MS (HAMS) (Table 4a). The HETs were further subdivided into a very high-efficacy therapy (VHET) subgroup.

There are currently two schools of thought in terms of DMT initiation, namely the escalation approach and induction with HET approach. In the escalation approach, METs are initiated with a switch to HET in the presence of continuing disease activity despite treatment adherence[1, 51]. The latter approach initiates HET at the time of diagnosis (induction) with the aim to hit the disease hard from the start[1].

A Swedish MSBase retrospective study involving 544 patients found that HET commenced within 2 years of disease onset is associated with less disability after 6 to 10 years compared to a later initiation (EDSS score at 6 years: 2.2 vs 2.9, $p<0.0001$; EDSS score at 10 years: 2.3 vs 3.5, $p<0.0001$)[9]. Another retrospective study which compared the high utilisation of early HET in the Swedish registry (34.5%) to the mostly escalation approach of the Danish registry (7.6%), showed that the former was associated with a 29% relative reduction in the rate of confirmed disability progression (HR 0.71, 95 % CI 0.57; 0.90, $p = 0.004$)[51]. Brown et al., in their retrospective study involving 1555 patients with RRMS showed a significantly lower risk of conversion to SPMS in the HET group comprising of fingolimod, alemtuzumab or natalizumab, compared to the MET group consisting of interferon beta and glatiramer acetate (HR 0.66, 95 % CI 0.44; 0.99, $p = 0.046$; 5-year absolute risk of 7 % vs 12 %)[8].

Current evidence from randomized controlled trials, systematic reviews, and real world data support the early initiation of HET for its benefits in reducing relapses, risk of disability progression in the short term, delaying secondary progression and reducing inflammatory disease activity in the brain[8, 9, 40, 51]. New concepts include selection of DMTs that may reduce RAW, and possibly PIRA[52-54]. Nonetheless, data remain insufficient to definitively establish the superiority of early HET over the traditional escalation approach. Two ongoing clinical trials are directly comparing the effectiveness of these two approaches, namely the named TRaditional versus Early Aggressive

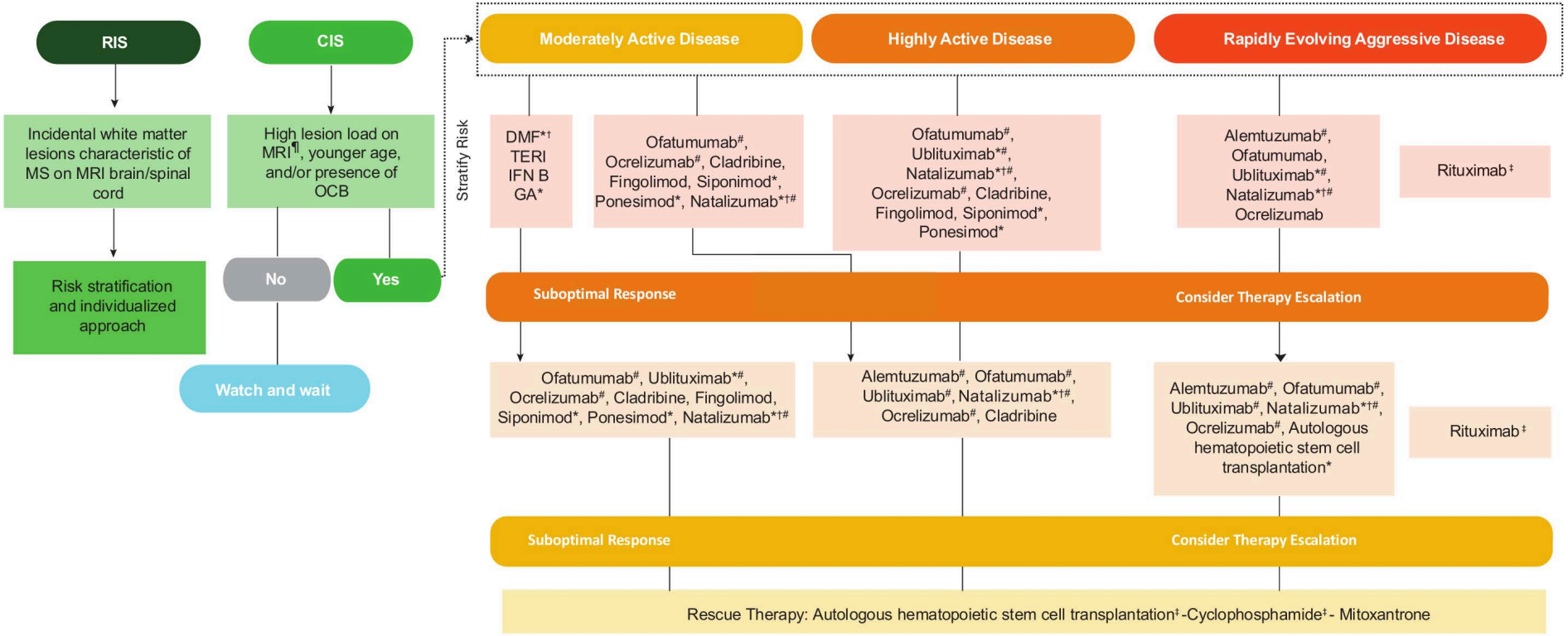
Therapy for Multiple Sclerosis (TREAT-MS; NCT03500328)[55] and Determining the Effectiveness of earLy Intensive versus Escalation approaches for the Treatment of Relapsing-remitting Multiple Sclerosis (DELIVER-MS; NCT03535298)[56]. The results of both trials will provide us with a more robust evidence-based approach to the management of pwMS.

As long-term disability in MS is predicted by early high disease activity, patients with highly active and aggressive MS should be initiated on a HET from the outset. Patients with active MS can be treated with either group of DMT taking into consideration the prognostic markers, risk-benefit ratio, gender, and the presence of co-morbidities. Patients treated with a MET should be switched to HET in the event of persistent disease activity such as clinical relapses and increasing MRI activity.

See Figure 1 and Tables 1, 2, 4a, and 5.

Recommendation 1b: Early initiation of HETs (Achieved 93.3% agreement based on the Likert Scale thresholds)

i.	The panel recommends that relapsing MS patients with multiple poor prognostic factors (Table 2) and high disease activity should be offered **HETs early** (Figure 1).
ii.	Patients with low or modest disease activity may be offered HETs especially if it is their preference.



**Not currently registered in Malaysia, †Currently available via Special Medicine Approval, ‡The use of rituximab in multiple sclerosis is off-label, #These drugs are considered very high-efficacy therapies, ¶ Typical lesions in the brain and spinal cord characteristic of MS*

Abbreviations: CIS = clinically isolated syndrome; DMF = dimethyl fumarate; GA = glatiramer acetate; IFNB = interferon beta; MRI = magnetic resonance imaging; OCB = oligoclonal bands; RIS = radiologically isolated syndrome; RRMS = relapsing-remitting multiple sclerosis; Teri = teriflunomide

Figure 1. Algorithm for disease-modifying treatment of CIS and RRMS

Q2. Clinically isolated syndrome: Should patients with clinically isolated syndrome (CIS) be treated with DMTs?

With the 2017 iteration of the McDonald criteria[6] and the proposed 2024 revision[7], CIS that fulfils clinical, paraclinical and neuroimaging criteria for MS is now considered part of the MS spectrum, after mimickers have been excluded. This facilitates earlier diagnosis and initiation of DMTs in real-world clinical settings.

CIS presentations involving typical regions such as the optic nerve, spinal cord, or brain, being on the margins of the proposed McDonald 2024 criteria, are associated with a high risk of progression to MS[57-63].

Current data suggests that CIS patients who do not fulfill the current McDonald criteria would benefit from individual risk stratification for CDMS and prognostic assessment to guide decisions on initiating treatment[60, 64] (See Table 2 and 3). Recent studies have shown that combining clinical predictors with biomarkers (such as the presence of three or more typical T2-hyperintense lesions on brain MRI, positive CSF oligoclonal bands or elevated kappa free light chain index, and increased serum or CSF neurofilament light chain) can predict conversion to MS within a year[58-60, 63, 64].

Large, randomised placebo-controlled trials have shown that early initiation of DMTs such as interferon beta, glatiramer acetate, teriflunomide, and cladribine in CIS can significantly reduce relapse rates and delay disability progression compared to no treatment [8, 9, 65-69]. Moreover, recent FDA approvals of HETs have extended indications to include CIS and relapsing forms of MS[1, 39, 46]. Rituximab has also shown promising results in CIS as demonstrated in a subset of the RIFUND study[68].

To conclude, treatment decisions for CIS should be individualised based on a patient's risk of conversion to MS and tailored to the local setting.

Refer to Figure 1 for the treatment algorithm.

Table 2: Prognostic factors associated with poorer outcomes in CIS and MS[70, 71]

Demographic and environmental factors	• Older age • Male sex • Non-White population • Low vitamin D levels • Smoking • Presence of comorbid conditions
Clinical factors	• Polysymptomatic onset • Early cognitive impairment • Brainstem, cerebellar or spinal cord involvement at onset • Primary progressive disease subtype • Poor recovery from the first relapse • High relapse rate (for MS) • Short interval between the first and second relapses (for MS) • Higher EDSS score at diagnosis
Radiological factors	• High T2 lesion number • High T2 lesion volume • Presence of gadolinium-enhancing lesions • Presence of infratentorial lesions • Presence of spinal cord lesions • Presence of whole brain atrophy • Presence of grey matter atrophy
Biomarkers	• Presence of IgG and IgM oligoclonal bands in the cerebrospinal fluid • Retinal nerve fiber layer thinning detected on OCT • Presence of high CSF neurofilament light chains (cNfL) and glial fibrillary acidic protein (cGFAP) levels at baseline

MS = multiple sclerosis; EDSS = Expanded Disability Status Scale; T2 = T2-weighted (MRI sequence); IgG = immunoglobulin G; IgM = immunoglobulin M; OCT = optical coherence tomography

Table 3: Current definitions of CIS types.

CIS type	Features
Aggressive CIS at onset*	Characterised by poor recovery and involvement of critical regions such as the optic nerve, spinal cord, brainstem, or cortical/subcortical structures, after excluding alternative diagnoses. MRI of the brain and spine demonstrates features associated with high risk for MS[46, 72]. HET should be considered.
CIS at high risk for MS*	Defined by high MRI lesion load in the brain and/or spine ($\geq$4 lesions in typical areas) without evidence of dissemination in time or the presence of OCBs or kappa free light chains[7, 72]. DMTs may be considered after carefully excluding mimickers.
CIS at intermediate risk for MS	Characterised by 1-3 typical T2 brain lesions with no DIT and after ruling out mimickers. Further investigations such as cerebrospinal fluid OCBs, kappa free light chains, identification of paramagnetic rim lesions (PRL), or central vein sign (CVS) may help inform decisions regarding early DMT initiation after shared decision-making. If additional tests are negative or diagnosis remains uncertain, observation with regular clinical assessment and serial MRI monitoring is recommended[7, 46].

