ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The Atlas of MS estimates there are 2.8 million people living with MS (pwMS). 85% of these are initially diagnosed with relapsing forms of MS (RMS). There is unequal access to disease-modifying therapies (DMTs) globally, with 14% of countries not having access to any on-label DMTs. Low income countries (LICs), lower middle income countries (LMICs) and upper middle income countries (UMICs) are affected more than high income countries (HICs) by lack of access to DMTs . Evidence for both on-label and off-label DMTs should be considered when considering essential medicines for MS. PICO 1: The Panel decided to review DMTs for active and/or worsening forms of relapsing MS to consider the most appropriate treatment approach. PICO 2: The Panel decided to review DMTs for not active and not worsening or indeterminate forms of relapsing MS to consider the most appropriate treatment approach. PICO 3: The Panel decided to review DMTs for active and/or worsening forms of relapsing MS when there is a lack of treatment response to consider the most appropriate treatment approach. Panel members with COI for DMTs reviewed for RMS: Anthony Traboulsee, Jagannadha Avasarala, Carlos Navas, Maya Zeineddine, Riley Bove, Dina Jacobs, Shanthi Viswanathan, Bassem Yamout, Kathy Costello. Undetermined COI: Hans-Peter Hartung.	

Desirable Effects

How substantial are the desirable anticipated effects for each intervention?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Trivial: **Small:** **Moderate:** **Large:** Interferon beta 1a, Natalizumab, Dimethylfumarate, Alemtuzumab, Ocrelizumab, Cladribine, Mitoxantrone, Fingolimod, Interferon beta 1b, Glatiramer acetate **Varies:** **Don't know:**	The evidence base on disease-modifying treatments (DMTs) for relapsing multiple sclerosis (RMS) was retrieved through a systematic review of the biomedical literature developed according to the Cochrane methodology. The search was performed on February 11, 2022. Included studies were randomised-controlled trials (RCTs). Thirty treatments (with registered indications for MS, as well as non-licensed but used off-label in clinical practice), compared vs placebo or vs any other DMT, were included in a network metanalysis (NMA). Direct, pairwise comparisons were assessed assuming placebo as the common comparator, a choice that inevitably resulted in not including in the analysis comparisons with active comparator. However, in the NMA, estimates from indirect comparisons included also such evidence, provided that a comparison with placebo was included in the loop. An alternative NMA featuring interferon beta 1a as the common comparator, given its higher relevance than placebo in current clinical practice, was performed by the evidence review team upon request by MEMP. However, the panel concluded that choosing placebo as the common comparator allowed a more comprehensive assessment. Among people with RMS, three populations were identified by MEMP: with active RMS, with non-active RMS and with active RMS when there is a lack of treatment response (switching). We retrieved 50 RCTs (36,541 participants in total) eligible for analysis. Twenty studies included only people with active RMS. Twenty-six studies included a mixed population of people with active RMS 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 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 RMS and in two other studies (240 participants in total) the RMS	Due to the complexity of the network meta-analysis, only randomised controlled-trials (RCTs) were assessed. There is a considerable number of non-randomised controlled studies that may also provide important insight to comparative effectiveness. In light of the complexity of the methodology, it was not feasible to systematically assess and consider these for the recommendations. The panel 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. Outcome selection can have a significant impact on the calculated balance of effects. The panel noted that the effect of ocrelizumab on relapse reduction, shown in two large trials versus interferon beta 1a, has not been included in this analysis as the outcome measure, Annualised Relapse Rate (ARR), was not selected as the panel's measure of relapses. The effect of ofatumumab on relapses was not measured for the same reason. The panel noted that the evidence is indirect for non-active populations and when switching due to lack of treatment response,. The panel agreed to not consider the following results: - For relapse 12 months, treatment with a mix of interferon beta 1a and 1b, the results show values that suggests more relapses. The issue can be illustrated from the network plot. The effect is *indirect* via azathioprine and the confidence intervals are very wide. There is very high imprecision. Similar issue for 24 months relapse. The trials do not report which interferon product the patients were on. The trials are small: one study has 47 patients for each arm and the other has 70 to 76 patients in each arm. The panel decided to remove this intervention as the concept of ‘interferon products’ may not be an appropriate intervention as the interferon beta 1a and 1b show different profiles. The evidence for either 1a or 1b have much larger trials and some *direct* evidence as well. - For the outcome new or enlarging T2-weighted MRI lesions at 12 months, there are very few direct comparisons, but a wide and open NMA loop (GA-fingolimod - ifn beta 1b – immunoglobulin – ifn beta 1a - placebo). Fingolimod and GA show more T2 weighted-lesions at 12 months. The confidence intervals are very wide. These off-scale confidence intervals are also seen for interferon beta 1b and natalizumab. The panel decided to disregard this outcome from analysis. The panel noted that confidence intervals were again very wide for the very

	phenotype was not reported. The panel agreed in considering as the evidence base the analysis including all retrieved RCT as representative of people with active RMS. 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 favour of the intervention, with two notable exceptions: ozanimod and interferon beta products (beta 1a and 1b considered together), showing values in favour 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 CIs, came from only indirect comparisons in the network evidence (see network plot), 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 favour 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 favour 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 (see "Additional Considerations"). Direct evidence about the frequency of relapse at 36 months vs. placebo was available only for interferon beta 1b, with values favouring 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 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 favour 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 (see "Additional Considerations"). **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 favour of the intervention. **Cognitive decline** was assessed in no study comparing a DMT vs placebo, therefore no estimates on this outcome were available in the NMA.	small studies.

