Recommendations for Essential Medicines for Multiple Sclerosis in Low-Resource Settings

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ABSTRACT

Background

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system that, when untreated, can lead to significant disability in young adults. Despite the increase in the number of disease-modifying therapies (DMTs), many people living with MS in low-resource settings do not have access to treatment.

Objective

To develop recommendations on the minimum essential DMTs for MS that should be available in low-resource settings.

Methods

The Multiple Sclerosis International Federation established an independent, international panel including healthcare professionals and people with MS. This panel, in collaboration with the Cochrane MS Group and McMaster GRADE Centre, reviewed evidence for use of MS DMTs following standardized GRADE protocols including consideration of balance of benefits and harms; certainty of evidence; resources required and cost-effectiveness; and values, equity, feasibility, and availability in low-resource settings.

Results

For active and/or worsening forms of relapsing MS, the panel recommends use of ocrelizumab, cladribine, fingolimod, dimethyl fumarate, interferon beta, and glatiramer acetate. For active and/or worsening forms of progressive MS, the panel recommends use of rituximab, ocrelizumab, glatiramer acetate, fingolimod and interferon beta.

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Conclusions

Recommendations for the minimum essential DMTs for MS in low-resource settings were developed based on robust consideration of evidence and relevant context.

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INTRODUCTION

Objective

These recommendations aim to provide evidence-based guidance regarding which disease-modifying therapies (DMTs) for MS should be available, at a minimum, in low-resource settings. The project scope was defined at the start (1). These recommendations are *not* meant to suggest MS DMTs not listed here are ineffective or other DMTs should not be available to people with MS (pwMS). For the purpose of these recommendations, low-resource settings are not limited to low- and lower-middle income countries (2), but include specific populations in higher-income countries, for example refugees and people without medical insurance coverage (3).

The target audience for these recommendations are policymakers, patient advocacy groups, healthcare workers, and pwMS. Policymakers interested in these recommendations include those involved in developing formularies for governments, public or private insurance programmes, hospitals and other types of healthcare providers. PwMS, healthcare workers and advocacy groups may use these recommendations in an evidence-based approach to improve access to MS DMTs. This document may also serve as the basis for adaptation by local, national, regional, international and/or organisation guideline panels. Finally, these recommendations informed an application to the World Health Organization (WHO) for inclusion of MS DMTs in the Essential Medicines List (EML) (4).

The health problem

MS is affects 2.2-2.9 million people globally, with prevalence increasing worldwide (5,6). In many countries it is the most common cause of non-traumatic disability in young adults (7). Effective DMTs exist, helping to reduce and/or prevent relapses and future disability. Twenty

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DMTs have been approved by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) as of 2022, and at least ten others are commonly used off-label (8). Access to DMTs varies substantially by region, country and sub-population within a country. The Multiple Sclerosis International Federation (MSIF) Atlas of MS shows that pwMS in 72% of countries face barriers accessing DMTs, including DMTs being entirely unavailable, unreliable supplies of DMTs, and DMTs being inaccessible due to personal or health-system costs (9).

There is an urgent need to make MS treatments accessible for all pwMS to prevent long-term disability and reduce healthcare disparities. However, treatment of MS does not follow a "one size fits all" approach. The choice of which DMT to initiate for an individual is complex, with consideration of personal factors (e.g. age, family planning status, co-morbidities) and disease-specific factors (e.g. form of MS, frequency and severity of past relapses, radiographic lesion burden). Furthermore, not all individuals will respond equally well to each DMT, and breakthrough disease or side-effects may necessitate a switch to a different DMT. Therefore, it is essential that a range of DMTs are available, and these recommendations include multiple DMTs as minimal essential medications that should be available in low-resource settings.

Target populations

The panel considered two populations separately: (1) active and/or worsening relapsing forms of MS, and (2) active and/or worsening progressive forms of MS. Only adult populations were considered, and both radiologically isolated syndrome and clinically isolated syndrome were outside the scope of these recommendations.

The panel recognized there has been a shift in the classification of MS subtypes in recent years. As such, the panel opted to use the Lublin definitions for relapsing (active), progressive and worsening disease (Table 1, (10)).

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METHODS

The process followed the Guidelines International Network (GIN)-McMaster Guideline Developers Checklist and the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach while utilizing GRADE's Guideline Development and Implementation tool GRADEpro (11–13). Systematic reviews of evidence were conducted by the Cochrane Review Group for Multiple Sclerosis and Rare Diseases of the CNS, and the McMaster Centre facilitated the guideline development process, including ensuring adherence to the GRADE approach. The panel, comprising 25 members, was international and multi-disciplinary and included clinical MS specialists, MS researchers, people with expertise in health economics, pharmaceutical policy and psychology, and pwMS from Uruguay, Serbia, Namibia and Morocco.

Tables 2 and 3 provide additional information on the GRADE certainty of evidence ratings and how to interpret guidelines generated by this process. This process, previously undertaken by MSIF, is described elsewhere (14). Detailed methods are available in Supplemental File 1. Although the levels and the significance of those are described as 'quality' in the GRADE handbook and supporting published paper (15), in this publication we use the term 'certainty' in line with current GRADE methods. 'Low' or 'very low' certainty should not be misinterpreted as a lack of evidence, but rather an assessment of the certainty that can be placed in that body of evidence.

These recommendations, which were developed for low-resource settings, take into consideration 12 criteria from the GRADE evidence-to-decision (EtD) framework (16): the healthcare problem importance, values, desirable effects, undesirable effects, the balance of desirable and undesirable effects, certainty of evidence, resources required, cost-effectiveness, equity, acceptability, feasibility, and availability.

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Ethical approval. This process used only publicly available information and expert opinion. No identifiable information was collected, and experts consented to their participation. Therefore, no ethics board approval was required.

SUMMARY OF RECOMMENDATIONS

Summaries of all recommendations are provided below. Detailed recommendations, including the way in which individual criteria were applied to each recommendation, can be found in Supplemental File 2. The full Evidence-to-Decision frameworks and all supporting documents can be found here: https://www.msif.org/documents-memp-etd/.

Recommendations for Relapsing Forms of MS

Recommendation 1: The MSIF Essential Medicine Panel (MEMP) suggests for, in priority order (conditional recommendation): 1. cladribine (low certainty ⊕⊕◯◯), 2. dimethyl fumarate (low certainty ⊕⊕◯◯), 3. fingolimod (low certainty ⊕⊕◯◯), 4. ocrelizumab (very low certainty ⊕◯◯◯), 5. interferon beta 1b (very low certainty ⊕◯◯◯), 6. interferon beta 1a (low certainty ⊕⊕◯◯), 7. glatiramer acetate (very low certainty ⊕◯◯◯), for the treatment of active and/or worsening relapsing forms of MS.

Remark: The recommendation is conditional due to low and very low certainty of evidence.

Justification: Cladribine is a feasible and acceptable option in low-resource settings due to balance of effects, mode of administration (oral), short treatment period, low maintenance for screening and monitoring, low discontinuation rate, easy storage, and favourable cost-effectiveness. Dimethyl fumarate is a feasible and acceptable option in low-resource settings due to balance of effects, mode of administration (oral), low maintenance for screening and monitoring, and easy storage, but has a higher discontinuation rate compared to other oral

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treatments. Fingolimod is a feasible and acceptable option in low-resource settings due to balance of effects, mode of administration (oral), easy storage, but requires more maintenance for screening and monitoring, and has a risk of rebound of MS disease activity if access to treatment is discontinued suddenly, e.g., due to unreliable supply of medicine. Ocrelizumab is a feasible and acceptable option in low-resource settings due to balance of effects, low maintenance for screening and monitoring, low discontinuation rate, less frequent administration, but requires infusion facilities and cold storage at the healthcare facility. Interferons beta 1a and 1b are feasible and acceptable options in low-resource settings due to balance of effects, low maintenance for screening and monitoring, but are less acceptable due to mode and frequency of administration (injection), requirement of cold-storage by person with MS, and frequency of flu-like side effects. Glatiramer acetate is a feasible and acceptable option in low-resource settings due to balance of effects, very low maintenance for screening and monitoring, but is less acceptable due to mode and frequency of administration (injection), and requirement of cold-storage by pwMS.

Recommendation 2. MEMP suggests either for or against, in priority order (conditional and neutral recommendation, dependent on setting) the use of: 1. natalizumab (low certainty ⊕⊕◯◯), 2. alemtuzumab (low certainty ⊕⊕◯◯), for the treatment of active and/or worsening relapsing forms of MS.

Remark: Feasibility of pre-tests, monitoring requirements, cost and affordability are concerns limiting the application of these DMTs in some low-resource settings. The panel felt a recommendation either for or against these medicines for low-resource settings was appropriate, despite evidence of clinical benefit. In settings where the feasibility challenges related to costs and long-term monitoring (and surety of supply for natalizumab) are surmountable, these treatments may be considered.