** The new 2024 McDonald criteria is pending publication, and this may be considered multiple sclerosis in the future.*

CIS = clinically isolated syndrome; DIT = dissemination in time; DMTs = disease-modifying therapy; HET = high-efficacy therapy; MRI = magnetic resonance imaging; MS = multiple sclerosis; OCBs = oligoclonal bands; T2 – T2-weighted (MRI sequence)

Recommendation 2: Clinically isolated syndrome (Achieved 93.75% agreement based on the Likert scale thresholds)

i.	Patients with CIS who meet the diagnostic criteria for MS (based on the latest revisions)[7, 72] should undergo careful risk stratification according to prognostic factors and the risk of further disease activity, after exclusion of common MS mimickers (Table 2 and Table 3)[8, 57-59, 61-66].
ii.	Treatment of patients with CIS who meet the diagnostic criteria for MS should be individualised, with modest or high-efficacy DMTs based on the prognostic stratification (Table 2), risk for further disease, and progression[8, 57-59, 61-66]
iii.	**CIS diagnosed as MS** with multiple poor prognostic factors (Table 2) may benefit from early initiation of HET[8, 57-59, 61-66].
iv.	DMTs may be considered **for CIS at high risk for MS** (Table 3) after careful exclusion of MS mimickers[8, 57-59, 61-66]

Q3. Radiologically isolated syndrome: Should patients with radiologically isolated syndrome (RIS) be treated with DMTs?

Radiologically isolated syndrome (RIS) was defined in 2009 as the presence of asymptomatic, incidentally identified demyelinating-appearing white matter lesions in the CNS (brain and or spinal cord) in individuals lacking symptoms typical of MS [73]. Observational studies have found that up to 30 - 45% of patients presenting with an RIS will present with neurological symptoms, either acute or progressive. Ten-year follow-up of patients with RIS have shown that 51% of patients develop a clinical event[73, 74]. In the future, RIS fulfilling the 2024 revised McDonald criteria will be part of the MS spectrum.

Despite increasing evidence that RIS may represent a subset of individuals with a tendency to develop MS later, uncertainty remains about the best way to approach the diagnosis and management of this syndrome[73-75]. Independent predictors of RIS converting to CDMS includes younger age, male gender, CSF oligoclonal bands (OCBs), infratentorial and spinal cord lesions, and gadolinium-enhancing lesions [73-75]. One factor alone increased the risk by 29% and all four by 87%[73-75]. The 5-year risk of converting to CDMS from RIS increased from 29% to 38% when baseline spinal cord lesions and CSF-restricted OCBs were present[73-75].

Treatment trials of RIS with DMTs are limited. The ARISE trial (Assessment of Tecfidera in Radiologically Isolated Syndrome), demonstrated that dimethyl fumarate treatment in people with RIS reduced the risk of a first clinical demyelinating event (unadjusted hazard ratio, 0.18 [95% CI, 0.05–0.63]; P=.007; 82% risk reduction) and the number of new or newly enlarging T2 lesions when adjusted for the number of enhancing lesions at baseline (rate ratio, 0.2 [95% CI, 0.04–0.94]; P=.042)[76]. The TERIS trial (Teriflunomide in Radiologically Isolated Syndrome) demonstrated that using teriflunomide in people with RIS reduced the risk of a first clinical demyelinating event (unadjusted hazard ratio, 0.37 [95% CI, 0.16–0.84]; P=.02; 63% risk reduction) but did not show significant reductions in new MRI lesions or changes in patient-reported outcomes [77]. Overall, both trials provide evidence supporting the early use of DMT initiation in delaying or preventing the development of the first clinical event in RIS [76, 77]. However, because some individuals remain as RIS, it is crucial to identify those with a higher number of risk factors to optimise disease outcomes by early intervention while minimising adverse events[2, 47, 73-75, 78]. As many clinicians and general neurologists are still unfamiliar with the concept of RIS, along with a lack of clinical guidelines, discussion with a neurologist/MS specialist may be beneficial. Data on the prevalence of RIS locally in Malaysia is also limited.

Recommendation 3: Radiologically isolated syndrome (Achieved 86.7% agreement based on the Likert Scale thresholds)

i.	The panel acknowledges the evolving evidence for the inclusion of RIS in the diagnostic spectrum of MS, the benefits of early treatment, and a number of early treatment trials of RIS that have been completed[7, 76, 77]. However, the decision to treat RIS locally necessitates careful deliberation of risk for further disease and needs to be individualised (Figure 1).
ii.	The panel advises pending education of RIS recognition and stratification, they are unable to recommend the treatment of RIS locally in all cases in view of the risk of misdiagnosis or overdiagnosis. The panel suggests revisiting this in the future.
iii.	Each RIS case should be evaluated carefully and the decision to treat would be based on the potential risk of RIS for further disease activity, patient's preference and adverse effect profile.
iv.	Discussion with an MS specialist, regular clinical follow-up, and 6 monthly to annual neuroimaging surveillance may assist in deciding on further management.

Q4. Acute relapse: Which treatments should be started in an acute relapse of MS/CIS?

The panel agreed that significant symptomatic relapses, defined by new clinical findings in the absence of infection or other causes of pseudo relapse, should be treated. Whereas the management of asymptomatic new enhancing or large lesions in the brain, spinal cord or brainstem, or a minor relapse (e.g., mild sensory symptoms), require individualised assessment based on their potential to cause future symptoms or disability.

The Optic Neuritis Treatment trial (ONTT) reported on patients with optic neuritis (ON) treated within 8 days of onset with either oral prednisone 1 mg/kg daily for 14 days, intravenous methylprednisolone (IVMP) 250 mg every 6 hours for 3 days followed by oral prednisone 1 mg/kg daily for 11 days and then a 4 day taper, or oral placebo[79]. IVMP followed by oral prednisone taper led to faster recovery compared to the placebo group ($p < .001$ for visual field, $p = 0.02$ for contrast sensitivity, and $p = 0.09$ for visual acuity), however there was no effect on visual outcomes at 6 months and 1 year[79]. Most recovery occurred within 2 weeks. Notably, treatment with oral prednisone alone did not improve the outcome and was associated with increased recurrence of optic neuritis[79].

The panel reviewed the use of oral methylprednisolone as an alternative to IVMP for the management of acute relapses in MS. Taking into account cost considerations and patient preference, the panel agreed that high-dose oral corticosteroids, specifically oral methylprednisolone 1000 mg or oral prednisolone 1250 mg daily for 3 to 5 days, may be considered on a case-by-case basis as a viable alternative to IV therapy. This recommendation is supported by evidence suggesting comparable efficacy between oral and IV corticosteroids, although tolerability of the oral route requires monitoring, particularly for gastrointestinal and systemic side effects [80-83]. Despite its convenience, however, high dose prednisolone/methylprednisolone tablets are not widely available in many countries including Malaysia.

Some patients may be refractory to steroid treatment, defined by worsening in EDSS ≥1 within 2 weeks of treatment initiation[81]. Only about 30% of patients achieve complete remission within 14 days following a relapse, while the majority experience an incomplete response[84-89]. In such steroid refractory cases, early initiation of therapeutic plasma exchange (TPE) or immunoadsorption (IA) has shown benefit, particularly in cases with lack of response or EDSS worsening [84-89]. Alternatively, IVMP has been tried up to maximum of 2000 mg daily within 2 weeks of the initial event[81]. Of note, one study found IA to be more effective than double-dose IVMP[88].

Patients receiving oral MP or IVMP should be counseled on the immediate and delayed side effects[81]. The panel does not recommend ACTH or IV immunoglobulin due to high cost and insufficient evidence[90, 91]. The use of tapering dose of oral steroids in MS relapses was not found to be beneficial in improving disability or outcomes in non-ON relapses[92].

Recommendation 4: Acute relapse (Achieved 93.75% agreement based on the Likert scale thresholds)

i.	In the treatment of an acute relapse of MS, the panel recommends the use of IV methylprednisolone (IVMP) at a daily dose of 500-1000 mg per day for 3-5 days. In cases of optic neuritis relapse, IVMP should be followed by an oral prednisolone taper[79-83, 86, 93].
ii.	For patients who do not respond to initial steroid therapy: • The panel recommends therapeutic plasma exchange (TPE) or immunoadsorption (IA) rather than repeated dosing of IVMP[84, 88]. • The timing of TPE should be as early as possible upon completing the IVMP after stratifying the type and severity of the relapse post steroids[84, 88].

Q5. Active and highly active RRMS: Which DMTs should be started in active and highly active RRMS?

Prescribing DMTs should follow a shared decision-making model. Treatment should be individualised, based on the MS subtype, disease activity, prognosis (Table 2), patient-related factors, reproductive plans, ease of access, and adverse event profiles. The goals of therapy are to reduce relapses, slow disease progression, limit MRI disease activity, minimise brain atrophy, and preserve brain health.

Currently, there are 27 FDA approved on-label MS DMTs [72]. Table 5 summarises the currently available DMTs for the treatment of RRMS in Malaysia showing their impact on the annualised relapse rate (ARR), MRI lesion load (gadolinium-enhancing and new T2 lesion), disability progression, and associated side effects from pivotal phase 3 trials.

Systematic reviews, meta-analyses, phase 3 randomised controlled trials, and real world data have shown that HETs such as alemtuzumab, natalizumab, anti-CD20s, cladribine, and S1P receptor modulators, consistently outperform moderate-efficacy therapies (METs) such as interferon beta, teriflunomide, fumarates, in reducing relapse rates and MRI disease activity, while also providing modest benefits in slowing disability progression and, where data are available, PIRA[8, 9, 40, 51, 65, 94, 95]. Careful pre-screening and monitoring of side effects are needed when prescribing these DMTs (see Table 5).

Rituximab, cladribine, and glatiramer acetate were recently added to the WHO Essential Medicines List due to their availability and ease of use in the case of rituximab and cladribine, and safety in pregnancy in the case of glatiramer acetate[22]. Recent systematic reviews and meta-analyses suggest that all the anti-CD20 therapies have comparable efficacy[40, 96] and should be considered in all forms of relapsing MS. However, Roos et al (2023) reported that ocrelizumab may provide greater benefit than rituximab in terms of relapse reduction[97]. From a cost perspective, rituximab, as a biosimiliar, is more economical locally[98], although it needs careful monitoring due to risk of infections and hypogammaglobulinemia[99].

See Table 1 for the definitions of active and highly active RRMS, and Figure 1 for the treatment algorithm.

Recommendation 5a: Active RRMS (Achieved 86.7% agreement based on the Likert scale thresholds)

i.	The panel recommends that, having carefully stratified pwMS based on disease activity and prognostic profiling (Table 1 and Table 2), all patients with active RRMS should be offered DMTs without delay by their treating neurologist[1, 39, 42, 72, 100].
ii.	Based on current evidence, the panel favoured HETs for active RRMS[1, 43, 46, 100] (Table 4a).
iii.	This strategy should balance patients' age, expectations, mode of administration, comorbidities, reproductive needs, ease of access/availability, and risk of adverse events[70].
iv.	Patients should be given sufficient time and clear, evidence-based information to support shared decision-making on the following: • Types of DMTs available • Mode of administration • Monitoring needed • Efficacy data • Safety • Cost • Availability and sustainability of access to DMTs • Contraceptive, reproductive and immunisation guidance
v.	The panel agreed that the ultimate aim is to achieve a disease free state (no evidence of disease activity) or minimal disease state with acceptable quality of life[101].