Estimates of effects, credible intervals, and certainty of the evidence for comparison immunomodulators and immunosuppressants for relapsing multiple sclerosis

Frequentist NMA-SoF table

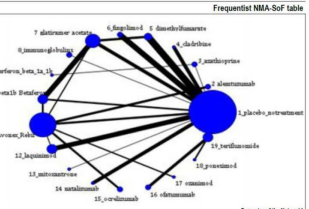
Patient or population: Patients with RMS

Interventions: alemtuzumab, azathioprine, cladribine, dimethylfumarate, fingolimod, glatiramer acetate, immunoglobulins , interferon beta 1a -1b, interferon beta1b (Betaferon), interferon beta1a (Avonex, Rebif), laquinimod, mitoxantrone, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, teriflunomide

Comparator (reference): Placebo

Outcome: Disability at 24 months

Setting(s): Outpatient



Geometry of the Network*

Total studies: Total Participants:	Relative effect** (95% CI)	Anticipated absolute effect*** (95% CI)			Certainty of the evidence	Ranking	Interpretation of Findings
		With Placebo	*With* intervention	Difference			
Alemtuzumab No Direct evidence	**RR 0.67** (0.46 to 0.99)	**188 per 1,000**	**126 per 1,000**	**62 fewer per 1.000** (from 101 fewer to 2 fewer)	⊕⊕◯◯ Low Due to Imprecision[1]		
Azathioprine (Direct evidence; 1 RCT; 59 participants)	**RR 0.60** (0.22 to 1.63)	**188 per 1,000**	**113 per 1,000**	**75 fewer per 1.000** (from 146 fewer to 118 more)	⊕◯◯◯ Very low Due to Imprecision[2]		
Cladribine (Direct evidence; 1 RCT; 1326 participants)	**RR 0.72** (0.56 to 0.91)	**188 per 1,000**	**135 per 1,000**	**53 fewer per 1.000** (from 83 fewer to 17 fewer)	⊕⊕◯◯ Low Due to Imprecision[3]		
Dimethylfumarate (Direct evidence; 2 RCT; 2307 participants)	**RR 0.65** (0.55 to 0.77)	**188 per 1,000**	**122 per 1,000**	**66 fewer per 1.000** (from 84 fewer to 43 fewer)	⊕⊕◯◯ Low Due to Imprecision and Risk of Bias[4]		
Fingolimod (Direct evidence; 2 RCT; 2355 participants)	**RR 0.68** (0.56 to 0.83)	**188 per 1,000**	**128 per 1,000**	**60 fewer per 1.000** (from 83 fewer to 32 fewer)	⊕⊕◯◯ Low Due to Imprecision and Risk of Bias[5]		
Glatiramer acetate (Direct evidence; 3 RCT; 1014 participants)	**RR 0.74** (0.61 to 0.89)	**188 per 1,000**	**139 per 1,000**	**49 fewer per 1.000** (from 73 fewer to 21 fewer)	⊕◯◯◯ Very Low Due to Imprecision and Risk of Bias[6]		
Immunoglobulins (Direct evidence; 2 RCT; 190 participants)	**RR 0.75** (0.41 to 1.37)	**188 per 1,000**	**141 per 1,000**	**47 fewer per 1.000** (from 111 fewer to 69 more)	⊕◯◯◯ Very Low Due to Imprecision[7]		
Interferon beta 1a -1b No direct evidence	**RR 3.19** (0.31 to 33.21)	**188 per 1,000**	**599 per 1,000**	**411 more per 1.000** (from 130 fewer to 1.000 more)	⊕◯◯◯ Very Low Due to Imprecision and Risk of Bias[8]		
Interferon beta 1b (Betaferon) (Direct evidence; 1 RCT; 372 participants)	**RR 0.77** (0.62 to 0.94)	**188 per 1,000**	**145 per 1,000**	**43 fewer per 1.000** (from 71 fewer to 11 fewer)	⊕⊕◯◯ Low Due to Imprecision[9]		
Interferon beta 1a (Avonex, Rebif) (Direct evidence; 2 RCT; 1069 participants)	**RR 0.92** (0.73 to 1.16)	**188 per 1,000**	**173 per 1,000**	**15 fewer per 1.000** (from 51 fewer to 30 more)	⊕⊕◯◯ Low Due to Imprecision[10]		
Laquinimod (Direct evidence; 3 RCT; 3451 participants)	**RR 0.78** (0.63 to 0.96)	**188 per 1,000**	**146 per 1,000**	**41 fewer per 1.000** (from 69 fewer to 8 fewer)	⊕◯◯◯ Very Low Due to Imprecision and Risk of bias[11]		
Mitoxantrone (Direct evidence; 1 RCT; 51 participants)	**RR 0.20** (0.05 to 0.83)	**188 per 1,000**	**38 per 1,000**	**150 fewer per 1.000** (from 178 fewer to 32 fewer)	⊕◯◯◯ Very Low Due to Imprecision and Risk of Bias[12]		
Natalizumab (Direct evidence; 1 RCT; 942 participants)	**RR 0.59** (0.46 to 0.75)	**188 per 1,000**	**111 per 1,000**	**77 fewer per 1.000** (from 101 fewer to 47 fewer)	⊕⊕⊕◯ Moderate Due to Imprecision[13]		
Ocrelizumab No direct evidence	**RR 0.61** (0.41 to 0.90)	**188 per 1,000**	**115 per 1,000**	**73 fewer per 1.000** (from 111 fewer to 19 fewer)	⊕◯◯◯ Very Low Due to Imprecision and Risk of Bias[14]		
Ofatumumab No direct evidence	**RR 0.54** (0.38 to 0.77)	**188 per 1,000**	**101 per 1,000**	**86 fewer per 1.000** (from 116 fewer to 43 fewer)	⊕◯◯◯ Very Low Due to Imprecision and Risk of Bias[15]		
Ozanimod No direct evidence	**RR 1.19** (0.74 to 1.91)	**188 per 1,000**	**223 per 1,000**	**6 more per 1.000** (from 49 fewer to 171 more)	⊕◯◯◯ Very Low Due to Imprecision[16]		
Ponesimod No direct evidence	**RR 0.63** (0.41 to 0.96)	**188 per 1,000**	**118 per 1,000**	**69 fewer per 1.000** (from 111 fewer to 8 fewer)	⊕◯◯◯ Very Low Due to Imprecision and Risk of Bias[17]		
Teriflunomide (Direct evidence; 1 RCT; 1088 participants)	**RR 0.76** (0.61 to 0.95)	**188 per 1,000**	**143 per 1,000**	**45 fewer per 1.000** (from 73 fewer to 9 fewer)	⊕◯◯◯ Very Low Due to Imprecision and Risk of Bias[18]		
Placebo	Reference Comparator	No estimable	No estimable	No estimable	Reference Comparator		