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Justification: The panel noted that the evidence on balance of the effects clearly favours the use of natalizumab and alemtuzumab. Despite the demonstrated benefit, the panel noted feasibility issues for low-resource settings in access to and cost of pre-screening and monitoring required (including monthly blood tests and three-monthly urine tests), regular John Cunningham virus (JCV) testing and MRI monitoring for progressive multifocal leukoencephalopathy (PML). These tests are essential for the safe use of these DMTs and not currently available in many low-resource settings. High cost of medicines was also noted for budget impact, although cost-effectiveness studies favoured alemtuzumab. The two DMTs had very similar net balance of effects, but the safety profile of natalizumab was considered better as the risk of PML can be prognosticated and minimized. Alemtuzumab is associated with a broader suite of less severe but more frequent side effects.

Recommendation 3. MEMP suggests against (conditional recommendation) the use of mitoxantrone (very low certainty ⊕◯◯◯) for the treatment of active and/or worsening relapsing forms of MS.

Justification: The panel noted significant post-marketing surveillance safety concerns and long-term monitoring requirements with mitoxantrone, creating barriers to feasibility and acceptability. This recommendation was against mitoxantrone despite balance of effects probably favouring the intervention based on included studies, which predated post-marketing surveillance and safety concerns.

Recommendations for Progressive Forms of MS

Recommendation 1: MEMP suggests for, in priority order (conditional recommendation): 1. rituximab (very low certainty ⊕◯◯◯), 2. glatiramer acetate (very low certainty ⊕◯◯◯), 3. ocrelizumab (very low certainty ⊕◯◯◯) 4. interferon beta 1a (low certainty ⊕⊕◯◯), 5.

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fingolimod (low certainty ⊕⊕◯◯), 6. interferon beta 1b (very low certainty ⊕◯◯◯) for active and/or worsening progressive forms of MS.

Remark: The recommendation is conditional due to low and very low certainty of evidence.

Justification: Rituximab is a feasible and acceptable option in low-resource settings due to balance of effects, mode of administration (6-monthly infusions), low maintenance for screening and monitoring with low risk of rebound effect if treatment is discontinued, and low discontinuation rate, but requires infusion facilities and cold storage at the healthcare facility. Glatiramer acetate is a feasible and acceptable option in low-resource settings due to balance of effects, very low maintenance for screening and monitoring, but is less acceptable due to mode and frequency of administration (injection), and requirement of cold-storage by pwMS. Ocrelizumab is a feasible and acceptable option in low-resource settings due to balance of effects, low maintenance for screening and monitoring, low discontinuation rate, mode of administration (6-monthly infusions), but requires infusion facilities and cold storage at the healthcare facility. It is less acceptable than rituximab due to the significant cost of the medication. Interferons beta 1a and 1b are feasible and acceptable options in low-resource settings due to balance of effects, low maintenance for screening and monitoring, but are less acceptable due to mode and frequency of administration (injection), requirement of cold-storage by pwMS and type of adverse events. Fingolimod is a feasible and acceptable option in low-resource settings due to balance of effects, mode of administration (oral), easy storage, but requires more maintenance for screening and monitoring, and has a risk of rebound of MS disease activity if access to treatment is discontinued suddenly, e.g., due to unreliable supply of medicine.

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Recommendation 2: MEMP suggests either for or against, in priority order (conditional and neutral recommendation, dependent on setting): 1. siponimod (low certainty ⊕⊕◯◯), 2. natalizumab (very low certainty ⊕◯◯◯), 3. immunoglobulins (very low certainty ⊕◯◯◯) for active and/or progressing progressive forms of MS.

Remark: Feasibility of pre-tests, monitoring requirements, cost and affordability are concerns limiting the application of these DMTs in some low-resource settings. The panel felt a recommendation either for or against these medicines for low-resource settings was appropriate, despite evidence of clinical benefit. Immunoglobulin use was noted to be rare even in high-income settings, with efforts to reduce demand for immunoglobulin in many countries.

Justification: The panel noted that the evidence on balance of the effects clearly favours siponimod and natalizumab. Despite the demonstrated benefit, the panel noted variable feasibility issues for low-resource settings in the access to and cost of pre-screening and monitoring required, e.g., for siponimod CYP2C9 genotyping and for natalizumab regular JCV testing and MRI monitoring for PML. These tests are essential for the safe use of these DMTs and not widely available in low-resource settings. It was noted that the high cost of these medicines resulted in a significant budget impact. Natalizumab and siponimod were noted to be used routinely in high-income settings, whereas the use of immunoglobulin was rare.

Recommendation 3: MEMP suggests for, in priority order (conditional recommendation): 1. azathioprine (very low certainty ⊕◯◯◯), 2. methotrexate (very low certainty ⊕◯◯◯) in clinical settings where no alternative treatments are accessible for active and/or non-active progressive forms of MS.

Remark: This recommendation is based on very low certainty evidence and is, therefore, conditional to other treatment options not being accessible. Use in research settings may also be appropriate due to the need for higher quality evidence for these medicines, although trials

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with placebo would be considered unethical. Furthermore, these medications are expected to have primarily immunosuppressive effects, and their effect on neurodegeneration is unknown. As such, they should be used with additional caution in cases without clear evidence of disease activity.

Justification: Azathioprine and methotrexate have a conditional recommendation with a condition of no alternative DMTs being accessible, where the alternative would be no treatment. This condition was due to the evidence base being very limited and more research would be required to ascertain effects of these DMTs in progressive forms of MS. The DMTs are oral treatments, widely available in health systems with a low cost, not requiring cold-chain, making them a feasible option in low-resource settings. The ranking is based on balance of effects.

Values and preferences

The Panel noted there was probably no uncertainty or variability in the importance that patients place on the outcomes identified as critical (described in Supplemental File 1).

How to use these recommendations

These recommendations are primarily intended to help policymakers in low-resource settings make decisions about which MS DMTs should be available for different populations, i.e., people with relapsing and progressive forms of MS. These recommendations are for the minimal standard of treatment that should be available in all settings regardless of specific barriers to access and resource limitations. Use of these recommendations to reduce access to DMTs is a misinterpretation. Clinicians and pwMS in low-resource settings can use them to make decisions about treatment choices, but these recommendations are not meant to be used in place of clinical guidelines where they are available in the national/local setting. Other purposes include advocacy for improved access to MS treatments and clinical education.

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These recommendations are not suggesting that medications that were not recommended are ineffective or not useful for treating MS. Rather, they are meant to be context-specific recommendations about the minimum medications for treatment of MS that should be available in low-resource settings. Where countries have good access to a range of DMTs, these recommendations should not be used to restrict access to DMTs that have a good evidence base for efficacy and safety in treating MS, replacing them with those where the evidence around efficacy and safety is less certain.

Generic and biosimilar versions of the recommended medicines should be appropriately tested, in line with the standards applied by stringent regulators. (17,18) Quality of manufacturing must be monitored, and adverse events properly recorded and reported.

These recommendations are not intended to be interpreted as a standard of care. Clinicians must make decisions based on an individual's clinical presentation, ideally using a shared decision-making process that considers an individual's values and preferences with respect to their treatment. Importantly, given the focus of these recommendations on diverse low-resource settings, decisions are likely to be constrained by availability of treatments as well as by realities of individual clinical settings and local resources, including, but not limited to, institutional policies, time limitations, and insurance systems which may impact safe implementation of these DMTs, including access to adequate and regular safety monitoring.

Finally, as science advances and new evidence is generated, recommendations may become outdated. Following these recommendations cannot guarantee successful outcomes. MSIF does not warrant or guarantee any products described in these recommendations.

DISCUSSION

We present recommendations that DMTs should be provided for people with both active and/or worsening relapsing and progressive forms of MS in low-resource settings. In developing

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these recommendations, the panel explicitly considered factors important in healthcare decision making in low-resource settings including feasibility (e.g., pre-testing and monitoring requirements), availability, cost, and equity.

These recommendations have several limitations. First, evidence from non-randomized controlled trials was not included in this process due to the complexity of adding them to the network meta-analyses that formed the evidence base. For example, although rituximab is generally considered a highly effective therapy for relapsing forms of MS and is widely used in many parts of the world (8), it was not considered in this process because the randomized controlled trials for rituximab in relapsing MS did not meet the pre-specified inclusion criteria for the outcomes considered in our evidence review. We are aware that there are credible studies of rituximab completed in non-randomized settings (e.g. cohorts and registries) and another guideline panel assessing its off-label use as an MS DMT recently recommended it (19).

Second, this process utilized a novel approach to calculating the net benefit of each DMT that included the use of health state utility values (HSUVs) to develop a weighted relative risk of each outcome and then summing the benefits and harms. This approach had two inherent limitations. First, well-accepted HSUVs for the outcomes of interest in MS are not available. As such, the HSUVs utilized for these calculations were either derived from smaller studies in MS cohorts or modified from other disease states by utilizing expert input from the panel. As such, changes to the HSUVs utilized in this process would likely have changed the overall net benefit calculations for the DMTs. While this would be less likely to alter the overall recommendations, it is likely that the ranked prioritization of drugs within each recommendation may have been altered if different HSUVs were utilized. In the same way, the net benefit score was calculated by subtracting a summed total of all harms from a summed total of all benefits. Given that ten outcomes were considered and that not all studies assessed the same outcomes or even the same number of outcomes, studies which had a great number of outcomes contributing to this calculation had the potential to have a larger net benefit as a result. Again,

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this would be unlikely to change the overall classification of each DMT within the recommendations, but is likely to have impacted the ranked prioritization of the DMTs within each recommendation.