Recommendation 5b: Highly active RRMS (Achieved 86.7% agreement based on the Likert Scale thresholds)

i.	The panel recommends that patients with highly active RRMS, including those who are treatment-naïve, should be offered HETs (Table 4a).
ii.	The panel acknowledges evidence suggesting the benefits of earlier treatment with HET rather than MET, particularly in patients with highly active disease and multiple poor prognostic factors (Table 2).
iii.	PwMS should be fully informed about the potential side effects, routes of administration, screening for co-morbidities and the monitoring required during treatment. (Table 5)

Table 4a: Classification of DMTs for RRMS in descending order of efficacy on annualised relapse rates, accounting for adverse effects and ease of use[40, 97, 102].

Classification	DMT
Moderate-efficacy therapies (MET) for relapsing-remitting multiple sclerosis	Dimethyl fumarate*† Teriflunomide Interferon beta-1a (44µg subcutaneous) Glatiramer acetate*
High-efficacy therapies (HET) for relapsing-remitting multiple sclerosis†	Alemtuzumab# Ofatumumab# Ublituximab*# Natalizumab*†# Ocrelizumab# Rituximab#‡ Cladribine Fingolimod Ozanimod* Ponesimod*

**Not currently registered in Malaysia*
†Currently available via Special Medicine Approval
‡The use of rituximab in multiple sclerosis is off-label
#These drugs are considered very high-efficacy therapies (VHET) based on the systematic review (Samjoo, et. al, 2023)

NB: Intramuscular and long-acting interferon beta, interferon beta-1b, diroximel fumarate, monomethyl fumarate, and subcutaneous ocrelizumab are not currently available in Malaysia.

Table 4b: DMTs for progressive MS[1, 43, 46, 103-106]

Classification	DMT
Therapies for early primary progressive multiple sclerosis	Ocrelizumab Rituximab‡
Therapies for active secondary progressive multiple sclerosis	Siponimod* Ocrelizumab Alemtuzumab Ofatumumab Natalizumab *† Rituximab‡ Cladribine Teriflunomide Glatiramer acetate* Interferon beta

NB: There is a lack of evidence for efficacy of drugs in progressive MS except for ocrelizumab and siponimod
** Not currently registered in Malaysia*
† Currently available via Special Medicine Approval
‡ The use of rituximab in multiple sclerosis is off-label

Table 5: DMTs for the treatment of RRMS and Progressive MS

DMT, dose, and indication	↓ ARR (%)	↓ GdE (%)	↓ New T2L (%)	↓ CDP (%)	Side effects	Recommended pre-treatment testing	Recommended monitoring
Interferon-beta[107, 108] (beta-1a) Dose (SC): 44 ug 3X/week Ind: RRMS, active SPMS	32-34	67-83	75-78	29	Flu-like symptoms, headache, depression, transaminitis, worsening of rheumatologic condition (rare) [109, 110]	FBC (with differential) and LFTs	FBC (with differential) and LFTs repeated at 1, 3, and 6 months, then periodically. Thyroid function tests every 6 months if positive history of thyroid dysfunction. Monitor for depression and suicidal thoughts.
Glatiramer acetate[111] Dose (SC): 20 mg daily/40 mg 3X/week Ind: RRMS, active SPMS	29	35	-	28	Injection-site reactions, lipoatrophy and skin necrosis at injection sites, chest pain, vasodilatory reactions[112, 113]	FBC (with differential)	No routine laboratory monitoring required.
Teriflunomide[114] Dose (PO): 14 mg od Ind: RRMS, active SPMS	36	80	69	26	Liver injury, GI upset, hair thinning, reactivation of latent TB, headache, teratogenicity [115]	FBC (with differential) and LFTs Establish baseline blood pressure. Pregnancy test if applicable. TB screening.	FBC (with differential) periodically. Monthly LFTs for the first 6 months, then every 6 months thereafter. Blood pressure every visit.
Dimethyl fumarate[116, 117] Dose (PO): 120mg bd for 7 days, then 240mg bd Ind: RRMS, active SPMS	44-53	74-90	71-85	38	Flushing, GI symptoms, lymphopenia, transaminitis, infection risk (including PML), teratogenicity[115]	FBC (with differential) and LFTs (AST, ALP, bilirubin)	FBC (with differential): repeat at 6 months, and every 6-12 months thereafter. Consider stopping if lymphopenia ($<0.5 \times 10^9$/L) persists >6 months. LFTs as clinically indicated. Monitor for infections. Monitor for signs and symptoms of PML.

Fingolimod[118] Dose (PO): 0.5 mg od Ind: RRMS, active SPMS	54	82	75	32	Lymphopenia, transaminitis, infection risk (VZV, PML), cardiac arrhythmias, macular oedema, skin malignancy, teratogenicity[119]	FBC (with differential), LFTs Ophthalmic exam ECG Pregnancy test if applicable. Skin examination VZV serology and vaccinate if seronegative. Complete recommended vaccines* ≥4 weeks (live/live-attenuated) and ≥2 weeks (inactivated) before first dose.	FBC and LFTs at 3 and 6 months, then every 6 months thereafter. FDO: hourly HR and BP monitoring; ECG after 6 hours. Ophthalmic exam at 3–4 months. Monitor for infection during treatment and for 2 months after discontinuation Blood pressure every visit Skin examination every 3 months. Routine cancer screening according to standard guidelines. Monitor rebound disease activity post-discontinuation Monitor for signs and symptoms of PML.
Ponesimod[120] Dose titration (PO): Day 1-2: 2 mg od Day 3-4: 3 mg od Day 5-6: 4 mg od Day 7: 5 mg od Day 8: 6 mg od Day 9: 7 mg od Day 10: 8 mg od Day 11: 9 mg od Day 12-14: 10 mg od Maintenance (PO) Day 15 onwards: 20 mg od Ind: RRMS, active SPMS	30.5	55.7	58.5	17 (12 week confirmed disability accumulation, p = 0.29)	Infections, bradyarrhythmia and atrioventricular conduction delays, respiratory effects, liver injury, cutaneous malignancies, fetal risk, macular edema, posterior reversible encephalopathy syndrome[121]	FBC (with differential), LFTs Ophthalmic exam ECG Skin examination VZV serology and vaccinate if seronegative Complete recommended vaccines* ≥4 weeks (live/live-attenuated) and ≥2 weeks (inactivated) before first dose.	FBC and LFTs at 3 and 6 months, then every 6 months thereafter. FDO only if cardiac condition. Ophthalmic exam at 3–4 months, then annually. Blood pressure every 1-3 months Skin examination annually.
Ozanimod[122] Dose titration (PO): Day 1-4: 0.23 mg od	76	53	42	7.6 (3 month confirmed disability	Infections, PML, bradyarrhythmia and atrioventricular conduction delays,	FBC (with differential), LFTs Ophthalmic exam EC	FBC and LFTs at 3 and 6 months, then every 6 months thereafter. FDO if cardiac condition.

Days 5-7: 0.46 mg od Maintenance (PO) Day 8 onwards: 0.92mg od Ind: RRMS, active SPMS				progression)	liver injury, fetal risk, increased blood pressure, respiratory effects, macular edema, cutaneous malignancies, posterior reversible encephalopathy syndrome[123]	Skin examination VZV serology and vaccinate if seronegative. Complete recommended vaccines* ≥4 weeks (live/live-attenuated) and ≥2 weeks (inactivated) before first dose.	Ophthalmic exam at 3–4 months, then annually. Blood pressure monitoring. Skin examination every 3 months.
Siponimod[103] Dose titration (PO): Day 1:0.25 mg Day 2:0.25 mg Day 3: 0.50mg Day 4:0.75mg Day 5:1.25mg Maintenance: (PO) 2mg od Ind: RRMS, active SPMS Note: Dose differs in patients with a CYP2C9*1/*3 or *2/*3 genotype Contraindicated in CYP2C9*3/3* genotype	55	86	81	21	Lymphopenia, transaminitis, infection risk (VZV, PML), cardiac arrhythmias, macular oedema, convulsions, skin malignancy, teratogenicity[124]	FBC (with differential), LFTs Ophthalmic exam ECG CYP2C9 genotyping Pregnancy test if applicable. Skin examination VZV serology and vaccinate if seronegative. Complete recommended vaccines* ≥4 weeks (live/live-attenuated) and ≥2 weeks (inactivated) before first dose.	FBC and LFTs at 3 and 6 months, then every 6 months thereafter. FDO only if cardiac condition. Ophthalmic exam at 3–4 months, then annually.
Cladribine[125] Total dose is 3.5mg/kg over 2 years. Year 1: 1.75mg/kg. Split dose to Month 1 (1 or 2 tablets PO over 4 or 5 days), followed by Month 2 (1 or 2 tablets PO over 4 or 5 days)	58	86	73	47	Lymphopenia, liver/ hematology toxicity, infection risk (VZV reactivation), malignancy, teratogenicity[126]	FBC, LFTs, thyroid function tests. HBV†, HCV, HIV, TB screening. Pregnancy test if applicable. MRI for PML VZV serology and vaccinate if seronegative.	FBC before each treatment cycle, and at 2 and 6 months post-treatment. LFTs before each treatment cycle. Anti-herpes prophylaxis if lymphocyte counts <200 cells/µl. Routine cancer screening according to standard guidelines.

Year 2: 1.75mg/kg. Split dose to Month 1 (1 or 2 tablets PO over 4 or 5 days), followed by Month 2 (1 or 2 tablets PO over 4 or 5 days) Further doses beyond year 3 on a case-by-case basis. Ind: RRMS, active SPMS						Complete recommended vaccines* ≥4 weeks (live/live-attenuated) and ≥2 weeks (inactivated) before first dose.	Monitor for signs and symptoms of PML.
Natalizumab[127] Dose (IV): 300 mg monthly Ind: RRMS, active SPMS	68	92	83	42	Infusion reaction, strong association with PML, other infection risk (Herpes zoster, respiratory and urinary), liver failure[128]	FBC (with differential) and LFTs JCV antibody test with index (where available). MRI for PML	FBC (with differential) and LFTs periodically. JCV antibody negative patients: Re-test every 12 months; JCV antibody positive: Monitor index annually for conversion to high-titer. Monitor for signs and symptoms of PML. MRI for PML: Every 6 months if JCV antibody negative; every 3 months if JCV antibody positive.
Ocrelizumab[104, 129] Induction dose (IV): 300 mg 2 weeks apart Maintenance (IV): 600 mg 6 monthly Ind: RRMS, SPMS, PPMS	46-47	94-95	77-83	40	Infusion reaction, hypogammaglo-bulinemia, hepatitis B reactivation, possible malignancy risk.[130, 131]	FBC with differential HBV† and TB screening Serum immunoglobulin levels Pregnancy test if applicable MRI for PML Complete recommended vaccines* ≥4 weeks (live/live-attenuated) and ≥2 weeks (inactivated) before first dose.	FBC with differential, serum immunoglobulins levels, pregnancy test (if applicable) prior to each infusion. Monitor for signs and symptoms of PML.
Ofatumumab[53, 132]	58	98	82-85	34	Infusion reaction, hypogammaglo-bulinemia,	FBC with differential	FBC (with differential) periodically.