NMA-SoF table definitions

* Solid lines represent direct comparisons

** Network Meta-analysis estimates are reported as risk ratio. CI: confidence interval.

*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

GRADE Working Group grades of evidence (or certainty in the evidence)

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnote

1 Absolute observed point estimate falls in the moderate positive effect, 95% CI range from moderate positive effect to trivial positive: downgraded two levels.

2 Absolute observed point estimate falls in the moderate positive effect, 95% CI range from large positive effect to large negative effect: downgraded three levels

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Estimates of effects, credible intervals, and certainty of the evidence for comparison immunomodulators and immunosuppressants for relapsing multiple sclerosis

Frequentist NMA-SoF table

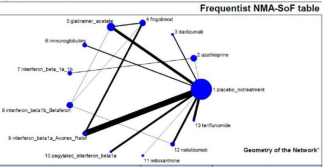
Patient or population: Patients with RMS

Interventions: Azathioprine, daclizumab, fingolimod, glatiramer acetate, Immunoglobulins, interferon beta 1a -1b, interferon beta1b (Betaferon), interferon beta1a (Avonex, Rebif), pegylated interferon beta1a, mitoxantrone, natalizumab, teriflunomide

Comparator (reference): Placebo

Outcome: Relapse at 12 months

Setting(s): Outpatient



Geometry of the Network*

Total studies: Total Participants:	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CrI)			Certainty of the evidence	Ranking	Interpretation of Findings
		With Placebo	*With* intervention	Difference			
Azathioprine (Direct evidence; 1 RCT; 59 participants)	**RR 0.91** (0.58 to 1.43)	**412 per 1,000**	**375 per 1,000**	**37 fewer per 1,000** (from 173 fewer to 177 more)	⊕◯◯◯ Very Low Due to Imprecision[1]		
Daclizumab (Direct evidence; 1 RCT; 621 participants)	**RR 0.55** (0.42 to 0.73)	**412 per 1,000**	**227 per 1,000**	**185 fewer per 1,000** (from 239 fewer to 111 fewer)	⊕⊕⊕◯ Moderate Due to Imprecision[2]		
Fingolimod No direct evidence	**RR 0.48** (0.39 to 0.57)	**412 per 1,000**	**198 per 1,000**	**214 fewer per 1,000** (from 251 fewer to 177 fewer)	⊕⊕⊕◯ Moderate Due to Risk of bias[3]		
Glatiramer acetate (Direct evidence; 2 RCTs; 1454 participants)	**RR 0.64** (0.55 to 0.75)	**412 per 1,000**	**264 per 1,000**	**148 fewer per 1,000** (from 185 fewer to 103 fewer)	⊕⊕◯◯ Low Due to Imprecision and risk of bias[4]		
Immunoglobulins (Direct evidence; 2 RCT; 91 participants)	**RR 0.60** (0.47 to 0.79)	**412 per 1,000**	**247 per 1,000**	**165 fewer per 1,000** (from 218 fewer to 87 fewer)	⊕⊕⊕◯ Moderate Due to Imprecision[2]		
Interferon beta 1a -1b No direct evidence	**RR 1.42** (0.78 to 2.60)	**412 per 1,000**	**585 per 1,000**	**173 more per 1,000** (from 91 fewer to 659 more)	⊕◯◯◯ Very Low Due to Imprecision and Risk of bias[5]		
Interferon beta 1b (Betaferon) No direct evidence	**RR 0.82** (0.50 to 1.33)	**412 per 1,000**	**338 per 1,000**	**74 fewer per 1,000** (from 206 fewer to 136 more)	⊕◯◯◯ Very Low Due to Imprecision and Risk of bias[6]		
Interferon beta 1a (Avonex, Rebif) (Direct evidence; 1 RCT; 560 participants)	**RR 0.76** (0.68 to 0.85)	**412 per 1,000**	**313 per 1,000**	**99 fewer per 1,000** (from 132 fewer to 62 fewer)	⊕⊕◯◯ Low Due to Imprecision[7]		
Pegylated interferon beta1a (Direct evidence; 1 RCT; 1512 participants)	**RR 0.68** (0.56 to 0.82)	**412 per 1,000**	**280 per 1,000**	**132 fewer per 1,000** (from 181 fewer to 74 fewer)	⊕⊕◯◯ Low Due to Imprecision and Risk of bias[8]		
Mitoxantrone (Direct evidence; 1 RCT; 51 participants)	**RR 0.40** (0.21 to 0.74)	**412 per 1,000**	**165 per 1,000**	**247 fewer per 1,000** (from 326 fewer to 107 fewer)	⊕⊕◯◯ Low Due to Imprecision and Risk of bias[9]		
Natalizumab (Direct evidence; 1 RCT; 942 participants)	**RR 0.52** (0.43 to 0.63)	**412 per 1,000**	**214 per 1,000**	**198 fewer per 1,000** (from 235 fewer to 152 fewer)	⊕⊕⊕⊕ High		
Teriflunomide (Direct evidence; 1 RCT, 1169 participants)	**RR 0.66** (0.55 to 0.78)	**412 per 1,000**	**272 per 1,000**	**140 fewer per 1,000** (from 185 fewer to 91 fewer)	⊕⊕◯◯ Low Due to Imprecision and Risk of bias[8]		