Third, to ensure comparability among study results, outcomes were pre-defined in detail by the committee. If the studies in the evidence base reported these outcomes in a way that was incongruent with such definitions, these outcomes were not included in the analysis. For example, due to the heterogeneity in how relapses were reported in different studies, relapses could not be included as an outcome for several DMTs. Therefore, the prioritized rankings of DMTs within each category should be interpreted with caution.

Finally, the systematic review of cost-effectiveness selected 51 studies published since 2012. Methodology varied from study to study. Methodological inconsistency in cost-effectiveness studies, including whether or not they included indirect costs, was an identified limitation.

FUTURE RESEARCH

The panel noted several evidence gaps during its review and identified priorities for future research. Deeper understanding of comparative effectiveness could be gained from a systematic review of all non-randomized controlled studies for all DMTs. Further research is needed into the effectiveness of medications used off-label in clinical practice, including off-label cladribine, and those which may be more accessible due to availability of follow-on products (including rituximab, azathioprine and methotrexate). More research into short- and long-term side effects of these treatments is also required. An evaluation of long-term risks and benefits of siponimod, diroximel fumarate, and ofatumumab, which are increasingly used across populations, is also needed.

A greater understanding of comparative cost-effectiveness is necessary, including analyses across the full duration of treatment, considering any additional courses of induction

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therapies for medications with shorter durations of use (e.g. alemtuzumab and cladribine); and independent cost-effectiveness analyses for all DMTs in different resource settings, particularly outside of high-income countries. Inclusion of indirect as well as direct costs through a common methodology would enhance the comparative usefulness of cost-effectiveness data.

CONCLUSIONS

We propose that DMTs should be available for people with both relapsing and progressive forms of MS in low-resource settings. We recommend which DMTs should be considered when selecting a minimum number for low-resource settings to ensure all pwMS have access to treatment and to improve global health equity. While not without limitations, these recommendations represent the first guidance for MS treatment availability developed specifically to consider factors important to policymakers in low-resource settings and based on an extensive process of assessing the underlying evidence.

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DECLARATION OF CONFLICTING INTERESTS

Deanna Saylor, Jagannadha Avasarala, Elisa Baldin, Ivana Bogdanovic, DK Chawla, Cinzia Del Giovane, Najoua El-Abkari, Graziella Filippini, Marien Gonzalez-Lorenzo, Aukje K Mantel-Teeuwisse, Silvia Minozzi, Francesco Nonino, Bianca Ozcan, Elisabetta Pasi, Andrea Prato Chichiraldi, Ben Ridley, Irene Tramecere, Janis SN Tye, Simona Vecchi and Feng Xie have no conflicts of interest to declare.

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Tomas Kalincik has served on scientific advisory boards for MS International Federation and World Health Organisation, BMS, Roche, Janssen, Sanofi Genzyme, Novartis, Merck and Biogen, steering committee for Brain Atrophy Initiative by Sanofi Genzyme, received conference travel support and/or speaker honoraria from WebMD Global, Eisai, Novartis, Biogen, Roche, Sanofi-Genzyme, Teva, BioCSL and Merck and received research or educational event support from Biogen, Novartis, Genzyme, Roche, Celgene and Merck.

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TABLE 1. Lublin definitions used to define active, progressive and worsening multiple sclerosis (MS) (8).

Term	**Definition**
Active disease	Relapses, acute or subacute episodes of new or increasing neurologic dysfunction followed by full or partial recovery, in the absence of fever or infection.
Progressive disease	Steadily increasing objectively documented neurologic dysfunction/disability without unequivocal recovery (fluctuations and phases of stability may occur).
Worsening MS	Documented objective worsening of neurologic dysfunction/disability, as (8)a result of relapses or progressive disease.

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TABLE 2. GRADE approach to rating the certainty in the body of evidence for each effect estimate generated for each outcome and each intervention (9). The symbols next to each rating are used throughout the manuscript to illustrate the certainty of the evidence. 'Low' or 'very low' certainty should not be misinterpreted as a lack of evidence, but rather an assessment of the certainty that can be placed in that body of evidence.

GRADE Terminology	**Definition**
Domains considered	Risk of bias, imprecision, inconsistency, and magnitudes of the estimates of effects, indirectness of the evidence, risk of publication bias, presence of large effects, dose-response relationship, and assessment of the effect of residual, opposing confounding
Ratings	
High certainty (⊕⊕⊕⊕)	High certainty in the evidence about the effects
Moderate certainty (⊕⊕⊕◯)	Moderate certainty in the evidence about the effects
Low certainty (⊕⊕◯◯)	Low certainty in the evidence about the effects
Very low certainty (⊕◯◯◯)	Very low certainty in the evidence about the effects

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TABLE 3. Interpretation of conditional and neutral recommendations per GRADE standards.

GRADE interpretation of strong and conditional recommendations by patients, clinicians, health care policy makers, and researchers (reproduced with permission) (15)

Implications for:	**Strong recommendation**	**Conditional recommendation**
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
Clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients, and clinicians must help each patient to arrive at a management decision consistent with the patient's values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
Policy makers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation, according to the guideline, could be used as a quality criterion or performance indicator.	Policy making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help to identify possible research gaps.

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SUPPLEMENTAL FILE 1: DETAILED METHODS

Organization, Panel Composition, Planning, and Coordination

The work of this panel was coordinated by MSIF, facilitated by the McMaster University GRADE Center and was funded by MSIF. MSIF appointed individuals to the guideline panel. Systematic reviews of evidence were conducted by the Cochrane Review Group for Multiple Sclerosis and Rare Diseases of the CNS, and the McMaster Center facilitated the guideline development process, including ensuring adherence to the GRADE approach. The panel, comprising 25 members, was international and multi-disciplinary and included clinical MS specialists (neurologists, nurse practitioners, nurses, pharmacists), MS researchers, a health economist, a pharmaceutical policy expert/pharmacoepidemiologist, a psychologist, an internal medicine physician, and people affected by MS from Uruguay, Serbia, Namibia and Morocco. Participants were selected to ensure diverse representation in terms of geographical region (19 countries, 48% from Upper-Middle Income Countries (UMIC) or Lower-Middle Income Countries (LMICs) (1)), area of expertise, representation of key neurological organizations involved in guideline development, sex, race and ethnicity. The panel was chaired by one clinical chair (D.S.) and two methodology co-chairs (T.P., H.J.S.), and an observer from the World Health Organization Brain Health Unit (N.S.) was also invited to attend all meetings. The membership of the panels and the systematic review team have been published in Appendices 15.1.3 and 15.1.4 of the WHO EML application(2).

Funding and Management of Conflicts of Interest

Development of these recommendations was funded by MSIF. Funding from for-profit companies was not accepted, and representatives from the pharmaceutical industry were not involved in the panel formation or guideline development process. MSIF supported panel appointments, coordinated meetings, and prepared meeting materials and minutes but had no

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role in choosing the guideline questions or determining the recommendations. MSIF also provided funding to the Cochrane MS group to facilitate the completion of systematic evidence reviews and consulting fees to the McMaster team. However, the guideline panel did not receive any payments or reimbursements from MSIF for their work on these guidelines.

Potential conflicts of interest were carefully managed in accordance with the GIN principles,(3,4) throughout the panel's work, with individual conflicts judged by the National Center for Clinical Evidence, Quality and Safety of Care (CNEC) of the Istituto Superiore di Sanita. Full reports can be found here (5).

Formulating Specific Clinical Questions and Determining Outcomes of Interest

The panel used the GRADEpro Guideline Development Tool (6) and group discussion to brainstorm and finalize PICO (Patient, Intervention, Comparator, Outcome) questions.

1.) Populations: relapsing MS with active and/or worsening disease; relapsing MS with not active, stable or indeterminate disease; relapsing MS with active and/or worsening disease when there is a lack of treatment response to current treatment; progressive MS with active and/or progressing disease; progressive MS with not active and not progressing disease or indeterminate; and progressive MS with active and/or progressing disease when there is a lack of treatment response to current treatment.

2.) Interventions and Comparators: on-label DMTs, including teriflunomide, leflunomide, dimethyl fumarate, diroximel fumarate, monomethyl fumarate, fingolimod, siponimod, ozanimod, ponesimod, cladribine, alemtuzumab, laquinimod, natalizumab, ocrelizumab, ofatumumab, daclizumab, glatiramer acetate, interferon-beta 1a, peg-Interferon-beta 1a, interferon-beta 1b; off-label and commonly used DMTs that have evidence meeting inclusion criteria of the systematic reviews and meta-analyses, including azathioprine, rituximab, cyclophosphamide, methotrexate, mitoxantrone,

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steroids, fludarabine, minocycline, mycophenolate mofetil, and immunoglobulins. Non-pharmacologic interventions (e.g. stem cell transplant) were considered to be out of the scope of this guideline panel.