Titration dose (SC): 20 mg at week 0,1,2,4 then monthly Ind: RRMS, active SPMS					hepatitis B reactivation[133]	HBV† and TB screening Serum immunoglobulin levels Complete recommended vaccines* ≥4 weeks (live/live-attenuated) and ≥2 weeks (inactivated) before first dose.	Serum immunoglobulin levels every 6 months. Monitor for signs and symptoms of PML.
Ublituximab[134] Initial dose (Day 1): 150mg IV 2 weeks later: 450mg IV Maintenance: 450mg IV 6 monthly (after day 1) Ind: RRMS, active SPMS	50-58	96-97	90-92	-	Infusion reaction, hypogammaglo-bulinemia, infection risk (HSV, VZV), respiratory tract infection and hepatitis B reactivation[135]	FBC with differential. HBV† screening. Serum immunoglobulin levels. Pregnancy test if applicable. Complete recommended vaccines* ≥4 weeks (live/live-attenuated) and ≥2 weeks (inactivated) before first dose.	No routine laboratory monitoring between doses. Serum immunoglobulin levels periodically. Monitor for signs and symptoms of PML. Pregnancy test (if applicable) prior to each infusion.
Alemtuzumab[136, 137] Initial dose: 12 mg IV daily X5 days Repeat 12 months later: 12 mg IV od X3 days Repeat doses beyond the 2nd year if needed Subsequent treatment courses of 12 mg IV od x 3 days may be administered, as needed, at least 12 months after the last dose.	49-55	62-63	17-32	30-42	Autoimmune disease (thyroid, immune thrombocytopenia purpura, Goodpasture syndrome, hepatitis), infection risk (HSV, VZV), hemophagocytic lymphohistiocyto-sis, stroke,	FBC (with differential) and LFTs. Serum creatinine. Thyroid function tests. Urinalysis with urine cell counts. HBV† and TB screening. Pregnancy test if applicable. Skin examination.	Monitor patients for two hours after each infusion for any serious infusion reaction. FBC (with differential) monthly for 4 years. Thyroid function tests every 3 months for 4 years. Renal function (serum creatinine, urinalysis) monthly for 4 years. LFTs periodically Skin exam annually for melanoma detection.

Ind: RRMS, active SPMS					malignancy, teratogenicity[138]	VZV serology and vaccinate if seronegative. Complete recommended vaccines* ≥6 weeks before first dose.	Monitor for signs and symptoms of PML.
Rituximab[68, 139, 140] Dose: Induction 1g IV at day 1 and day 15, followed by 500 mg to 1g IV every 6 months for 2 years, then further doses based on CD19 and immunoglobulin levels Ind: RRMS, active SPMS, PPMS	56	91-92	75-99 at 48 weeks	14.5-30.2 RRMS: 48 weeks CDP RTX vs placebo, (p=0.7)[28] PPMS:96-week rates CDP RTX vs placebo (p=0.14)[31]	Infusion reaction, hypogammaglo-bulinemia, hepatitis B reactivation[68, 139]	FBC with differential. HBV† and TB screening. Serum immunoglobulin levels. Pregnancy test if applicable. Complete recommended vaccines* ≥4 weeks (live/live-attenuated) and ≥2 weeks (inactivated) before first dose.	FBC with differential, serum immunoglobulins levels, pregnancy test (if applicable) prior to each infusion. Cardiac monitoring during infusions in patients with cardiac history. Monitor for signs and symptoms of PML.

ARR = annualised relapse rate; bd = twice daily; DMT = disease-modifying therapy; CDP = confirmed disability progression; ECG = electrocardiogram; FBC = full blood count; FDO = first dose observation; GdE = gadolinium-enhancing lesions on MRI; HBV = hepatitis B virus; HCV = hepatitis C virus; IFN = interferon; ind = indication; IV = intravenous; LFTs = liver function tests; MRI = magnetic resonance imaging; od = once daily; PML = progressive multifocal leukoencephalopathy; PO = oral; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SPMS = secondary progressive multiple sclerosis; T2L = T2 hyperintense lesions on MRI; VZV = varicella-zoster virus, CDP: confirmed disability progression

†If HBV antibodies <10 IU, vaccinate according to local vaccination schedules.

**Vaccinations (e.g., HPV, influenza, pneumococcal, COVID-19, BCG) should be given as per locally recommended vaccination protocols*

Q6. Fulminant/Aggressive MS: Which DMTs should be started in fulminant or aggressive MS?

There are several definitions for fulminant or aggressive MS, however, there is currently no consensus on this. The term aggressive MS has been used to describe a disease course marked by rapid disability accumulation, frequent severe relapses with incomplete recovery and poor response to DMTs.

The British Columbia group identified aggressive MS using criteria such as reaching an EDSS ≥6 within 5 years of onset, by age 40, or conversion to SPMS within 3 years of relapsing onset[50]. Meanwhile, Correale et al. identified several clinical, demographic and radiological features associated with aggressive MS. These included male gender, age >40 at onset, African American or Hispanic race, frequent severe relapses with incomplete recovery, early cognitive dysfunction, poor steroid response, rapid disability accrual (EDSS >6 within 5 years), high T2 lesion burden (>20 lesions at onset), >2 gadolinium enhancing lesions, T1 black holes, infratentorial or spinal cord lesions, early cortical and deep grey matter atrophy, and smouldering lesions[141].

Given these complexities, the panel has proposed a pragmatic definition tailored to the local context (see Table 1). Patients with aggressive/fulminant MS have a very narrow window of opportunity for treatment. Prompt initiation or switch to HET is essential. However, there is a lack of data and clinical trials to guide treatment decisions in this group of patients. Prognostic markers must be used to identify these patients early on (Table 2).

The panel acknowledges the emerging evidence supporting the use of autologous hematopoietic stem cell transplantation (AHSCT) as a treatment option in aggressive/fulminant MS. Systematic reviews, meta-analyses, and consensus recommendations from groups such as ECTRIMS and the European Society for Blood and Marrow Transplantation (EBMT) Working Group have reviewed the potential benefits of AHSCT and endorsed its use in patients who failed HET or who present with aggressive disease[142-144]. However, AHSCT requires referral to specialised centers with experienced multidisciplinary teams including MS specialists and hematologists, with the necessary infrastructure to perform the procedure safely and to manage its associated risks and complications. Currently AHSCT is only performed at selected tertiary centers in Malaysia on a case-by-case basis with hematological support. It is not widely available locally and is not FDA-approved at this time.

Recommendation 6: Fulminant/Aggressive MS (Achieved 86.7% agreement based on the Likert Scale thresholds)

i.	The panel recommends that patients with fulminant or aggressive disease be offered very high-efficacy therapies (VHETs) such as alemtuzumab, natalizumab, ofatumumab, ocrelizumab or rituximab, depending on availability and accesibility (See Figure 1 and Table 4a).
ii.	If there is inadequate response to one type of HET, switching to another agent with a different mechanism of action may be tried.

Q7. Secondary progressive MS: Which DMTs should be started in secondary progressive MS (SPMS)?

Current knowledge suggests progression starts early in MS across all spectrums. Progression independent of relapse activity (PIRA) refers to insidious disability accumulation independent of relapse associated disability/worsening[54] (Table 1). A number of recent studies have shown benefit of siponimod, ocrelizumab, ofatumumab, cladiribine and ponesimod in active SPMS[1, 40, 46, 96].

Many of the newer therapies have received FDA approval for use in relapsing MS including active SPMS, while Bruton's tyrosine kinase (BTK) inhibitor tolebrutinib has received FDA breakthrough therapy designation and is pending approval for non-relapsing SPMS[145] (See Figure 1, Table 4b, and Table 5). However, siponimod and tolebrutinib are currently not available in Malaysia. Historically, interferon beta-1b and mitoxantrone were approved for SPMS with relapses based on earlier clinical trials, but are now rarely prescribed except in selected cases[146, 147].

Recent systematic reviews have demonstrated short-term benefits of anti-CD20 monoclonal antibodies including rituximab, in stabilising disease progression and reducing relapses in patients with SPMS[99]. For active and/or worsening forms of progressive MS including SPMS, several studies including systematic reviews have reported the benefits of using ocrelizumab, rituximab, glatiramer acetate, fingolimod and interferon beta[98, 148, 149] (See Table 4b).

Recommendation 7: Secondary progressive MS (Achieved 86.7% agreement based on the Likert Scale thresholds)

i.	The panel recommends that SPMS patients **may** be offered treatment with any of the MET or HET DMTs regardless of whether they are treatment-naïve, newly diagnosed, or progressing from relapsing MS. (See Figure 1, Table 4b, and Table 5)
ii.	Active SPMS patients who are still showing disease activity clinically (e.g. relapses) and/or with an EDSS 4-6.5 with new MRI activity are likely to benefit the most from DMTs.
iii.	Proper counselling regarding the potential benefits, risks, monitoring requirements. and management of expectations are essential before initiating treatment in SPMS.

Q8. Primary progressive MS: Which DMTs should be started in primary progressive MS (PPMS)?

Treatment of PPMS remains an unmet need with ongoing research. A recent network meta-analysis using GRADE methodology recommended rituximab, ocrelizumab, glatiramer acetate, fingolimod, and interferon beta for active and/or worsening forms of progressive MS [98]. However, other studies and real-world data have not demonstrated benefits for interferon beta or fingolimod in PPMS[150, 151].

The pivotal one-year ORATORIO trial involving PPMS patients without relapses showed that ocrelizumab significantly reduced disability progression, timed 25-foot walk deterioration, development of new MRI lesions and brain volume loss compared to placebo [104]. The benefits of ocrelizumab needs to be balanced against the risks of infection, malignancy, and infusion-related reactions[131].

See Figure 1 and Tables 4 to 6.

Recommendation 8: Primary progressive MS (Achieved 86.7% agreement based on the Likert Scale thresholds)

i.	The panel recommends that patients with primary progressive MS **may** benefit from **ocrelizumab or off label rituximab,** although the evidence is limited[98, 104, 140].
ii.	PPMS patients who may benefit the most are those with EDSS < 7, still ambulatory with or without support in the absence of severe disability.

Q9. Monitoring: How should patients on DMTs be monitored?

The Magnetic Resonance Imaging in MS (MAGNIMS) Study Group acknowledged the challenges in defining and assessing treatment response in MS, and has concluded that there is currently no universally accepted consensus on the definition of treatment response. While No Evidence of Disease Activity (NEDA) is a promising endpoint in experimental settings, its long-term attainability beyond 1-2 years remains challenging in real-world clinical practice. Clinical or MRI activity alone may be insufficient to accurately assess treatment response. Therefore, composite measures are preferred and several scoring systems have been proposed, as outlined in Table 6. The panel felt that any of these may be adopted locally depending on access to neurologists and tools.

After DMT initiation, pwMS should be monitored for signs of ongoing disease activity as indicated by ≥1 clinical relapses, appearance of new or enlarging lesions on brain MRI (≥3 lesions), appearance of ≥1 lesions on spinal cord MRI, the presence of at least one gadolinium-enhancing lesion, or a confirmed increase in the EDSS score by ≥1 point sustained over 6 to 12 months compared to the previous year.

MRI monitoring

The presence of active lesions on brain MRI at baseline or during the first years after treatment initiation is a predictor of treatment response. The 2021 MAGNIMS-CMSC-NAIMS group consensus[152] recommends obtaining a brain MRI before starting DMT (with gadolinium contrast if the drug label requires it).