Placebo	Reference Comparator	No estimable	No estimable	No estimable	Reference Comparator		

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Estimates of effects, credible intervals, and certainty of the evidence for comparison immunomodulators and immunosuppressants for relapsing multiple sclerosis

Frequentist NMA-SoF table

Patient or population: Patients with RMS

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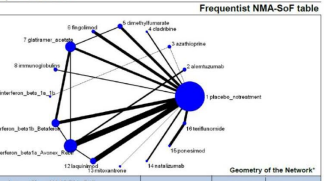
Comparator (reference): Placebo

Outcome: Relapse at 24 months

Setting(s): Outpatient



Geometry of the Network*

Total studies: Total Participants:	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CrI)			Certainty of the evidence	Ranking	Interpretation of Findings
		With Placebo	*With* intervention	Difference			
Alemtuzumab No direct evidence	**RR 0.57** (0.47 to 0.68)	**510 per 1,000**	**291 per 1,000**	**219 fewer per 1,000** (from 270 fewer to 163 fewer)	⊕⊕⊕⊕ High		
Azathioprine (Direct evidence; 1 RCT; 59 participants)	**RR 0.77** (0.51 to 1.18)	**510 per 1,000**	**392 per 1,000**	**117 fewer per 1,000** (from 250 fewer to 92 more)	⊕◯◯◯ Very Low Due to Imprecision[1]		
Cladribine (Direct evidence; 1 RCT; 1326 participants)	**RR 0.53** (0.44 to 0.64)	**510 per 1,000**	**270 per 1,000**	**240 fewer per 1,000** (from 285 fewer to 183 fewer)	⊕⊕⊕⊕ High		
Dimethylfumarate (Direct evidence; 2 RCTs; 2307 participants)	**RR 0.62** (0.55 to 0.70)	**510 per 1,000**	**316 per 1,000**	**194 fewer per 1,000** (from 229 fewer to 153 fewer)	⊕⊕⊕◯ Moderate Due to Risk of bias[2]		
Fingolimod (Direct evidence; 2 RCTs; 2355 participants)	**RR 0.54** (0.48 to 0.60)	**510 per 1,000**	**275 per 1,000**	**234 fewer per 1,000** (from 265 fewer to 204 fewer)	⊕⊕⊕◯ Moderate Due to Risk of bias[3]		
Glatiramer acetate (Direct evidence; 3 RCsT; 1014 participants)	**RR 0.84** (0.76 to 0.93)	**510 per 1,000**	**428 per 1,000**	**82 fewer per 1,000** (from 122 fewer to 36 fewer)	⊕⊕⊕◯ Moderate Due to Imprecision[4]		
Immunoglobulins (Direct evidence; 2 RCTs; 192 participants)	**RR 0.73** (0.59 to 0.90)	**510 per 1,000**	**372 per 1,000**	**138 fewer per 1,000** (from 209 fewer to 51 fewer)	⊕⊕◯◯ Low Due to Imprecision[5]		
Interferon beta 1a -1b No direct evidence	**RR 1.21** (0.66 to 2.19)	**510 per 1,000**	**617 per 1,000**	**107 more per 1,000** (from 173 fewer to 607 more)	⊕◯◯◯ Very Low Due to Imprecision and Risk of bias[6]		
Interferon beta 1b (Betaferon) (Direct evidence; 1 RCT; 372 participants)	**RR 0.85** (0.76 to 0.94)	**510 per 1,000**	**433 per 1,000**	**76 fewer per 1,000** (from 122 fewer to 31 fewer)	⊕⊕◯◯ Low Due to Imprecision[6]		
Interferon beta 1a (Avonex, Rebif) (Direct evidence; 3 RCTs; 1629 participants)	**RR 0.84** (0.78 to 0.91)	**510 per 1,000**	**428 per 1,000**	**82 fewer per 1,000** (from 112 fewer to 46 fewer)	⊕⊕⊕◯ Moderate Due to Imprecision[7]		
Laquinimod (Direct evidence; 3 RCTs; 3457 participants)	**RR 0.83** (0.76 to 0.91)	**510 per 1,000**	**423 per 1,000**	**87 fewer per 1,000** (from 122 fewer to 46 fewer)	⊕⊕◯◯ Low Due to Imprecision and Risk of bias[8]		
Mitoxantrone (Direct evidence; 1 RCT; 51 participants)	**RR 0.47** (0.27 to 0.80)	**510 per 1,000**	**240 per 1,000**	**270 fewer per 1,000** (from 372 fewer to 102 fewer)	⊕⊕◯◯ Low Due to Imprecision and Risk of bias[9]		
Natalizumab (Direct evidence; 1 RCT; 942 participants)	**RR 0.56** (0.48 to 0.65)	**510 per 1,000**	**285 per 1,000**	**224 fewer per 1,000** (from 265 fewer to 178 fewer)	⊕⊕⊕⊕ High		
Ponesimod No direct evidence	**RR 0.58** (0.48 to 0.70)	**510 per 1,000**	**296 per 1,000**	**214 fewer per 1,000** (from 265 fewer to 153 fewer)	⊕⊕⊕◯ Moderate Due to Risk of bias[2]		
Teriflunomide (Direct evidence; 1 RCT; 1088 participants)	**RR 0.82** (0.71 to 0.94)	**510 per 1,000**	**418 per 1,000**	**92 fewer per 1,000** (from 148 fewer to 31 fewer)	⊕◯◯◯ Very Low Due to Imprecision and Risk of bias[10]		
Placebo	Reference Comparator	No estimable	No estimable	No estimable	Reference Comparator		