3.) Outcomes: The panel first brainstormed and prioritized nine outcomes, and then voted that all of these were critical outcomes. The final prioritized outcomes were: mortality, quality of life impairment, MS relapse, disability or dependency (as determined by the Expanded Disability Status Scale), cognitive decline, new gadolinium-enhancing T1-weighted lesions on MRI, new or enlarging T2-weighted lesions on MRI, serious adverse events, and discontinuation of treatment due to adverse effects (tolerability).

Definitions

As noted above, people with MS were categorized according to the Lublin phenotypes (Table 1, main manuscript) (7). Outcome data required a minimum of one year (52 weeks) to be considered. Relapse rate was defined as the proportion of people having a relapse within defined time periods. As such, outcomes reported as annualized relapse rates were not included. Full details of all health outcome descriptors have been previously published (8,9).

Evidence Review

Evidence on all available immunomodulators and immunosuppressants for MS was searched and synthesized by means of two network meta analyses (NMAs), one on relapsing MS (10) and one on progressive MS (11). All reviews were performed according to the methodology recommended by Cochrane (12). Randomized controlled trials (RCTs) that studied one or more agents for use in relapsing MS and progressive MS, comparing them to placebo or to another active agent, were included. Only RCTs were included due to the complexity of the analysis to be performed (considering direct as well as indirect comparisons) and the high

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number of interventions and outcomes. In addition, drug-specific short- and long-term adverse effects were not considered. Only serious adverse effects (SAEs), mortality and discontinuation due to adverse effects and mortality were included among the undesirable outcomes.

Eligible study references were identified through systematic searches of the following bibliographic databases: Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), latest issue; MEDLINE (PubMed); EMBASE (Embase.com). No search limitations with respect to study outcomes, methods of analysis or language were applied. The following databases were also searched for ongoing studies: World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch); US National Institutes of Health clinical trial register (www.clinicaltrials.gov). All search strategies were designed and conducted by an information specialist (10,11). We checked reference lists of all included studies and any relevant systematic reviews identified for additional references to studies. Any relevant retraction statements and errata for included studies were examined. Panel members were invited to review the retrieved and selected reports and to provide expert input or additional eligible references if deemed necessary. All searches were initially conducted to include evidence published up to 21/9/2021 and subsequently updated by means of a top-up search on 8/8/2022 prior to final voting on recommendations to ensure all current evidence was considered at the time of finalization.

In addition, risk of bias was assessed for each study by the Cochrane team using the Cochrane Collaboration's risk-of-bias tool for randomized trials of interventions (ROBINS-I). Finally, the certainty of evidence, also sometimes referred to as the confidence in estimated effects or quality of evidence, was assessed for each effect estimate of each outcome of interest using the GRADE approach and rated from very low to high (Table 2, main manuscript) (13,14). 'Low' or 'very low' certainty should not be misinterpreted as a lack of evidence, but rather an assessment of the certainty that can be placed in that body of evidence.

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Finally, the Cochrane team together with the GRADE Rome Centre and the WHO Collaborating Centre in Evidence-Based Research Synthesis and Guideline Development of Bologna, Italy, also conducted evidence searches related to baseline risks, values, preferences, costs and cost-effectiveness for each intervention under consideration.

Development of Recommendations

Under the direction of the McMaster University Grade Centre (H.S., T.P.), the GRADE "Evidence-to-Decision" (EtD) framework was applied to each guideline question using the GRADEpro Guideline Development Tool (6). However, given the large number of interventions under consideration (i.e. 30 DMTs), the guideline panel made a pragmatic decision to only consider approximately 10 interventions for the full EtD framework. As such, 30 DMTs were narrowed to 10 DMTs for full consideration for relapsing MS and 11 DMTs for full consideration for progressive MS. These decisions were based on the balance of desirable and undesirable effects (net balance) as extracted from the NMAs (9). Of note, the net balance calculations were generated by attributing a magnitude of effect to each relative risk extracted from the NMAs according to that outcome's impact on health state utility values (HSUVs). The HSUVs were either derived directly from MS studies or were drawn from studies of other health conditions and adjusted for characteristics of MS populations based on the judgement of the panel. Of note, in order to avoid duplication between outcomes in HSUV calculations where $\geq$2 time-points were measured for the same outcome, only the outcome with higher certainty was used. If certainty was the same, the longer time-frame was used. Where more than one MRI outcome was reported for an intervention, an average of the results (expressed as HSUVs) was used. If both SAEs and discontinuation due to AEs were reported, only discontinuation due to AEs was used. Of note, the net balance did not correct for the number of outcomes included, so some DMTs had more outcomes contributing to the net benefit calculation than others.

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Using 15 regular conference calls between 02/08/2021 and 16/06/2022, the panel developed guideline recommendations based on evidence summarized in the EtD tables, which included intervention effects, values and preferences, costs, cost effectiveness, equity, accessibility, feasibility, and availability. Where evidence was not available for a particular domain and a given intervention, the panel came to a consensus judgement in order to complete each EtD table. Full EtD tables and the Summary of Finding tables on which they are based are available online (9). EtD tables were considered and guidelines finalized first for relapsing MS, and then the process was repeated for progressive MS.

For each recommendation, the guideline panel came to consensus judgment on all domains of the EtD tables by explicitly taking the perspective of low-resource settings. For example, in rating equity, the panel considered whether more widespread availability of a given intervention would increase, decrease or have no effect on health equity for people with MS living in a low-resource setting. Similarly, cost and cost-effectiveness were considered primarily from the perspective of health systems in low-resource settings.

For resources required, the panel set the following thresholds compared to placebo, from a global perspective with a focus on LMICs and based on medium/minimum wage and health care expenditure in LMICs: (a) large costs: ≥$1000/year/patient; (b) moderate costs: ≥$100 - $999/year/patient; and (c) negligible/cost-savings: less than $100/year/patient. These thresholds were based on the experience of neurologists and people with MS on the Panel from low and lower-middle income countries, and the wider Panel accepted their judgement. Differences in cost between countries as well as the cost of generics and biosimilars (where costs for those could be ascertained) were also considered.

Drugs could be rated cost-effective whilst still being high cost. For example, alemtuzumab and, to a lesser extent, cladribine, have high upfront costs, but they also have a reduced number of treatment cycles that helps to offset these costs, hence being rated as cost-effective.

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The panel agreed on all recommendations, including their direction and strength, as well as their associated remarks and qualifications, by consensus based on all aspects of the 13 EtD criteria (not just their desirable and undesirable effects). Final recommendations were reviewed and approved by all panel members. All meetings were recorded, and minutes were circulated after each meeting for edits and feedback to ensure all panel members felt the minutes accurately reflected the content of the meetings.

Interpretation of Conditional Recommendations

All recommendations were labeled as “conditional” based on very low or low certainty of evidence upon which the recommendations were based. Further information regarding interpretation of conditional GRADE recommendations for healthcare policy makers, researchers, clinicians and patients can be found in Table 3 of the main manuscript.

Document Review

Draft recommendations were reviewed, revised and finalized by all members of the panel by December 2022. They were subsequently made publicly available online between 12/01/2023 and 27/01/2023 for open comment (15). Three individuals/organizations submitted comments which were incorporated into this document, but no changes were made to the recommendations based on these comments.

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SUPPLEMENTAL FILE 2: DETAILED RECOMMENDATIONS WITH FULL RATIONALE

RECOMMENDATIONS

Relapsing Forms of Multiple Sclerosis

Which DMTs should be available for the treatment of active and/or progressing forms of relapsing MS in low-resource settings?

The full EtD table can be found online, along with the summary of judgements for all DMTs and all factors considered.(1). Based on the balance of effects (Figure 1A) and the wider EtD framework, the MEMP guideline panel suggests:

Recommendation 1. For, in priority order (conditional recommendation): 1. cladribine (⊕⊕◯◯), 2. dimethyl fumarate (⊕⊕◯◯), 3. fingolimod (⊕⊕◯◯), 4. ocrelizumab (⊕◯◯◯), 5. interferon beta 1b ⊕◯◯◯), 6. interferon beta 1a (⊕⊕◯◯), 7. glatiramer acetate (⊕◯◯◯).

Remark: The recommendation is conditional due to low and very low certainty of evidence.