Brain MRI should be done at baseline and repeated 3-6 months after starting DMT (without contrast unless clinically indicated) as a re-baseline scan to assess pre-treatment disease activity and to avoid misattributing disease activity during this period to treatment failure. Subsequently, routine brain MRI using standardised protocols should be performed yearly to monitor disease progression and treatment response. Longer intervals may be acceptable in clinically stable patients after several years. Routine spinal cord or optic nerve MRI are not recommended unless clinically indicated, e.g., in myelitis or ON. If subclinical disease activity is seen or clinical suspicion arises without MRI confirmation, a repeat MRI in 6 months may be warranted[152].

Refer to Appendix 5a and 5b for the recommended imaging protocols and timing of follow-up.

Functional assessments

The EDSS is widely used for assessing overall neurological disability in pwMS[153]. EDSS should be evaluated at 6-monthly intervals or more frequently if progression or relapse is suspected[154].

The timed 25-Foot Walk (T25FW) is a reliable measure of ambulatory function in pwMS and is appropriate for assessing overall walking ability in clinical settings. A ≥20% worsening in T25FW is considered a clinically significant progression[155].

Where possible, the Single Digit Modality Test (SDMT) and 9-Hole Peg Test (9-HPT) should be included in the assessment of disability progression. The SDMT evaluates cognitive processing speed, the most common cognitive impairment in pwMS. A raw score change of 4 points (or a 10% change) indicates clinically significant progression[156]. The 9-HPT is sensitive to upper limb dysfunction and manual dexterity impairment and is particularly useful in assessing disease progression in non-ambulant patients. A ≥20% worsening in 9-HPT time is typically considered clinically significant for disease progression[157]. Training and access to these tests are important.

Other biomarkers

Additional biomarkers such as brain atrophy measurements, serum/CSF neurofilament light chains (NfL), glial fibrillary acidic protein (GFAP) and optical coherence tomography (OCT) are gaining interest. However, the panel does not recommend their routine use at this time due to limited availability of testing, high cost, and lack of validation in Asian populations. This recommendation will be revisited in the future.

Safety monitoring

PwMS will also need long-term monitoring for risks such as John Cunningham (JC) virus seroconversion, comorbidities, and malignancies which may neccesitate changes in therapy[1, 43]

See Table 5 for the detailed pre-screenings and safety monitoring requirements of each DMT.

Recommendation 9: Monitoring (Achieved 86.7% agreement based on the Likert Scale thresholds)

i.	The panel recommends using a combination of parameters to assess treatment response including: • Clinical relapses, • MRI activity such as new/enlarging/gadolinium-enhancing lesions in the brain and spinal cord, • EDSS and • Timed 25-foot walk (T25FW)
ii.	When starting a new DMT, pwMS should be pre-screened for latent infections, have their immunisation status updated, and be monitored according to the pre- and post-initiation recommendations for the chosen DMT (Table 5).
iii.	Following initiation of DMT, monitoring requirements may include (refer to Table 5): • Blood tests, performed monthly or 3 monthly during the initial phase, and • Once clinically stable, blood testing frequency may be extended to 6 monthly • Neuroimaging every 6 - 12 months to assess treatment response • Ongoing surveillance for infection risks (e.g., JC virus seroconversion, VZV, TB, hepatitis) and age-related comorbidities
iv.	PwMS who are stable on maintenance DMT should be reviewed by a neurologist at least 4 - 6 monthly, with regular clinical evaluations, EDSS assessments, and annual MRI.

Q10. Treatment failure: What is the definition of treatment failure or breakthrough disease and how should it be managed?

The panel acknowledged the absence of evidence on a standard criteria for defining treatment failure[158]. It is characterised by ongoing relapses, new or enlarging MRI brain/cord lesions, and/or progression of disability as assesed by EDSS or T25FW[43] (Refer to Table 6 for internationally establised criteria). Cognition, brain volume, OCT, and patient reported outcomes have not been incorporated as yet. A change in therapy should be considered in cases of treatment failure (refer to Table 8 for washout periods when switching DMTs).

See Figure 1 and Tables 6, 7 and 8 for further information.

Recommendation 10: Treatment failure (Achieved 93.75% agreement based on the Likert scale thresholds.)

i.	The panel agreed that treatment failure needs to be identified as early as possible after carefully ruling out non-adherence, treatment interruption, pseudorelapses, depression and fatigue as causes for treatment fluctuations[159].
ii.	The panel made the following recommendations: • It is vital to allow adequate time for DMTs to produce their full therapeutic effect. • This period may range from 6 months to 1 year before full clinical benefit is seen[159, 160].
iii.	In pwMS experiencing rapid clinical deterioration (aggressive/fulminant MS), re-evaluation of treatment should be done immediately.
iv.	For pulse therapies such as cladribine and alemtuzumab, • The full therapeutic effect would only be evident after completion of two treatment cycles given one year apart. • In most cases, it is reasonable to tolerate minor disease activity on these two medications, and treatment change should not be considered until 6 months after the second cycle[159].

	• However, if one or more significant relapses occur after the first cycle, changing to a faster acting HET may be considered.
v.	In pwMS on MET who continue to show disease activity despite treatment adherence for at least 6 to 12 months, treatment escalation should be considered[160].
vi.	In pwMS on HET with evidence of disease activity, switching to another HET with a different mechanism of action should be considered[159].

Table 6: Summary of criteria to monitor treatment response and thresholds/criteria for treatment failure.

Parameters	**Modified Rio score[161]**	**MAGNIMS[162]**	**Canadian MS working group[163]**	**ECTRIMS/ Spanish Society of Neurology[164]**	**AAN guideline[39]**
Clinical relapse	1 relapse (1 point) ≥2 relapse (2 points)	1 relapse (1 point) ≥2 relapse (2 points)	≥2 relapse (major)	≥1 relapse between year 1 and 2 after DMT onset	≥1 relapse
MRI activity	>4 new T2 lesions (1 point)	≥3 new T2 lesions (2 points)	≥3 new T2 lesions or ≥1 spinal lesion (major)	≥3 new T2 lesions	≥2 new T2 lesions
Disability progression (EDSS)			>1 point over 6 months	≥1 point over 1 year	Increase in disability over 1 year
Treatment failure criteria	≥2 points	≥2 points	Any major or multiple minors	Any 1	Any 1

EDSS = Expanded Disability Status Scale; DMT = disease modifying therapy; MRI = magnetic resonance imaging

Table 7: Recommendations for switching therapies in treatment failure

Initial therapy	Switching therapy
Moderate-efficacy therapy, e.g., IFN, GA, DMF, teriflunomide	• Escalation to HET, such as alemtuzumab, B cell depleting therapies, S1P modulators, or natalizumab[41]
High-efficacy therapy	• Lateral shift between alemtuzumab, B cell depleting therapies, natalizumab, cladribine, and S1P modulators • In refractory or highly aggressive MS, consider VHET or cyclophosphamide, mitoxantrone, or AHSCT[165].
Alemtuzumab	• For suboptimal response after 2 years, administer a third course of alemtuzumab or switch to a different VHET[166].
Cladribine	If treatment failure occurs: • Within 2 years: If not fulminant/aggressive disease, complete the full course or switch to a different HET. If fulminant or aggressive disease, switch to a VHET. Refer to Figure 1. • Years 3-4: Administer 3rd cladribine course or switch to a different HET[159]. • Year 5 and beyond: Considered as initial cladribine responders, may repeat the full course of cladribine treatment or switch to a different HET[167].

AHCT = autologous haematopoietic stem cell transplantation; DMF = dimethyl fumarate; GA = glatiramer acetate; HET = high-efficacy therapy; IFN = interferon; S1P = sphingosine-1-phosphate; MS = multiple sclerosis; VHET = very high-efficacy therapy

Table 8. Washout period for switching between disease modifying therapies[168, 169]

From \ To	MET (IFNB, GA, DMF, TER)	HET
Interferon beta	No washout	No washout
Glatiramer acetate	No washout	No washout
Teriflunomide	No washout (consider REP for switch to DMF)	Consider REP if rapid switch intended
Dimethyl fumarate	No washout if ALC ≥800	No washout if ALC ≥800
Fingolimod	No washout (ALC ≥800 for switch to DMF)	1 month
Siponimod	10 days	10 days
Natalizumab	No washout	1 month
Ocrelizumab	3 months or until B-cell repletion, IgG levels normal, and no infection	3-6 months or until B-cell repletion, IgG levels normal, and no infection
Ofatumumab	No washout if B-cell repletion, IgG levels normal, and no infection	1 month or until B-cell repletion, IgG levels normal, and no infection
Rituximab	No washout if B-cell repletion, IgG levels normal, and no infection	No washout if B-cell repletion, IgG levels normal, and no infection
Alemtuzumab	No washout, wait until clinical/MRI activity and ALC ≥800	No washout, wait until clinical/MRI activity and ALC ≥800
Cladribine	No washout, wait until clinical/MRI activity and ALC ≥800	No washout, wait until clinical/MRI activity and ALC ≥800

ALC = absolute lymphocyte count (/mm³); DMF = dimethyl fumarate; GA = glatiramer acetate; HET = high-efficacy therapy; IFNB = interferon beta; IgG = immunoglobulin G; MET = modest-efficacy therapy; REP = rapid elimination; TER = teriflunomide

NB. There is limited data available to guide switching from ofatumumab and rituximab in MS. Recommendations for these are from experience and expert consensus, and should be individualised based on immunological profile and clinical context.

Q11a. Pregnancy and breastfeeding: When and how should pwMS be counselled for pregnancy and breastfeeding?

Pregnancy counselling should be initiated early in pwMS ideally during routine care or when pregnancy is being considered. The counselling should address the pre-conception phase, pregnancy, breastfeeding, and the postpartum period. For pwMS with stable disease activity for at least one year, pregnancy can be considered[170]. The risk of relapses typically decreases during pregnancy but increases in the 3 months postpartum[171, 172]. Patients should be counselled that MS does not impair fertility or increase miscarriage risk, and that the risk of the child developing MS is less than 5%[173].

Assisted reproductive technology (ART) techniques are considered safe in pwMS[174], but timing should align with MS treatment plans. Counselling should also include information on the risks of relapse during and after pregnancy, disease trajectory, DMT withdrawal, and the safety and efficacy of contraceptive methods. All contraceptive options are safe for pwMS[175], and contraception should be discussed with those not planning a pregnancy.

Although there is no evidence of increased risk of pregnancy complications from MRI during the first trimester, the panel felt that MRI should be performed only if necessary during the first trimester. Beyond the first trimester, MRI is considered safe. The use of gadolinium contrast should be avoided during any stage of pregnancy as it is associated with an increased risk of stillbirths, neonatal deaths, congenital abnormalities, and the development of autoimmune disease, as it crosses the placenta[176].

Recommendation 11a: Pregnancy counselling (Achieved 93.75% agreement based on the Likert scale thresholds)

i.	**The panel recommends** that women with MS keen to conceive should have disease activity under control for at least ≥1 year before trying to get pregnant[170]. Women with MS (WWMS) should be counselled that current data suggests that MS ● Does not affect pregnancy adversely ● Does not-directly affect fertility ● Does not increase the risk of miscarriage during pregnancy.
ii.	**The panel recommends that pregnancy** counselling and planning be offered early to all pwMS. Counselling should provide reassurance that MS is not considered a high-risk pregnancy[177] and the risk of MS in the unborn child is low. Counselling should also cover the reduced risk of relapse during pregnancy and the increased risk during the postpartum period, the appropriate timing for DMT withdrawal, and an individualised plan for resuming DMTs after delivery.
iii.	**The panel recommends that counselling should also address fertility, the need for fertility counselling if needed,** and reassurance that ART does not trigger MS relapses[170, 178].
iv.	**The panel recommends that, if not planning a pregnancy, all WWMS should be advised on contraception** while on DMTs[179].
v.	**The panel recommends** that all types of contraceptives are safe for pwMS[180].
vi.	The panel recommends **deferring routine MRI** scans during pregnancy. In the event that MRI is deemed necessary, the study should be performed after the first trimester. New/enlarged T2 lesions should be sufficient to detect disease activity, avoiding the administration of gadolinium.