NMA-SoF table definitions
* Solid lines represent direct comparisons
** Network Meta-analysis estimates are reported as risk ratio. CI: confidence interval.
*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

GRADE Working Group grades of evidence (or certainty in the evidence)
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes
1 Absolute observed point estimate falls in the large positive effect, 95% CI range from large positive effect to moderate negative effect: downgraded three levels.
2 Downgraded one level for risk of bias.
3 Absolute observed point estimate falls in the moderate positive effect, 95% CI range from moderate positive effect to small positive effect: downgraded one level.
4 Absolute observed point estimate falls in the large positive effect, 95% CI range from large positive effect to small positive effect: downgraded two levels.
5 Absolute observed point estimate falls in the moderate negative effect, 95% CI range from large positive effect to large negative effect: downgraded three levels. Further downgraded one level for risk of bias.
6 Absolute observed point estimate falls in the moderate positive effect, 95% CI range from moderate positive effect to trivial positive effect: downgraded two levels.
7 Absolute observed point estimate falls in the moderate positive effect, 95% CI range from moderate positive effect to small positive effect: downgraded one level.
8 Absolute observed point estimate falls in the moderate positive effect, 95% CI range from moderate positive effect to small positive effect: downgraded one level. Further downgraded one level for risk of bias.
9 Absolute observed point estimate falls in the large positive effect, 95% CI range from large positive effect to moderate positive effect: downgraded one level. Further downgraded one level for risk of bias.
10 Absolute observed point estimate falls in the moderate positive effect, 95% CI range from large positive effect to trivial positive effect: downgraded three levels. Further downgraded one level for risk of bias.

Estimates of effects, credible intervals, and certainty of the evidence for comparison immunomodulators and immunosuppressants for relapsing multiple sclerosis

Frequentist NMA-SoF table

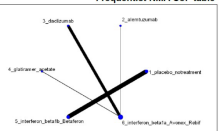
Patient or population: Patients with RMS

Interventions: interferon beta 1b (Betaferon)

Comparator (reference): Placebo

Outcome: Relapse at 36 months

Setting(s): Outpatient



Geometry of the Network*

Total studies: Total Participants:	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CrI)			Certainty of the evidence	Ranking	Interpretation of Findings
		With Placebo	*With intervention*	Difference			
Interferon beta 1b (Betaferon) (Direct evidence; 2 RCTs, 403 participants)	**RR 0.86** (0.67 to 1.11)	**862 per 1,000**	**741 per 1,000**	**121 fewer per 1,000** (from 284 fewer to 95 more)	⊕○○○ Very Low Due to Imprecision[1]		
Placebo	Reference Comparator	No estimable	No estimable	No estimable	Reference Comparator		

NMA-SoF table definitions
* Solid lines represent direct comparisons
** Network Meta-analysis estimates are reported as risk ratio. CI: confidence interval.
*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

GRADE Working Group grades of evidence (or certainty in the evidence)
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
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Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes
1 Absolute observed point estimate falls in the moderate positive effect, 95% CI range from large positive effect to moderate negative effect: downgraded three levels.