Justification for priority order: Priority order was based both on the net balance for each medication but also on additional EtD considerations most relevant to low-resource settings as detailed here. Cladribine is a feasible and acceptable option in low-resource settings due to balance of effects, mode of administration (oral), short treatment period, low maintenance for screening and monitoring, low discontinuation rate, easy storage, and favorable cost-effectiveness. Dimethyl fumarate is a feasible and acceptable option in low-resource settings due to balance of effects, mode of administration (oral), low maintenance for screening and monitoring, and easy storage, but has a higher discontinuation rate compared to other oral treatments. Fingolimod is a feasible and acceptable option in low-resource settings due to balance of effects, mode of administration (oral), easy storage, but requires more maintenance for screening and monitoring, and has a risk of rebound of MS disease activity if access to

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treatment is discontinued suddenly, e.g., due to unreliable supply of medicine. Ocrelizumab is a feasible and acceptable option in low-resource settings due to balance of effects, low maintenance for screening and monitoring, low discontinuation rate, less frequent administration, but requires infusion facilities and cold storage at the healthcare facility. Interferons beta 1a and 1b are feasible and acceptable options in low-resource settings due to balance of effects, low maintenance for screening and monitoring, but are less acceptable due to mode and frequency of administration (injection), requirement of cold-storage by person with MS, and type of adverse events. Glatiramer acetate is a feasible and acceptable option in low-resource settings due to balance of effects, very low maintenance for screening and monitoring, but is less acceptable due to mode and frequency of administration (injection), and requirement of cold-storage by the person with MS.

Recommendation 2: For or against (neutral recommendation, dependent on setting) in priority order (conditional recommendation): 1. natalizumab (⊕⊕◯◯), 2. alemtuzumab (⊕⊕◯◯), due to feasibility of pre-tests, monitoring requirements, cost and affordability limiting the application of these DMTs in some low-resource settings.

Remark: The recommendation is conditional due to low and very low certainty of evidence. In addition, the panel felt a recommendation for or against both these medicines for low-resource settings was appropriate, despite evidence of significant clinical benefit. In settings where the testing and monitoring requirements can be met reliably and where cost is not a barrier, these treatments have an important role to play.

Justification: Prioritization was based both on the net balance for each medication but also on additional EtD considerations most relevant to low-resource settings as detailed here. The panel noted that the evidence on balance of the effects clearly favours the use of natalizumab and alemtuzumab. Despite the demonstrated benefit, the panel noted variable feasibility issues for low-resource settings in the access to and cost of pre-screening and

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monitoring required (including monthly blood tests and three-monthly urine tests), regular JCV testing and MRI monitoring for PML. These tests are essential for the safe use of these DMTs and not currently available in many low-resource settings. High cost of medicines was also noted for budget impact, although cost-effectiveness studies favoured alemtuzumab. The two DMTs had very similar net balance of effects, but the safety profile of natalizumab was considered better as the risk of PML can be prognosticated and minimised. Alemtuzumab is associated with the broader suite of less severe but more frequent side effects.

Recommendation 3: Against (conditional recommendation): mitoxantrone (⊕◯◯◯), due to significant post-marketing surveillance safety concerns and long-term monitoring requirements.

Remark: The recommendation is conditional due to low and very low certainty of evidence.

Justification: The panel noted significant post-marketing surveillance safety concerns and long-term monitoring requirements with mitoxantrone, creating barriers to feasibility and acceptability. This recommendation was against mitoxantrone despite balance of effects probably favouring the intervention based on included studies, which did not include these post-marketing surveillance and safety concerns.

Summary of the Evidence. We retrieved 50 RCTs (36,541 participants in total) eligible for analysis (2). Twenty studies included only people with active relapsing MS. Twenty-six studies included a mixed population of people with active relapsing MS and lack of treatment response together with treatment-naive people. The proportion of people with previous lack of treatment response in these studies varied from 3% to 75% (median 33%). Separate results for people with previous lack of treatment response were not reported in studies and the inclusion criteria featured a number of different definitions for “allowed previous treatments” (more or less

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drug-specific and with different washout time windows, depending on the treatment). Such heterogeneity did not allow a meaningful data pooling of the population with previous lack of treatment response. Two small studies (88 participants in total) included people with non-active relapsing MS and in two other studies (240 participants in total) the relapsing MS phenotype was not reported. The panel agreed in considering that the evidence base the analysis found, including all retrieved RCTs, as representative of people with active relapsing MS.

Benefits. Among the desirable effects, disability worsening and frequency of relapse were assessed for most DMTs. Disability at 24 months assessed by means of the EDSS is the desirable effect on which most data were available, when considering placebo as the common comparator. All 18 DMTs with disability at 24 months data reported an absolute difference in favor of the intervention, with two notable exceptions: ozanimod and interferon beta products (beta 1a and 1b considered together), showing values in favor of placebo. However, such estimates need to be interpreted with caution, since both show a very low certainty due to imprecision (and also risk of bias for interferon beta products). In particular, the point estimate for interferon beta products, showing very wide confidence intervals (CIs), came from only indirect comparisons in the network evidence referring to two small studies (less than 250 participants in total) comparing beta interferons with azathioprine. Point estimates from studies directly comparing interferon beta 1a or beta 1b vs placebo, showed values in favor of the intervention. No study of DMTs vs placebo assessed disability at 36 months.

Relapse was assessed at 12 and 24 months for most DMTs, showing values in favor of the intervention. Considerations mentioned above on disability and the certainty of point estimates of beta interferon products, compared together vs. placebo, can be made about relapses. Direct evidence about the frequency of relapse at 36 months vs. placebo was available only for interferon beta 1b, with values favoring the intervention.

Data on MRI outcomes (new or enlarging T2-weigthed lesions and new gadolinium-enhancing positive T-1 weighted lesions) were available at 12 and 24 months. The majority of

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MRI estimates were available for DMTs compared to placebo relative to gadolinium-enhancing positive T1-weigthed lesions at 24 months. Most absolute point estimates were in favor of the intervention with some exceptions: for T2-weighted MRI lesions at 12 months most estimates came only from indirect evidence and wide loops in the network plot, with resulting very wide CIs and very low certainty mostly due to imprecision. Therefore, such values should be interpreted with caution.

Quality of life was assessed, by means of several different scales, for cladribine, teriflunomide, daclizumab, ozanimod and interferons beta 1b and 1a vs placebo, showing values in favor of the intervention. Cognitive decline was not assessed in any study comparing a DMT vs placebo. Therefore, no estimates on this outcome were available in the NMA.

Harms. Undesirable effects estimates were available for most DMTs, often showing wide CIs, including both, appreciable harm and appreciable benefit. Those on serious adverse events (SAEs) came mainly from direct comparisons vs placebo and were mostly in favor of placebo, except for a few DMTs (fingolimod, glatiramer acetate, interferon beta 1b and mitoxantrone). However, all point estimates showed wide CIs including appreciable harm and appreciable benefit, except daclizumab, showing a frequency of SAEs significantly higher than placebo. Notably, daclizumab was withdrawn from the market for safety issues. Predictably, the number of people discontinuing treatment due to adverse events was higher in the intervention group for almost all DMTs. Death, related to MS or to treatment with DMTs, is not expected to be a frequent event. In fact, all comparisons (direct and indirect) vs placebo were based on very few events, with small absolute differences and wide CIs.

Other EtD criteria. After assessment of certainty overall, the panel looked across all individual outcomes of all DMTs and considered whether there was less concern for imprecision, based on the trend in relation to certainty levels and direction of the individual outcomes. The panel decided to downgrade less for imprecision for the overall assessment for natalizumab, fingolimod and alemtuzumab. Regarding how much people value the outcomes

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considered, the panel judged there was probably no important uncertainty or variability in the value of any outcome without consideration of the HSUVs determined for each outcome.

For the balance of effects, the panel noted that the exact ranking of the DMTs should be interpreted with caution as this was based primarily on the net balance score. Medications with data for a greater number of outcomes had more contributions to the total benefit score and, thus, may be more likely to have a larger net benefit using this calculation method than medicines for which fewer outcomes were included in the score.

For resources required, the panel set the following thresholds compared to placebo, from a global perspective with a focus on LMICs and based on medium/minimum wage and health care expenditure in LMICs: (a) large costs: ≥$1000/year/patient; (b) moderate costs: ≥$100 - $999/year/patient; and (c) negligible/cost-savings: less than $100/year/patient. These thresholds were based on the experience of neurologists and people with MS on the Panel from low and lower-middle income countries, and the wider Panel accepted their judgement. Differences in cost between countries as well as the cost of generics and biosimilars (where costs for those could be ascertained) were also considered.

Based on these categories, DMTs were classified as follows: (a) large: interferon beta 1a, interferon beta 1b, natalizumab, fingolimod, siponimod, glatiramer acetate, rituximab, ocrelizumab; (b) moderate costs: azathioprine; and (c) negligible/cost-savings: methotrexate. To make the final judgements on resource requirements, the panel considered whether the additional costs such as infusion centers, storage requirements, and laboratory monitoring would change the judgements. It was concluded that they would only add more cost onto the 'large' costs, so the judgments remained the same.

For cost-effectiveness, we performed a systematic review of economic studies on available DMTs in the treatment of relapsing MS when compared to another active DMT or to no DMT, from any perspective published in 2012 or later. Fifty-one studies were selected, 36 of which were funded by the company producing the DMT assessed in the economic analysis with

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results invariably in favor of the drug (1). Only eight studies were performed outside of high-income countries. Alemtuzumab showed the highest number of comparisons vs other DMTs where it proved to be cost-effective. Such comparisons included several independent studies. Several studies suggested a superiority of cladribine over other DMTs in terms of cost-effectiveness, but they were all funded by the company producing the drug, and their results should be interpreted with caution. Similar considerations can be made for several other drugs, such as glatiramer acetate, interferon beta 1b, natalizumab, ocrelizumab, on which cost-effectiveness vs other alternatives has been assessed only by the company producing the drug. Of the six studies assessing the cost-effectiveness of treatment strategies, four were independent. Their results were inconsistent relative to the cost-effectiveness of oral agents.