Q11b and 11c. Pregnancy and breastfeeding: Which DMTs are considered safe in pregnancy and breast feeding?

DMTs in pregnancy

Recommendations for DMT use during pregnancy vary, as they are mostly based on real-world data and known drug mechanisms, given the absence of randomised controlled trials in this population. Clinicians must weigh the benefits of maternal disease control against fetal/neonatal risks of DMT exposure.

Data from long-standing postmarketing surveillance and observational studies support the relative safety of interferon beta and glatiramer acetate in pregnancy and breastfeeding[170, 181-183].

Dimethyl fumarate (DMF) may be continued until conception. Although a recent registry based observational study did not find an increased risk of major congenital anomalies or adverse fetal outcomes from DMF, its use during pregnancy remains cautious due to limited data overall[182].

Real-world data has so far not shown an increase in major congenital abnormalities with teriflunomide in pregnancy [184]. However it remains contraindicated in pregnancy due to its known teratogenic effects in animal models and extrapolation from pregnancy data of the drug leflunomide, whose active metabolite is teriflunomide [170]. Teriflunomide requires accelerated elimination using activated charcoal or cholestyramine until plasma levels drop to ≤0.02 mg/mL in the event of planned conception or a pregnancy occurring within two years of its discontinuation[115].

A recent study from the German MS and Pregnancy Registry [185] reported reduced birth weight with S1P receptor modulators and natalizumab in the third trimester. Higher rates of small-for-gestational-age infants were observed with S1P receptor modulators, anti-CD20 therapies, and the entire DMT exposed group. Severe infections were rare but more frequent with fumarates.

Natalizumab can be continued until conception and up to 30–34 weeks gestation using extended interval dosing [186]. Continuing natalizumab beyond 30 weeks gestation can reduce postpartum relapses, however there is an increased risk of hematological abnormalities in newborns [186]. Discontinuation of natalizumab early in pregnancy has been associated with rebound relapses, which can be severe [183].

Fingolimod is associated with a significant risk of rebound relapses following withdrawal and has demonstrated developmental toxicity in animal studies[170]. The FDA and European Medicines Agency (EMA) recommend discontinuing fingolimod at least 2

months before attempting conception, based on its pharmacokinetics and teratogenic risk.

Data from the aforementioned German MS and Pregnancy registry showed that while most pregnancies exposed to cladribine resulted in healthy outcomes, there was one major congenital anomaly reported from a small cohort of live births[187]. Although the rate was only slightly higher than background MS population estimates (3.7% vs. 4.2%), continued caution and further data are warranted[187]. The EMA recommends stopping cladribine at least 6 months prior to conception.

The main concern with alemtuzumab is the increased risk of maternal autoimmune complications such as thyroid disease and immune thrombocytopenia, which may also affect the fetus[188]. Both the FDA and EMA advise avoiding pregnancy for at least 4 months after the last infusion.

Safety data and recommendations on anti-CD20 therapies continue to evolve. The drug manufacturers advise avoiding pregnancy for at least 4 months after the last infusion of ocrelizumab, 6 months for ofatumumab, and 12 months for rituximab[131, 133, 189]. However, real world data on ocrelizumab exposed pregnancies have not shown an increased risk of pregnancy or infant adverse outcomes[190]. Rituximab has also shown acceptable safety when pregnancy occurred within 6 months of the last infusion, although some data report increased miscarriage rates potentially linked to maternal comorbidities[188]. There is limited data on ofatumumab. Animal studies have demonstrated immunological effects in the fetus[133]. Clinical trials and postmarketing surveillance have so far reported no adverse outcomes in the small number of pregnancies and live births following exposure to ofatumumab[188].

The main concern with anti-CD20 therapies is fetal B cell depletion. However, as IgG1 monoclonal antibodies, these drugs demonstrate minimal placental transfer during the first trimester but significant transfer after 20 weeks, suggesting that stopping treatment 3 - 6 months before conception is sufficient to minimise fetal exposure. Current expert opinion recommends stopping ocrelizumab and rituximab 3 months before conception or at the time of conception, while ofatumumab may continue until conception[188]. When clinically indicated, continuing anti-CD20 therapy during pregnancy is acceptable[183]. Neonates exposed to anti-CD20 therapy during pregnancy should avoid live vaccines until after the exclusion of B cell depletion[183, 188].

Resuming DMTs post-partum

Resumption of DMTs post-partum can reduce the risk of relapses. Choice and timing of DMT resumption should be individualised, balancing risk of relapse (especially within the first 3 months), pre-pregnancy and pregnancy disease activity, type of DMT used previously (those who stopped HET during pregnancy especially natalizumab and fingolimod should be prioritised for resumption), time elapsed since the last dose, and breastfeeding intentions[172, 173]. Early resumption of DMTs post-partum is recommended, especially if not breastfeeding. See the following section on DMTs during breastfeeding.

Recommendation 11b: DMTs in pregnancy (Achieved 93.3% agreement based on the Likert scale thresholds)

i.	The panel agreed that DMT use in pregnancy should be individualised, balancing between manufacturer's recommendations, guidelines/post marketing data, and real world data (Table 9). **The panel suggested the following:** ● Interferons, GA are safe up to conception and during pregnancy[191-193]. ● Teriflunomide should be stopped prior to conception and removed via an accelerated washout[115, 170, 184]. ● Dimethyl fumarate can be continued until conception[181, 182]. ● Natalizumab can be continued until conception[181, 194] and until week 30-34 of pregnancy with extended interval dosing[186]. ● Fingolimod should be stopped 2 months prior to conception. Newer S1P modulators may need only a shorter washout[170]. ● Alemtuzumab[181, 188] and Cladribine[181, 187] should be stopped 4 and 6 months respectively prior to conception.
ii.	**The panel felt that** **Ofatumumab** should be stopped at contraception discontinuation or when conception occurs in pwMS[188]. **Ocrelizumab** should not be routinely administered during pregnancy other than in the case of uncontrolled significant disease activity. The last infusion should occur 3 months before conception[183, 188], ideally without prolonged drug-free intervals.

	Rituximab may be given until 3 months prior to conception[188], after weighing the risk benefit ratio. Close monitoring of the neonate is required due to the potential for B cell depletion, including assessment of B cell counts prior to vaccination.
iii.	**The panel recommended** should accidental exposure to a DMT considered unsafe occur, prompt referral to a feto-maternal physician and detailed fetal monitoring performed for risk mitigation should be done.

DMTs and steroids during breastfeeding

Breastfeeding is encouraged in women with MS as it is protective against postpartum relapses. While interferon beta and GA have been established as safest in breastfeeding for some time, emerging evidence supports the safety of some newer DMTs. Observational studies so far suggest the safety of ofatumumab and ocrelizumab during lactation, with minimal/undetectable levels in breastmilk and infant serum, and no significant effect on fetal B cell depletion early postpartum[190, 195-197]. Similarly, studies have shown minimal transfer of rituximab in breastmilk[195, 198].

Caution is advised for breastfeeding on dimethyl fumarate due to the potential for significant transfer into breastmilk and unknown effects on the infant, although real world data from a small number of exposed infants suggest that it is likely safe[199, 200]. Natalizumab is considered likely safe during lactation owing to low transfer into breastmilk and minimal oral bioavailability[188]. Breastfeeding is not recommended during treatment with cladribine and alemtuzumab, and commencement of breastfeeding requires specific timing considerations due to the potential risks to the infant and limited safety data[188, 201]. Breastfeeding is not recommended during treatment with S1P receptor modulators due to limited safety data and the potential for significant transfer into breast milk[179, 201].

Intravenous corticosteroids, which were previously associated with a potential risk of first-trimester cleft lip and/or palate, have not been shown to significantly increase this risk in more recent studies[202].

Recommendation 11c: DMTs and steroids during breastfeeding (Achieved 93.75% agreement based on the Likert scale thresholds)

i.	The panel suggests interferon beta and GA may be used during breastfeeding[203-205].
ii.	The panel recommends that **most DMTs aside** from **interferon beta and GA** to be discontinued or used with caution. Refer to Table 9 for the recommendations of specific DMTs.
iii.	Ocrelizumab, ofatumumab and rituximab may be used with caution and monitoring of the infant during breastfeeding.
iv.	Intravenous steroids can be given for relapses during pregnancy and lactation[202].

Table 9: Summary of DMT use in pregnancy and breastfeeding

DMT	Discontinuation before pregnancy	When to stop DMT before pregnancy	Pregnancy	Breastfeeding
GA	Continue[191-193]		Compatible[192, 193]	Compatible[203-205]
IFN-B	Continue[191-193]		Compatible[191-193]	Compatible[203-205]
Dimethyl Fumarate	May continue until pregnancy is confirmed[181, 182]		Caution[182, 201]	Caution[199, 200]
Teriflunomide	Discontinue[170]	Charcoal/ cholestyramine washout for 11 days till the level < 0.02mg/L[170, 184]	Contraindicated [170, 184, 201]	Contraindicated[201]
Fingolimod	Discontinue[171]	2 months[171]	Contraindicated[179, 201]	Contraindicated[179, 201]
Cladribine	Discontinue[187]	6 months[187]	Contraindicated[187, 201]	Contraindicated [201] During and 1 week after last dose
Alemtuzumab	Discontinue[183]	4 months[177, 188]	Contraindicated[183, 201]	Caution* Start 4 months after last infusion[188, 201]
Natalizumab	May continue, especially in Highly Active cases[194]		Continue with extended dosing interval of 6-8 weeks till 30-34 weeks of gestation[186, 188]	Caution* Very low concentration in breastmilk[188]
Rituximab	Discontinue	Once pregnancy is confirmed or 3 months before conception[188]	Caution[201, 206]	Caution*
Ofatumumab	Discontinue	Once contraception stops or pregnancy is confirmed[188]	Caution*	Caution* Very low concentration in breastmilk[188 197]
Ocrelizumab	Discontinue	Once pregnancy is confirmed[188] or 3 months before conception[183, 188]	Caution*	Caution* Very low concentration in breastmilk[188, 190, 196]

* Limited evidence to provide recommendations. Continue if potential benefit justifies the potential risk

GA = glatiramer acetate; IFN-B = interferon beta

Q12. Cognition: What is the effect of DMTs on cognition?

DMTs can provide potential cognitive benefits, but their main purpose is to alter disease activity. The extent of cognitive improvements can vary from person to person, meaning not all patients will experience the same level of benefit. Furthermore, some DMTs may have side effects that could indirectly affect cognitive function. For instance, flu-like symptoms related to interferon beta therapy can temporarily impact cognitive performance.