Estimates of effects, credible intervals, and certainty of the evidence for comparison immunomodulators and immunosuppressants for progressive multiple sclerosis

Frequentist NMA-SoF table

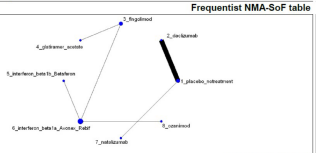
Patient or population: Patients with RMS

Interventions:

Comparator (reference): Placebo

Outcome: New gadolinium-enhancing positive T1-weighted MRI lesions 12 months

Setting(s): Outpatient



Geometry of the Network*

Total studies: Total Participants:	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CrI)			Certainty of the evidence	Ranking	Interpretation of Findings
		With Placebo	*With intervention*	Difference			
Daclizumab (Direct evidence; 1 RCT, 621 participants)	**RR 1.00** (0.97 to 1.04)	**956 per 1,000**	**956 per 1,000**	**0 fewer per 1,000** (from 29 fewer to 38 more)	⊕⊕⊕○ Moderate Due to Imprecision[1]		
Natalizumab (Direct evidence; 1 RCT, 942 participants)	**RR 0.11** (0.07 to 0.17)	**324 per 1,000**	**36 per 1,000**	**288 fewer per 1,000** (from 301 fewer to 269 fewer)	⊕⊕⊕⊕ High		
Placebo	Reference Comparator	No estimable	No estimable	No estimable	Reference Comparator		

NMA-SoF table definitions
* Solid lines represent direct comparisons
** Network Meta-analysis estimates are reported as risk ratio. CI: confidence interval.
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Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes
1 Absolute observed point estimate is null, 95% CI range from trivial positive effect to trivial negative effect: downgraded one level.

Estimates of effects, credible intervals, and certainty of the evidence for comparison immunomodulators and immunosuppressants for progressive multiple sclerosis

Frequentist NMA-SoF table

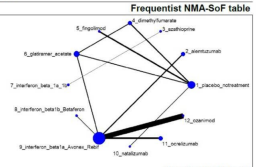
Patient or population: Patients with RMS

Interventions: Alemtuzumab, Dimethylfumarate,Fingolimod, Glatiramer acetate, Interferon beta1b (Betaferon), Interferon beta1a (Avonex, Rebif), Natalizumab, Ocrelizumab, Ozanimod

Comparator (reference): Placebo

Outcome: New gadolinium-enhancing positive T1-weighted MRI lesions 24 months

Setting(s): Outpatient



Geometry of the Network*

Total studies: Total Participants:	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CrI)			Certainty of the evidence	Ranking	Interpretation of Findings
		With Placebo	*With intervention*	Difference			
Alemtuzumab No direct evidence	**RR 0.13** (0.08 to 0.23)	**329 per 1,000**	**43 per 1,000**	**286 fewer per 1,000** (from 302 fewer to 253 fewer)	⊕⊕⊕○ Moderate Due to Risk of bias[1]		
Dimethylfumarate (Direct evidence; 1 RCT, 435 participants)	**RR 0.50** (0.37 to 0.69)	**329 per 1,000**	**164 per 1,000**	**164 fewer per 1,000** (from 207 fewer to 102 fewer)	⊕⊕○○ Low Due to Imprecision and Risk of Bias[2]		
Fingolimod Direct evidence; 1 RCT, 1044 participants)	**RR 0.29** (0.23 to 0.38)	**329 per 1,000**	**95 per 1,000**	**233 fewer per 1,000** (from 253 fewer to 204 fewer)	⊕⊕○○ Low Due to Imprecision and Risk of Bias[3]		
Glatiramer acetate (Direct evidence; 1 RCT, 305 participants)	**RR 0.59** (0.42 to 0.84)	**329 per 1,000**	**194 per 1,000**	**135 fewer per 1,000** (from 191 fewer to 53 fewer)	⊕○○○ Very low Due to Imprecision and Risk of Bias[4]		
Interferon beta 1b (Betaferon) No direct evidence	**RR 0.16** (0.08 to 0.31)	**329 per 1,000**	**53 per 1,000**	**276 fewer per 1,000** (from 302 fewer to 227 fewer)	⊕⊕○○ Low Due to Imprecision and Risk of Bias[5]		
Interferon beta 1a (Avonex, Rebif) No direct evidence	**RR 0.34** (0.21 to 0.55)	**329 per 1,000**	**112 per 1,000**	**217 fewer per 1,000** (from 260 fewer to 148 fewer)	⊕⊕○○ Low Due to Imprecision and Risk of Bias[6]		
Natalizumab Direct evidence; 1 RCT, 942 participants)	**RR 0.11** (0.07 to 0.17)	**329 per 1,000**	**36 per 1,000**	**293 fewer per 1,000** (from 306 fewer to 273 fewer)	⊕⊕⊕⊕ High		
Ocrelizumab No direct evidence	**RR 0.09** (0.05 to 0.16)	**329 per 1,000**	**30 per 1,000**	**299 fewer per 1,000** (from 312 fewer to 276 fewer)	⊕⊕⊕○ Moderate Due to Risk of bias[1]		
Ozanimod No direct evidence	**RR 0.30** (0.18 to 0.49)	**329 per 1,000**	**99 per 1,000**	**230 fewer per 1,000** (from 270 fewer to 168 fewer)	⊕⊕○○ Low Due to Imprecision and Risk of Bias[7]		
Placebo	Reference Comparator	No estimable	No estimable	No estimable	Reference Comparator		