Regarding equity, the panel noted that the following factors affect equity: cost/income, route of administration, access to healthcare facilities, storage, e.g. cold-chain requirements. However, frequency of administration needs to be carefully considered. For example, a twice annual infusion may be preferable and more equitable despite the infusion-related costs compared with a daily injectable medication requiring monthly refills and in-home refrigeration. Health equity considerations if not treated include direct costs of disability progression, unemployment, caring responsibilities for family, equipment and living arrangement modifications, not just cost of medicine. The panel judged 'reduced' equity for alemtuzumab and mitoxantrone. Both required extensive pre-tests and frequent monitoring. Alemtuzumab had high cost. Mitoxantrone had low cost, but had risk of very severe long-term health outcomes for patients, in addition to risks associated with their MS. The panel judged 'probably reduced' equity for natalizumab and ocrelizumab due to high cost and need to access healthcare facility for infusions. Natalizumab also requires JCV testing for PML. Cladribine and fingolimod were also judged as 'probably reduced', even though they are oral medications, due to contraindications in pregnancy. The monitoring and risk of rebound for fingolimod made it less equitable to dimethyl fumarate. Despite high cost similar to alemtuzumab, the monitoring

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requirements are considerably lower for cladribine than alemtuzumab. Interferon beta 1a, Interferon beta 1b, glatiramer acetate were considered to have 'probably no impact' due to safety in pregnancy, although they require regular injections and cold-chain. Dimethyl fumarate was judged as 'probably increased' as it is an oral medication with no cold-chain requirement, requires relatively little monitoring, is category B risk for pregnancy, and has an indication for pediatrics.

For acceptability, the panel considered on-label/off-label status, data regarding stopping the medication due to any cause, mode of administration, safety warnings, capacity to complete given safety monitoring in a low-resourced setting, and potential for disease rebound with supply interruptions. Natalizumab, fingolimod and dimethyl fumarate were judged 'probably yes' due to monitoring and side-effects causing people having to switch. Alemtuzumab was judged as 'probably yes' due to post-marketing safety warnings. Ocrelizumab and cladribine were both judged as 'yes'. Ocrelizumab was judged as 'yes' because its balance of effect is 'large'. Dropout data support fingolimod and ocrelizumab to be 'yes' rather than probably yes, but safety warnings and monitoring requirements for fingolimod places it in 'probably yes'. Mitoxantrone is no longer used in high-income countries due to post-marketing safety issues with cardiac toxicity and secondary cancers and leukemias. This may still be acceptable if other options are not available, but if other options exist, it is not used. Yearly echocardiogram needs to be done as the cardiac toxicity may be seen years later. The panel judged that acceptability of mitoxantrone was 'probably no' due to the toxicity noted in post-marketing evidence. The cost of all DMTs was considered large, so it did not help judgements on acceptability. Pregnancy safety issues should also be considered. Important to note, that in low-resource settings, any one DMT may be the only available option and people will still probably find it acceptable versus no treatment.

In considering feasibility, the panel noted that feasibility of implementation was affected by resource requirements, including cold chain requirements, healthcare infrastructure (e.g.

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infusion centers), on-label/off-label status (e.g. which may affect legality of prescribing a given medication), and access to pre-tests and monitoring (e.g. electrocardiogram and optical coherence tomography may only be available at national hospitals in some low-resource settings). As such, natalizumab and alemtuzumab were judged as 'varies' due to pre-tests and specialist care required. For alemtuzumab, even in high-income countries, not all clinics can administer it. For both, the amount of required monitoring is significant over a sustained period of time. Mitoxantrone was judged 'not feasible' due to the safety concerns, the required monitoring and the long-term monitoring. Concern for rebound effects in settings where medicine supply or access may be disrupted were raised for fingolimod and natalizumab, making them less feasible. All other DMTs were judged as 'probably yes'.

In regard to availability, the panel considered it across global settings surveyed in the MSIF atlas and using a threshold of 60 countries reporting use as "probably available." The panel did raise concern with this approach that concluding any of these DMTs are 'available' could be problematic as only 107 countries have provided data to the MSIF Atlas, and the ones not reporting are likely to be LMICs with poor availability. Ultimately, the panel made the following judgements: (1) Available in most settings: fingolimod, interferon beta-1a, interferon beta-1b; (2) Probably available in most settings: mitoxantrone; (3) Probably not available in most settings: alemtuzumab, cladribine, dimethyl fumarate; and (4) Varies: glatiramer acetate, ocrelizumab, natalizumab. The latter were judged as 'varies' as they were generally available in higher-income countries but not in low- and middle-income countries.

Other considerations. Due to the complexity of the NMAs, only randomized controlled-trials (RCTs) were assessed. There are a considerable number of non-randomized controlled studies that may also provide important insight into comparative effectiveness. In light of the complexity of the methodology, it was not feasible to systematically assess and consider these for the recommendations. Of note, rituximab was not considered in the RMS NMA because rituximab trials available at that time did not have outcomes meeting the pre-defined health

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outcome descriptors for this study. The panel also noted that different outcomes and different number of outcomes for desirable effects had been measured in the trials, and therefore the evidence between DMTs was not easy to compare.

The panel noted that for some DMTs no serious adverse events were reported due to data extraction having specific inclusion criteria. However, it is important to distinguish 'no data' from 'no serious adverse events'. All but ponesimod, azathioprine and pegylated-interferon have combined undesirable effects judged as ‘trivial’. Ponesimod, azathioprine and pegylated-interferon are rated as ‘small’. The panel also noted that only ‘discontinuation due to any cause’ were included in the net sum as also including ‘serious adverse events’ would have double-counted these events. Finally, the panel noted there were concerns with post-marketing surveillance from a safety standpoint. The panel noted that while the judgement of undesirable effects as ‘trivial’ is in line with the RCT data reviewed, this is not the view of clinical practice due to safety concerns that only came to light during post-marketing surveillance. A summary of extra safety considerations the panel discussed included: 1. Daclizumab and laquinomod are withdrawn from the market or were never approved by regulatory authorities. 2. Mitoxantrone: serious cardiac toxicity several years after use identified in post-marketing safety studies. 3. Alemtuzumab: use has been restricted by EMA following reports of rare but serious side effects, e.g. cardiovascular disorders and immune-related disorders in post-marketing safety studies. 4. Natalizumab: updated PML risk for JCV positive patients identified in post-marketing safety studies. 5. Fingolimod: rebound effect after treatment discontinuation and cardiovascular, liver and cancer risks identified in post-marketing safety studies.

Additional PICO questions. The panel initially decided to review evidence for active and worsening forms of relapsing MS, not active and not worsening forms of relapsing MS, and active and/or worsening forms of relapsing MS when there is a lack of treatment response to the current DMT. However, the systematic reviews either found only indirect evidence (not active and not worsening forms of relapsing MS) or no evidence (active and/or worsening forms of

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relapsing MS with lack of treatment response). It was decided that the evidence reviewed for active and/or worsening forms of relapsing MS could not be extrapolated to these populations, so the panel opted not to make any recommendations for these populations.

Progressive Forms of Multiple Sclerosis

Which DMTs should be available for the treatment of active and/or progressing forms of progressive MS in low-resource settings?

The full EtD table and the summary of judgements for all DMTs and all factors considered can be found online (1). Based on the balance of effects (Figure 1B) and the wider EtD framework, the MEMP guideline panel suggests:

Recommendation 1. For, in priority order (conditional recommendation): 1. rituximab (⊕◯◯◯), 2. glatiramer acetate (⊕◯◯◯), 3. ocrelizumab (⊕◯◯◯) 4. interferon beta 1a (l⊕⊕◯◯), 5. fingolimod (⊕⊕◯◯), 6. interferon beta 1b (⊕◯◯◯) for active and/or progressing progressive forms of MS.

Remark: The recommendation is conditional due to low and very low certainty of evidence.

Justification: Priority order was based both on the net balance for each medication but also on additional EtD considerations most relevant to low-resource settings as detailed here. Rituximab is a feasible and acceptable option in low-resource settings due to balance of effects, mode of administration (6-monthly infusions), low maintenance for screening and monitoring with low risk of rebound effect if treatment is discontinued, and low discontinuation rate, but requires infusion facilities and cold storage at the healthcare facility. Glatiramer acetate is a feasible and acceptable option in low-resource settings due to balance of effects, very low maintenance for screening and monitoring, but is less acceptable due to mode and frequency of

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administration (injection), and requirement of cold-storage by persons with MS. Ocrelizumab is a feasible and acceptable option in low-resource settings due to balance of effects, low maintenance for screening and monitoring, low discontinuation rate, mode of administration (6-monthly infusions), but requires infusion facilities and cold storage at the healthcare facility. It is less acceptable than rituximab due to significant cost of the medication. Interferons beta 1a and 1b are feasible and acceptable options in low-resource settings due to balance of effects, low maintenance for screening and monitoring, but are less acceptable due to mode and frequency of administration (injection), requirement of cold-storage by persons with MS and type of adverse events. Fingolimod is a feasible and acceptable option in low-resource settings due to balance of effects, mode of administration (oral), easy storage, but requires more maintenance for screening and monitoring, and has a risk of rebound of MS disease activity if access to treatment is discontinued suddenly, e.g., due to unreliable supply of medicine.