Emerging evidence indicates that starting DMTs early in patients with MS may improve cognitive functions. DMTs are intended to reduce neuroinflammation and brain atrophy, both of which are linked to cognitive decline in MS[207, 208]. Evidence supports cognitive benefits, particularly in processing speed, for agents such as interferon beta, fingolimod, siponimod, ofatumumab, ocrelizumab, ublituximab, natalizumab, cladribine, and rituximab[53, 129, 134, 209-214].

A meta-analysis of 41 studies involving 7,131 patients suggests that initiating HET early is associated with a greater reduction in disease progression compared to delaying treatment or following an escalation approach. The findings imply that timely treatment may help preserve cognitive functions by minimising irreversible clinical disability and neurodegeneration[215]. Further details on the effects of various DMTs on cognition are summarised in Appendix 4.

Recommendation 12: Effect of DMTs on cognition (Achieved 93.3% agreement based on the Likert scale thresholds)

i.	The panel recommended that early DMT initiation **may** have an effect on preservation or delaying cognitive deterioration[207] (Appendix 4).
ii.	Neurologists **should** screen pwMS for cognitive deterioration with standard tools such as the Symbol Digit Modality Test (SDMT) or Brief International Cognitive Assessment for MS (BICAMS) where available, and other validated assessment tools for cognitive testing[216].
iii.	PwMS who exhibit cognitive impairment should be managed through a multidisciplinary approach, including a neurologist, and where appropriate, a neuropsychiatrist or psychiatrist, and a clinical psychologist or neuropsychologist[217].

Q13. Discontinuing disease-modifying therapy: When should DMTs be stopped in pwMS?

As long as the disease remains stable and the treatment is well tolerated, age alone should not be a reason to discontinue DMTs. However, clinicians should remain vigilant for treatment-related complications that may become more common with increasing age or treatment duration. These include an increased risk of infections due to immunosenescence and immunodeficiency syndromes such as hypogammaglobulinemia, which predisposes to serious infections. Additionally, the presence of life-limiting co-morbidities such as advanced cardiovascular disease or cancer may alter the risk benefit ratio of continuing therapy and warrants its re-evaluation.

In studies of people with RRMS, discontinuing DMT was associated with an increased risk of relapse, disability progression, and radiological disease activity[218, 219]. Factors that predict a higher rate of relapses after stopping treatment include younger age, female sex, higher baseline EDSS, and recent relapse activity particularly within the 12 months preceding discontinuation. Certain DMTs, such as fingolimod and natalizumab, carry an additional risk of rebound or recurrence of disease activity upon withdrawal.

Discontinuation of DMT may be considered in older adults with stable disease, however there is currently no definitive age at which a patient can be assured of zero risk for relapse, and some elderly pwMS are reluctant to stop treatment. The DISCOMS trial (Discontinuation of DMTs in MS)[220], a randomised controlled study of older adults with stable RRMS, found that discontinuing therapy did not significantly increase relapse risk compared to continuing therapy over 2 years. On the other hand, continuing therapy provided modest benefit in preventing new MRI lesions, although the overall rates of clinical worsening were low in both groups. These findings suggest that DMT discontinuation may be safe in selected older adults with stable disease, provided that patients are closely monitored.

Decisions to stop therapy should remain individualised, taking into account patient preferences, co-morbidities, degree of disability, and the specific DMT involved.

Recommendation 13a: Continuing/discontinuing DMTs in stable disease (Achieved 86.7% agreement based on the Likert scale thresholds)

i.	The panel recommends that pwMS who are stable on a given DMT may continue therapy including HET regardless of age as long as the patients wants to continue, the disease is stable, in the absence of adverse events such as infections, immunodeficiencies, and co-morbidities complicating the treatment course[1, 43, 46, 218-220].
ii.	The panel recommends that co-morbidities in older adults be thoroughly evaluated, and that the decision to continue, de-escalate. or discontinue treatment be carefully assessed on an individual basis.

Recommendation 13b: Discontinuing DMTs in active or advanced disease (Achieved 86.7% agreement based on the Likert scale thresholds)

i.	Discontinuing or pausing treatment at a **patient's explicit request** may be done if adhering to clear guidelines for clinical and imaging monitoring, and counselling about the risk of rebound especially with fingolimod and natalizumab[1, 43, 46, 159, 160, 165, 221, 222].
ii.	If the patient continues to progress over time and becomes severely disabled, such as becoming bed bound, experiencing recurrent infections and developing life-limiting co-morbidities, treatment discontinuation **may** be considered following counselling[1, 43, 46, 159, 160, 165, 221, 222].

Q14. Health and well-being measures: What additional evidence is available to improve the health and well-being of pwMS?

Current evidence does not support any specific dietary intervention as a replacement for DMTs in halting inflammation or disease progression in MS[223]. However, maintaining a balanced diet low in saturated fats, avoiding smoking, and incorporating regular physical activity as part of an overall healthy lifestyle have been associated with improvements in several clinical parameters, including stamina, balance, fatigue, and overall quality of life for people with MS[224-226].

Research suggests that high-fat diets rich in saturated fats are associated with greater disease progression, whereas diets high in fruits, yogurt, and legumes may reduce the risk of MS onset and progression[223]. Specific dietary approaches such as the Mediterranean diet and ketogenic diet have shown potential benefits, including reduced inflammation, neuroprotection and promotion of central nervous system repair[223, 227].

Probiotics, by restoring microbial balance, may also help mitigate immune dysfunction noted in MS. Personalised dietary strategies targeting the gut microbiota hold promise for managing MS by modulating immune responses and slowing disease progression[228].

Recommendation 14: Improving health and well-being of pwMS (Achieved 93.3% agreement based on the Likert scale thresholds)

The panel **emphasises** the importance of healthy living, avoidance of smoking, identification and management of comorbidities, maintaining mental well-being, and provision of exercise for pwMS[229-232].

Q15. Vitamin D in MS: Should vitamin D be measured and should it be supplemented in pwMS?

There is currently insufficient evidence to recommend vitamin D supplementation as an adjuvant DMT in pwMS. Recent studies have demonstrated conflicting results, with trials in CIS showing no significant reduction in MRI disease activity following vitamin D supplementation[233-235]. Nevertheless, supplementation may still be appropriate in individuals who are vitamin D deficient or at increased risk of osteoporosis, particularly those exposed to repeated courses of corticosteroids[236].

Recommendation 15: Vitamin D in MS (Achieved 93.3% agreement based on the Likert scale thresholds)

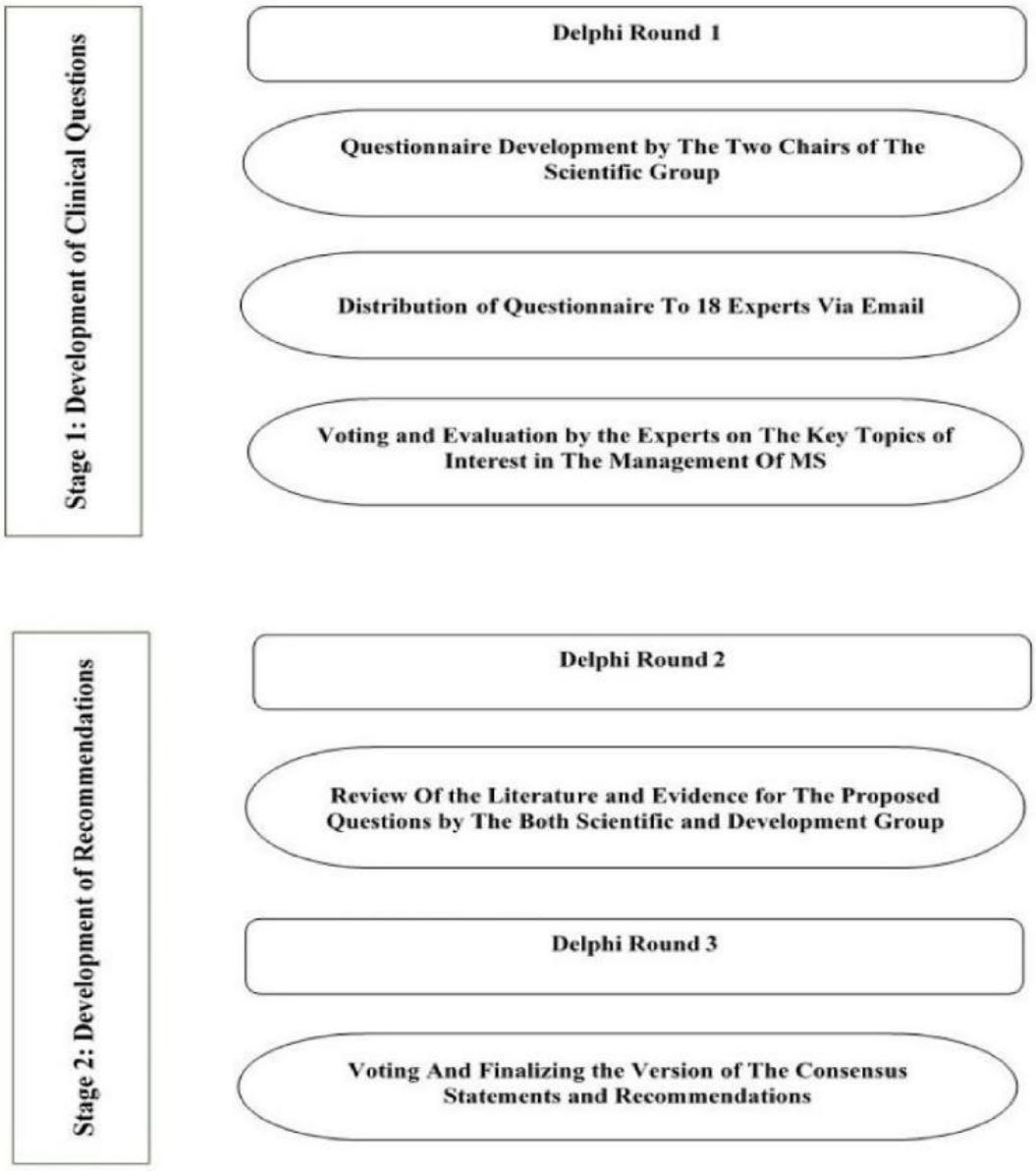
i.	All pwMS should have their baseline vitamin D levels checked[237, 238].
ii.	The panel recommends that all pwMS may be supplemented with oral vitamin D3 (cholecalciferol), ranging from 600 to 4000 IU per day, to maintain a target level of 50 – 125 nmol/L[239, 240].
iii.	For patients who are vitamin D deficient with a level <50 nmol/L, there is evidence that vitamin D supplementation reduces risk of relapse[241, 242]. Replacement dose is recommended (e.g., vitamin D3 50,000 IU per week for 8 - 12 weeks)[237-243].

Conclusion

The panel has attempted to review the literature thoroughly and to provide a comprehensive yet pragmatic summary of the most up-to-date evidence to guide the management of MS in Malaysia. Recommendations are presented in action boxes to make it easier to refer to. Vaccination guidance was not included in this consensus and will be addressed in a future publication. Similarly, symptomatic and neuropsychiatric treatments were not covered as it falls outside of the primary focus of this consensus, which is centered on disease-modifying therapies.