NMA-SoF table definitions
* Solid lines represent direct comparisons
** Network Meta-analysis estimates are reported as risk ratio. CI: confidence interval.
*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

GRADE Working Group grades of evidence (or certainty in the evidence)
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
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Explanatory Footnotes
1 Downgraded one level for risk of bias.
2 Absolute observed point estimate falls in the moderate positive effect, 95% CI range from moderate positive effect to small positive effect: downgraded one level. Further downgraded one level for risk of bias.
3 Absolute observed point estimate falls in the moderate positive effect, 95% CI range from large positive effect to moderate positive effect: downgraded one level. Further downgraded one level for risk of bias.
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Estimates of effects, credible intervals, and certainty of the evidence for comparison immunomodulators and immunosuppressants for relapsing multiple sclerosis

Frequentist NMA-SoF table

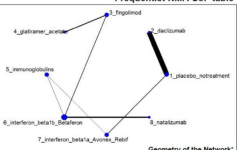
Patient or population: Patients with RMS

Interventions: Daclizumab, Fingolimod, Glatiramer acetate, Immunoglobulins, Interferon beta 1b (Betaferon), Interferon 1a (Avonex, Rebif), Natalizumab

Comparator (reference): Placebo

Outcome: New or enlarging T2-weighted MRI lesions 12 months

Setting(s): Outpatient



Geometry of the Network*

Total studies: Total Participants:	Relative effect** (95% CI)	Anticipated absolute effect*** (95% CI)			Certainty of the evidence	Ranking	Interpretation of Findings
		With Placebo	*With* intervention	Difference			
Daclizumab Direct evidence; 1 RCT; 621 participants)	**RR 1.00** (0.97 to 1.04)	**844 per 1,000**	**844 per 1,000**	**0 fewer per 1,000** (from 25 fewer to 34 more)	⊕⊕⊕○ Moderate Due to Imprecision[1]		
Fingolimod No direct evidence	**RR 1.89** (0.40 to 8.99)	**844 per 1,000**	**1,000 per 1,000**	**751 more per 1,000** (from 506 fewer to 1,000 more)	⊕○○○ Very Low Due to Imprecision and risk of bias[1]		
Glatiramer acetate No direct evidence	**RR 2.37** (0.50 to 11.30)	**844 per 1,000**	**1,000 per 1,000**	**1,000 more per 1,000** (from 422 fewer to 1,000 more)	⊕○○○ Very Low Due to Imprecision and risk of bias[1]		
Immunoglobulins No direct evidence	**RR 0.98** (0.30 to 3.28)	**844 per 1,000**	**827 per 1,000**	**17 fewer per 1,000** (from 591 fewer to 1,000 more)	⊕○○○ Very Low Due to Imprecision[1]		
Interferon beta 1b (Betaferon) No direct evidence	**RR 2.12** (0.45 to 9.97)	**844 per 1,000**	**1,000 per 1,000**	**945 more per 1,000** (from 464 fewer to 1,000 more)	⊕○○○ Very Low Due to Imprecision and risk of bias[1]		
Interferon beta1a (Avonex, Rebif) Direct evidence; 1 RCT; 942 participants)	**RR 0.51** (0.45 to 0.57)	**844 per 1,000**	**430 per 1,000**	**414 fewer per 1,000** (from 464 fewer to 363 fewer)	⊕⊕⊕⊕ High		
Natalizumab No direct evidence	**RR 2.01** (0.43 to 9.51)	**844 per 1,000**	**1,000 per 1,000**	**852 more per 1,000** (from 481 fewer to 1,000 more)	⊕○○○ Very Low Due to Imprecision and risk of bias[1]		
Placebo	Reference Comparator	No estimable	No estimable	No estimable	Reference Comparator		

NMA-SoF table definitions
* Solid lines represent direct comparisons
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*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

GRADE Working Group grades of evidence (or certainty in the evidence)
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
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Explanatory Footnotes
1 Absolute observed point estimate falls in the null effect, 95% CI range from trivial positive effect to trivial negative effect: downgraded one level.
2 Absolute observed point estimate falls in the large negative effect, 95% CI range from large positive effect to large negative effect: downgraded three levels. Further downgraded one level for risk of bias.
3 Absolute observed point estimate falls in the trivial positive effect, 95% CI range from large positive effect to large negative effect: downgraded three levels.