Recommendation 2. Either for or against (neutral recommendation, dependent on setting) in priority order (conditional recommendation): 1. siponimod (⊕⊕◯◯), 2. natalizumab (⊕◯◯◯), 3. immunoglobulins (⊕◯◯◯) for active and/or progressing progressive forms of MS.

Remark: The recommendation is conditional due to low and very low certainty of evidence. Additionally, the panel felt a recommendation either for or against these medicines for low-resource settings was appropriate, despite evidence of clinical benefit. Feasibility of pre-tests, monitoring requirements, cost and affordability are concerns limiting the application of these DMTs in some low-resource settings. Immunoglobulin use was noted to be rare even in high-income settings, with efforts to reduce demand for immunoglobulin in many countries.

Justification: Priority order was based both on the net balance for each medication but also on additional EtD considerations most relevant to low-resource settings as detailed here. The panel noted that the evidence on balance of the effects clearly favors siponimod and

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natalizumab. Despite the demonstrated benefit, the panel noted variable feasibility issues for low-resource settings in the access to and cost of pre-screening and monitoring required, e.g., for siponimod CYP2C9 genotyping and for natalizumab regular JCV testing and MRI monitoring for PML. These tests are essential for the safe use of these DMTs and not widely available in low-resource settings. It was noted that the high cost of medicines resulted in a significant budget impact. Natalizumab and siponimod were noted to be used routinely in high-income settings, whereas the use of immunoglobulin was rare.

Recommendation 3: For in priority order (conditional recommendation): 1. azathioprine (⊕○○○), 2. methotrexate (⊕○○○) in clinical settings where no alternative treatments are accessible for active and/or progressing progressive forms of MS.

Remark: This recommendation is conditional to other treatment options not being accessible due to the very low evidence-base available. Use in research settings may also be appropriate due to the need for higher quality evidence for these medicines, although trials with placebo would be considered unethical.

Justification: Azathioprine and methotrexate have a conditional recommendation for with a condition of no alternative DMTs being accessible, where the alternative would be no treatment. This condition was due to the evidence-base being very limited and more research would be required to ascertain effects of these DMTs in progressive forms of MS. The DMTs are oral treatments, widely available in health systems with a low cost, not requiring cold-chain, making them a feasible option in low-resource settings. The ranking is based on balance of effects.

Summary of Evidence. We retrieved 23 RCTs eligible for analysis (3), one of which reported no outcomes of interest (Etemadifar 2019). No study included only people with non-

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active disease or people with active progressive forms MS and lack of treatment response. Eighteen RCTs included only people with active progressive MS, 3 RCTs included a mixed population and, in 2 RCTs, the progressive MS phenotype was not reported.

We performed an overall analysis including all RCTs and a sensitivity analysis including only the 18 studies with active forms of PMS. However, such analysis could not include pivotal RCTs of treatments that were considered very important by the panel (among them the pivotal trial of the only DMT licensed for the treatment of primary progressive MS). Therefore, the panel agreed to consider as the evidence base the analysis including all retrieved RCTs. The resulting heterogeneity was considered acceptable by the panel, given the limited proportion (17%) of participants included in trials with a mixed population.

Benefits. Among the desirable effects, most studies assessed disability and relapse at 24 months. No study assessed cognitive decline. Disability at 24 and 36 months was reported in 11 and five studies, respectively. Point estimates were mostly in favor of the intervention compared to placebo. However, the certainty in such estimates was lowered by imprecision. Frequency of relapse was reported at 12, 24 and 36 months in one, six and four RCTs, respectively, with interferon-beta products and azathioprine providing estimates significantly better than placebo, although with moderate to very low certainty due to imprecision. Interferon-beta products, siponimod and fingolimod showed higher efficacy than placebo in regard to new gadolinium-enhancing T1-weighted MRI lesions and new or enlarging T2-weighted MRI lesions at 12, 24 and 36 months. Certainty in MRI outcomes was overall better than other outcomes due to lower imprecision of the point estimates. Quality of life was assessed in three RCTs on interferon-beta-1a, natalizumab and ocrelizumab, reporting point estimates favoring treatment vs placebo, although with moderate to low certainty due to imprecision.

Harms. Among the undesirable effects, SAEs were reported by 15 studies, while mortality and discontinuation due to adverse events were reported by 21 studies. For the latter, two studies reported no events in either arm and were excluded from analysis. Certainty of the

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evidence relative to SAEs was very low for most treatments, mainly due to imprecision of the estimates.

Other EtD Criteria. The panel used the same approach in assessing certainty overall as described for relapsing forms of MS and downgraded less for imprecision for the overall assessment for interferon beta-1a, siponimod and fingolimod. The panel noted similar concerns and judgements regarding values and balance of effects as for relapsing MS. Regarding resources required, the panel opted to use the same thresholds as for relapsing MS which resulted in the following judgements: (1) large (≥$1000/year/patient): interferon beta-1a, interferon beta-1b, natalizumab, fingolimod, siponimod, glatiramer acetate, rituximab, ocrelizumab; (2) moderate costs (≥$100 - $999/year/patient): azathioprine; (3) negligible/cost-savings (<$100/year/patient): methotrexate.

For cost-effectiveness, a systematic review of each available DMT in the treatment of progressive forms of MS when compared to another active DMT or no DMT which included all types of economic analysis. The search retrieved 5,235 references with 15 selected for full-text review and 7 studies ultimately included (1). All were performed in high-income countries except one that was developed in Peru, an upper middle-income country. Evidence on cost-effectiveness was only found for interferon, glatiramer acetate, ocrelizumab and siponimod. The studies on siponimod and the Peruvian study on interferon had risk of bias, as they were conducted by the pharmaceutical company or authors were employed by the company. The panel noted issues with inconsistency, variability and poor evidence-base. Generally, cost-effectiveness was found to be poor or acceptable for interferon, glatiramer acetate, and ocrelizumab. The only positive finding was for siponimod with active secondary progressive MS. The panel noted that the lack of studies is a remarkable limitation in our interpretations of true cost effectiveness. The panel also suggested that the evidence-base from the systematic review did not meet baseline requirements to be used for making judgements, and the cost-effectiveness of all DMTs were judged as 'varies'.

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The panel used the same considerations regarding equity from the discussions while making recommendations for relapsing forms of MS. When applied to progressive forms of MS, this resulted in the following judgements. Fingolimod, ocrelizumab, siponimod, natalizumab would probably reduce equity due to required pre-tests, monitoring, mode of administration, logistics and costs. The availability and cost of treatment were also considered. Glatiramer acetate, interferon beta-1a, interferon beta-1b, and methotrexate were judged as 'probably no impact' due to better availability, less pre-tests and monitoring requirements. The cold-storage and frequent injections were noted as barriers for interferon and glatiramer acetate. The panel judged that azathioprine and rituximab would 'probably increase' equity as they are already listed on the WHO Essential Medicines List (but not with an MS indication at the time the panel was reviewing the evidence) and many national essential medicine lists, thus increasing availability and feasibility. Azathioprine has recently been given an indication for use as a treatment for MS by the EMA (European Medicines Agency) (4). Their relatively low price was also noted. The panel judged immunoglobulin as likely to 'reduce' equity due to very high cost, poor access, difficulty in sourcing, and storage and cold-chain requirements.

For acceptability, the panel again used similar considerations as in the guidelines process for relapsing forms of MS. Again, the panel thought it was important to note that, in low-resource settings, any one DMT may be the only available option and people will still probably find it acceptable versus no treatment. Ultimately, the panel judged immunoglobulins as ‘probably no’ due to high cost, sourcing, storage and infusion requirements. All other DMTs were judged to be 'probably acceptable', with azathioprine and methotrexate 'acceptable' due to low cost, availability and oral mode of administration.

The panel used similar considerations to assess feasibility as during the relapsing MS guideline process with a specific emphasis on trying to separate feasibility from cost and arrived at the following judgements: (1) Yes: azathioprine, methotrexate; (3) Probably yes: fingolimod, ocrelizumab, rituximab, interferons, glatiramer acetate due to monitoring, infusion and cold-

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chain; (4) Varies: siponimod, natalizumab (monitoring, genetic screening, JCV/PML and cold-chain); (5) Probably no: immunoglobulins.

Using the MSIF Atlas data as discussed for relapsing forms of MS, the panel made the following judgements on availability: (1) Available in most settings: interferon beta-1a, interferon beta-1b, fingolimod, rituximab, azathioprine, methotrexate; (2) Probably not available in most settings: siponimod (due to its status as a newly approved on-label DMT), immunoglobulins; (3) Varies: glatiramer acetate, ocrelizumab, natalizumab (due to being primarily used in high-income countries versus low- and middle-income countries).