The panel acknowledges that MS management is a rapidly evolving field and that this document has its limitations, including constraints on the depth of discussion for each recommendation and the lack of local data and research. It is hoped that this consensus statement will help local clinicians in the management of people with MS and fill existing knowledge gaps. The panel plans to reconvene in the near future to further refine and update the document for local use.

Appendix 1. Flowchart of the Delphi process[23]

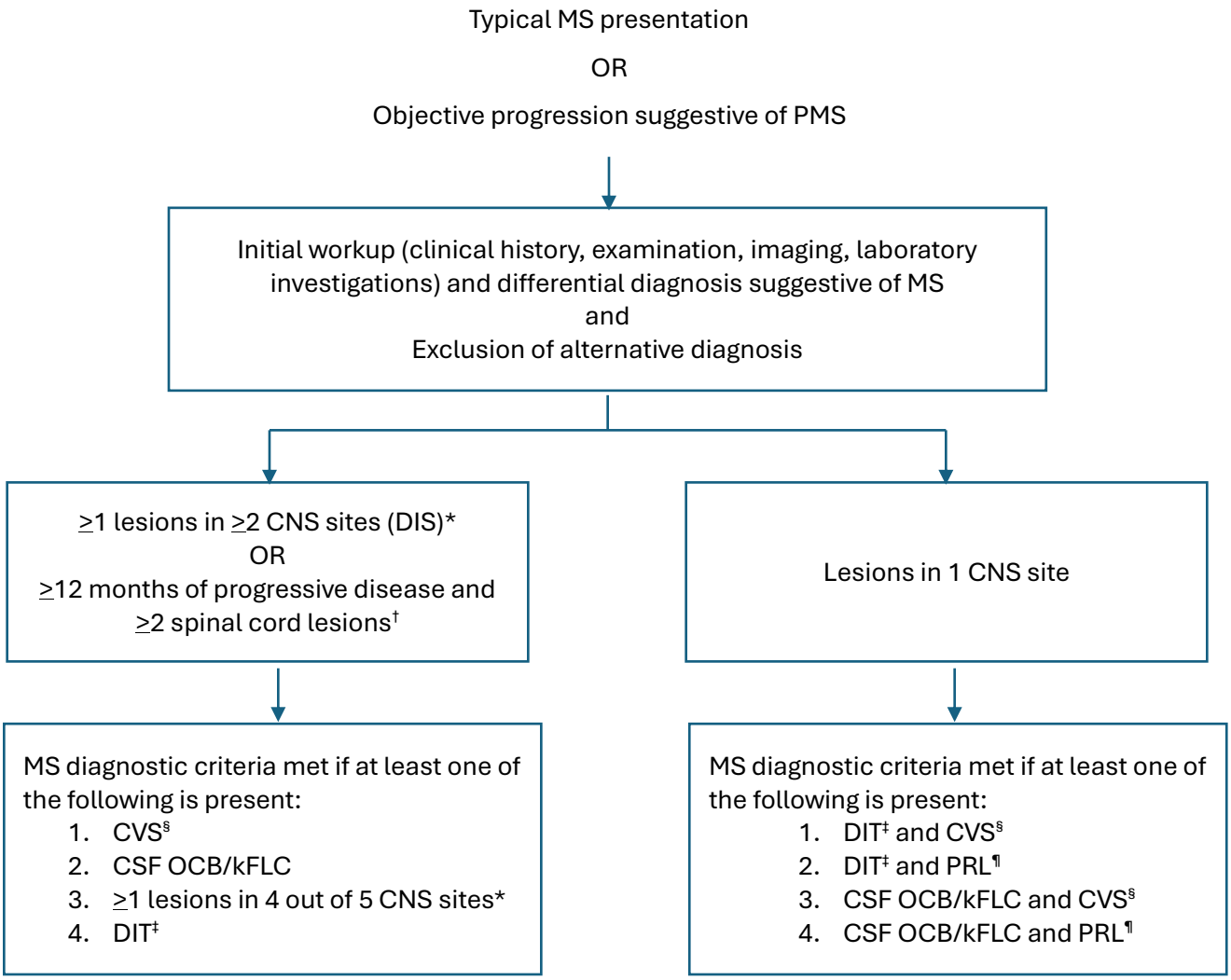


Appendix 2. Finalised list of questions to be addressed in the consensus

1.	Should MS patients be treated as early as possible?
2.	Should patients with CIS be treated with DMTs?
3.	Should patients with RIS be treated with DMTs?
4.	Which treatments should be started in an acute relapse of MS/CIS?
5.	Which DMTs should be started in active and highly active RRMS?
6.	Which DMTs should be started in fulminant/aggressive MS?
7.	Which DMTs should be started in secondary progressive MS?
8.	Which DMTs should be started in primary progressive MS?
9.	How should patients on DMTs be monitored?
10.	What is the definition of treatment failure or breakthrough disease and how should it be managed?
11.	11a. When and how should pwMS be counselled for pregnancy and breastfeeding? 11b. Which DMTs are considered safe in pregnancy? 11c. Which DMTs are considered safe in breastfeeding?
12.	What is the effect of DMTs on cognition in MS?
13.	When should DMTs be stopped in pwMS?
14.	What additional evidence is available to improve the health and well-being of pwMS?
15.	Should vitamin D be measured and should it be supplemented in pwMS?

NB. Changes were made after redeliberation

Appendix 3. Diagnostic algorithm for MS according to the 2024 McDonald criteria



Adapted from Miller et al., 2025[244]

CNS = central nervous system; CSF = cerebrospinal fluid; CVS = central vein sign; DIS = dissemination in space; DIT = dissemination in time; kFLC = kappa free light chains; PMS = progressive multiple sclerosis; OCB = oligoclonal bands; PRL = paramagnetic rim lesions

**DIS is demonstrated by the presence of ≥1 T2 hyperintense lesions in at least 2 of the following CNS sites on MRI: juxtacortical, periventricular, infratentorial, spinal cord, and optic nerve*

†The presence of ≥2 spinal cord lesions in patients with ≥12 months of progressive disease is considered evidence of DIS.

‡DIT is demonstrated by the presence of ≥1 new or enlarging T2 lesions, OR ≥1 Gad-enhancing lesion, OR a clinical attack

§CVS is demonstrated by the presence of ≥6 lesions with CVS. If <6 white matter lesions are present on the MRI, the number of lesions with CVS should be more than those without CVS

¶PRL is demonstrated by the presence of ≥1 PRL

Appendix 4. Effects of DMTs on cognition in MS

Category	DMTs	Cognitive Impact
Immunomodulators	Interferon beta[210, 245, 246]	Studies showed significant improvements in delayed visual memory, attention, and also preservation of cognition in patients receiving interferon beta-1b. Side effects such as flu-like symptoms and injection site reactions may influence cognitive task.
S1P receptor modulators	Fingolimod[212, 247, 248]	Potential cognitive benefits. Some studies have reported improvements in cognitive functions, such as processing speed There is limited data on potential cognitive risk.
	Siponimod[209]	May improve in cognitive processing speech based on the EXPAND trial. Further analysis indicated a reduction in cognitive worsening. The cognitive risks associated with siponimod include potential for progressive multifocal leukoencephalopathy.
	Ponesimod[120]	It demonstrated a significant reduction in brain volume loss compared to teriflunomide, which suggests potential neuroprotective effect; but there is lack of direct evidence on its impact on specific cognitive domains.
Anti-CD20 B-Cell depleting agents	Ofatumumab[53, 132, 249]	Post-hoc analysis of ASCLEPIOS I and II phase III trials demonstrated clinical meaningful improvement on processing speed. Potential cognitive risks include End-of-Dose (EOD) phenomena
	Ocrelizumab[214, 250, 251]	Analysis from the OPERA I and II phase III trials demonstrated protective effect on cognitive processing speed. Results from

		CONSONANCE study (PPMS and SPMS) demonstrated stable or improvement of processing speed. Potential risk includes wearing-off phenomenon.
	Rituximab (off-label)[211, 213, 249]	A study involving SPMS patients demonstrated significant improvements in verbal fluency and visuospatial memory; other study also showed potential prevention of cognitive decline. Patients may experience a 'wearing-off' phenomenon particularly fatigue and depression, which may impact on cognition.
	Ublituximab[134]	In the phase III ULTIMATE I and II trials, ublituximab demonstrated improvement in processing speed. There is limited data on cognitive adverse effects.
Anti-CD52 B- & T-cell depleting agents	Alemtuzumab[252-254]	A longitudinal observational study in patients with RRMS showed either stable cognitive function or improvement in processing speed. There is limited data on cognitive adverse effects.
Purine analogues	Cladribine[252, 255, 256]	In both CLARIFY-MS and MAGNIFY-MS studies, Cladribine showed no decline in processing speed and slight improvements in verbal and visuospatial memory. There is limited data on cognitive adverse effects.
	Azathioprine (off-label)[257]	There is a lack of specific evidence on its cognitive benefits. Although rare, there have been reported neuropsychiatric adverse effects such as headaches, confusion, and cognitive disturbances.
Anti-integrin monoclonal antibody	Natalizumab[258-261]	Natalizumab demonstrates sustained and stable cognitive function or may improve. Study has shown significant reduction in the impairments in memory, attention, and executive function. A rebound of cognitive impairment may be seen in those discontinued. Potential cognitive risks include the increased risk of PML

Appendix 5a. Summary of the MAGNIMS-CMSC-NAIMS consensus recommendations on MRI protocols in MS[152]

		BRAIN*	SPINAL CORD*	OPTIC NERVE
MRI field strength		≥1.5T (preferably 3T)	≥1.5T (3T has no added value)	≥1.5T
At diagnosis	Core sequences	1. FLAIR: 3D, 1mm isotropic with sagittal acquisition 2. T2: axial, 3mm with no gap 3. T1 post-Gad: axial ≤3 mm with no gap, or T1 post-Gad: 3D, 1 mm isotropic	1. T2, PD, STIR or PSIR (Choose two): ≤3 mm with no gap, from base of skull to conus 2. T1 post-gad: sagittal	1. T2 fat sat or STIR: axial and coronal, ≤2–3 mm with no gap 2. T1 C+ (Gd) fat sat: axial and coronal, ≤2–3 mm with no gap
	Optional sequences	1. DWI/ADC 2. DIR or PSIR (for cortical and juxtacortical lesions) 3. SWI (for central vein sign) 4. T1: 3D, 1 mm isotropic with sagittal acquisition, quantitative brain-volume assessment	1. T1: sagittal 2. T2 or GRE: axial, ≤5 mm with no gap, from base of skull to conus 3. T1 post-Gad: axial	-
During follow-up	Core sequences	1. FLAIR: 3D, 1mm isotropic with sagittal acquisition 2. T2: axial, 3mm with no gap	-	-
	Optional sequences	1. DWI/ADC (if PML is considered) 2. DIR or PSIR 3. T1: 3D, 1 mm isotropic with sagittal acquisition, quantitative brain-volume assessment 4. T1 post-Gad: axial ≤3 mm with no gap, or T1 post-Gad: 3D, 1 mm isotropic	Imaging of the spine in established MS cases is considered to be optional	-

Appendix 5b. Timing of follow-up imaging[152]

	Frequency of follow-up	**Gadolinium**
Clinically and radiologically isolated syndrome	6 – 12 months	Not recommended
New baseline (after initiating or switching disease modifying treatment)	3 – 6 months	Normally not required
Routine follow-up (stable patient)	Yearly	Normally not required

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