Other Considerations. Similar to relapsing MS, only RCTs were assessed due to complexity of the NMA methodology despite there being a considerable number of non-randomized studies that may also provide important insight to comparative effectiveness. The panel also noted that different outcomes and different number of outcomes for desirable effects had been measured in the trials making evidence between DMTs difficult to compare. As the understanding of PMS has evolved, trials have reported different outcomes. Furthermore, differences in trial design and being unable to include some outcomes in the NMA resulted in fewer outcomes being included for some DMTs compared to other DMTs. The panel also noted similar concerns regarding the assessment of harms as with relapsing MS. In particular, the panel noted extra safety considerations for natalizumab (i.e. updated PML risk for JCV+ individuals identified in post-marketing safety studies) and fingolimod (i.e. rebound effect with drug discontinuation and cardiovascular, liver and cancer risks identified in post-marketing safety studies).

Additional PICO questions. Similar to relapsing forms of MS, the panel also intended to review evidence for not active and not worsening forms of progressive MS and active and/or worsening forms of progressing MS when there is a lack of treatment response. However, the systematic reviews either found only indirect evidence (not active and not worsening forms of progressive MS) or no evidence (active and/or worsening forms of progressive MS with lack of

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treatment response). It was decided that the evidence reviewed for active and/or worsening forms of progressive MS could not be extrapolated to these populations, so the panel opted not to make any recommendations for these populations.

Figure 1. Summary table for balance of effects for relapsing forms (A) and progressive forms (B) of MS. DMTs that were selected by the panel and carried forward for full EtD analysis are highlighted in yellow. Full calculations of desirable and undesirable effects can be found in Supplemental file 1.

(A)

Rank	Intervention	# Outcomes	Certainty	Desirable Effects	Undesirable Effects	Net Balance	SumValue
1	Natalizumab	6	⊕⊕OO	Large Benefit	Trivial Harm	Large Benefit	0.2264
2	Alemtuzumab	5	⊕⊕OO	Large Benefit	Trivial Harm	Large Benefit	0.2092
3	Mitoxantrone	3	⊕OOO	Large Benefit	Trivial Harm	Large Benefit	0.2069
4	Interferon beta 1b	8	⊕OOO	Large Benefit	Trivial Harm	Large Benefit	0.2046
5	Fingolimod	5	⊕⊕OO	Large Benefit	Trivial Harm	Large Benefit	0.1960
6	Cladribine	6	⊕⊕OO	Large Benefit	Trivial Harm	Large Benefit	0.1662
7	Dimethylfumarate	5	⊕⊕OO	Large Benefit	Trivial Harm	Large Benefit	0.1643
8	Interferon beta 1a	8	⊕⊕OO	Large Benefit	Trivial Harm	Large Benefit	0.1445
9	Ocrelizumab	4	⊕OOO	Large Benefit	Trivial Harm	Large Benefit	0.1160
10	Daclizumab	8	⊕⊕OO	Large Benefit	Trivial Harm	Large Benefit	0.1144
11	Ponesimod	4	⊕OOO	Large Benefit	Small Harm	Large Benefit	0.1138
12	Glatiramer acetate	5	⊕OOO	Large Benefit	Trivial Harm	Large Benefit	0.0951
13	Ozanimod	6	⊕OOO	Large Benefit	Trivial Harm	Large Benefit	0.0890
14	Immunoglobulins	3	⊕OOO	Large Benefit	Trivial Harm	Large Benefit	0.0790
15	Teriflunomide	6	⊕OOO	Large Benefit	Trivial Harm	Large Benefit	0.0718
16	Azathioprine	3	⊕OOO	Large Benefit	Small Harm	Large Benefit	0.0640
17	Laquinimod	4	⊕OOO	Large Benefit	Trivial Harm	Large Benefit	0.0597
18	Pegylated Interferon	3	⊕OOO	Large Benefit	Small Harm	Moderate Benefit	0.0463
19	Ofatumumab	3	⊕OOO	Moderate Benefit	Trivial Harm	Moderate Benefit	0.0389

(B)

Summary of quantified desirable and undesirable effects – progressive forms of MS							
Rank	Intervention	# Outcomes	Certainty	Desirable Effects	Undesirable Effects	Net Balance	SumValue
1	Azathioprine	4	⊕OOO	Large Benefit	Trivial Harm	Large Benefit	0.1856
2	Siponimod	4	⊕⊕OO	Large Benefit	Trivial Harm	Large Benefit	0.0806
3	Methotrexate	3	⊕OOO	Large Benefit	Trivial Harm	Large Benefit	0.0755
4	Rituximab	4	⊕OOO	Moderate Benefit	Trivial Harm	Moderate Benefit	0.0529
5	Glatiramer acetate	3	⊕OOO	Moderate Benefit	Trivial Harm	Moderate Benefit	0.0459
6	Immunoglobulins	4	⊕OOO	Moderate Benefit	Trivial Harm	Small Benefit	0.0301
7	Natalizumab	4	⊕OOO	Moderate Benefit	Trivial Harm	Small Benefit	0.0300
8	Ocrelizumab	4	⊕OOO	Moderate Benefit	Trivial Harm	Small Benefit	0.0296
9	Interferon beta 1a	7	⊕⊕OO	Large Benefit	Moderate Harm	Small Benefit	0.0267
10	Fingolimod	3	⊕⊕OO	Moderate Benefit	Trivial Harm	Small Benefit	0.0209
11	Interferon beta 1b	4	⊕OOO	Moderate Benefit	Small Harm	Small Benefit	0.0162
12	Laquinimod	2	⊕OOO	Trivial Harm	Trivial Harm	Trivial Harm	-0.0086

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Supplemental file 3

Studies considered in evidence review – Relapsing MS (1)

1. **Achiron 1998** (2)
2. **ADVANCE 2014** (3–5)
3. **AFFIRM 2006** (6–9)
4. **ALLEGRO 2012** (10,11)
5. **ASCLEPIOS I 2020** (12)
6. **ASCLEPIOS II 2020** (12)
7. **ASSESS 2020** (13)
8. **BECOME 2009** (14–16)
9. **BEYOND 2009** (17,18)
10. **Bornstein 1987**(19)
11. **BRAVO 2014** (20)
12. **CAMMS223 2008** (21,22)
13. **CARE-MS I 2012** (23,24)
14. **CARE-MS II 2012** (24–26)
15. **CLARITY 2010** (27–33)
16. **CombiRx 2013** (34)
17. **CONCERTO 2021** (35,36)
18. **CONFIRM 2012** (37–42)
19. **DECIDE 2015** (43–49)
20. **DEFINE 2012** (41,42,50–54)
21. **Etemadifar 2006** (55)
22. **Etemadifar 2007** (56)
23. **Fazekas 1997** (57)
24. **FREEDOMS 2010** (58–63)
25. **FREEDOMS II 2014** (59,64)
26. **GALA 2013** (65–68)
27. **Gobbi 2013** (69,70)
28. **GOLDEN 2017** (71)
29. **Goodkin 1991** (72)
30. **IFNB MS Group 1993** (73)
31. **INCOMIN 2002** (74)
32. **Johnson 1995** (75)
33. **Knobler 1993** (76)
34. **Koch-Henriksen 2006** (77)
35. **Lewanska 2002** (78)
36. **MAIN TRIAL** (79)
37. **Millefiorini 1997** (80)
38. **Mokhber 2014** (81,82)
39. **MSCRG 1996** (83)
40. **OPERA I 2017** (84–87)
41. **OPERA II 2017** (84–87)
42. **OPTIMUM 2021**(88)
43. **PRISMS 1998** (89,90)
44. **RADIANCE 2019** (91,92)

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45. **REGARD 2008** (93)
46. **SELECT 2013** (49,94–99)
47. **SUNBEAM 2019** (100–102)
48. **TEMSO 2011** (103–107)
49. **TOWER 2014** (108–112)
50. **TRANSFORMS 2010** (113–117)

Studies considered in evidence review – Progressive MS (118)

1. **Anderson 2004** (119)
2. **ARPEGGIO 2020** (120)
3. **ASCEND 2018** (121)
4. **Bornstein 1991** (122)
5. **Cheshmavar 2020** (123)
6. **Ellison 1989** (124)
7. **Etemadifar 2019** (125)
8. **European Study Group 1998** (126)
9. **EXPAND 2018** (127,128)
10. **Goodkin 1995** (129)
11. **Hawker 2009** (130)
12. **Hommes 2004** (131)
13. **IMPACT 2002** (132)
14. **INFORMS 2016** (133,134)
15. **Komori 2016** (135)
16. **Leary 2003** (136)
17. **Montalban 2009** (137)
18. **NASP 2004** (138)
19. **ORATORIO 2017** (86,139–141)
20. **Pöhlau 2007** (142)
21. **PROMESS 2017** (143)
22. **SPECTRIMS 2001** (144)
23. **Wolinsky 2007** (145)

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