Estimates of effects, credible intervals, and certainty of the evidence for comparison immunomodulators and immunosuppressants for relapsing multiple sclerosis

Frequentist NMA-SoF table

Patient or population: Patients with RMS

Interventions: Fingolimod, natalizumab

Comparator (reference): Placebo

Outcome: New or enlarging T2-weighted MRI lesions 24 months

Setting(s): Outpatient

Geometry of the Network*

Total studies: Total Participants:	Relative effect** (95% CI)	Anticipated absolute effect*** (95% CrI)			Certainty of the evidence	Ranking	Interpretation of Findings
		With Placebo	*With* intervention	Difference			
Fingolimod Direct evidence; 1 RCT; 1046 participants)	**RR 0.62** (0.56 to 0.68)	**639 per 1,000**	**396 per 1,000**	**243 fewer per 1,000** (from 281 fewer to 204 fewer)	⊕⊕○○ Low Due to Imprecision and risk of bias[1]		
Natalizumab Direct evidence; 1 RCT; 1651 participants)	**RR 0.50** (0.45 to 0.55)	**854 per 1,000**	**427 per 1,000**	**427 fewer per 1,000** (from 470 fewer to 384 fewer)	⊕⊕⊕⊕ High		
Placebo	Reference Comparator	No estimable	No estimable	No estimable	Reference Comparator		

NMA-SoF table definitions
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Explanatory Footnotes
1 Absolute observed point estimate falls in the large positive effect, 95% CI range from large positive effect to moderate positive effect: downgraded one level. Further downgraded one level for risk of bias.

Estimates of effects, credible intervals, and certainty of the evidence for comparison immunomodulators and immunosuppressants for relapsing multiple sclerosis

Frequentist NMA-SoF table

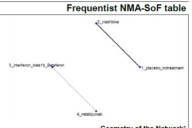
Patient or population: Patients with RMS

Interventions: Cladribine

Comparator (reference): Placebo

Outcome: QoL total - Non-MS related, EQ-5D VAS (Lower scores indicate worse disability)

Setting(s): Outpatient



Geometry of the Network*

Total studies: Total Participants:	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CrI)		Certainty of the evidence	Ranking	Interpretation of Findings
		With Placebo	*With* intervention			
Cladribine Direct evidence; 1 RCT; 1042 participants)	-	-	SMD **0.10 SD higher** (0.06 higher to 0.32 higher)	⊕⊕⊕○ Moderate Due to Imprecision[1]		
Placebo	Reference Comparator	No estimable	No estimable	Reference Comparator		

NMA-SoF table definitions
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High quality: We are very confident that the true effect lies close to that of the estimate of the effect
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Explanatory Footnotes
1 Absolute observed point estimate falls in the trivial positive effect, 95% CI range from trivial positive to small positive: downgraded one level.

Estimates of effects, credible intervals, and certainty of the evidence for comparison immunomodulators and immunosuppressants for relapsing multiple sclerosis

Frequentist NMA-SoF table

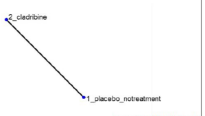
Patient or population: Patients with RMS

Interventions: Cladribine

Comparator (reference): Placebo

Outcome: QoL total - Non-MS related, EQ-5D Index

Setting(s): Outpatient



Geometry of the Network*

Total studies: Total Participants:	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CrI)		Certainty of the evidence	Ranking	Interpretation of Findings
		With Placebo	*With* intervention			
Cladribine Direct evidence; 1 RCT; 1042 participants)	-	-	SMD **0.24 SD higher** (0.11 higher to 0.37 higher)	⊕⊕⊕○ Moderate Due to Imprecision[1]		
Placebo	Reference Comparator	No estimable	No estimable	Reference Comparator		

NMA-SoF table definitions
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Explanatory Footnotes
1 Absolute observed point estimate falls in the small positive effect, 95% CI range from trivial positive to small positive: downgraded one level.

Estimates of effects, credible intervals, and certainty of the evidence for comparison immunomodulators and immunosuppressants for relapsing multiple sclerosis

Frequentist NMA-SoF table

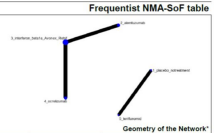
Patient or population: Patients with RMS

Interventions: Teriflunomide

Comparator (reference): Placebo

Outcome: QoL physical - Non-MS related (SF-36) (Lower scores indicate worse disability)

Setting(s): Outpatient



Geometry of the Network*

Total studies: Total Participants:	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CrI)		Certainty of the evidence	Ranking	Interpretation of Findings
		With Placebo	*With* intervention			
Teriflunomide Direct evidence; 1 RCT; 1169 participants)	-	-	SMD **0.1 SD higher** (0.02 lower to 0.22 higher)	⊕◯◯◯ Very Low Due to Imprecision and risk of bias[1]		
Placebo	Reference Comparator	No estimable	No estimable	Reference Comparator		

NMA-SoF table definitions
* Solid lines represent direct comparisons
** Network Meta-analysis estimates are reported as risk ratio. CI: confidence interval.
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High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes
1 Absolute observed point estimate falls in the trivial positive effect, 95% CI range from trivial negative to small positive: downgraded two levels. Further downgraded one level for risk of bias.

Estimates of effects, credible intervals, and certainty of the evidence for comparison immunomodulators and immunosuppressants for relapsing multiple sclerosis

Frequentist NMA-SoF table

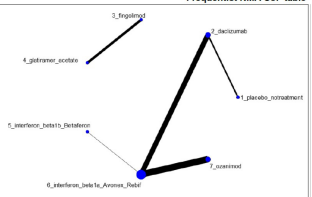
Patient or population: Patients with RMS

Interventions: Daclizumab, Interferon beta 1b (Betaferon), Interferon beta 1a (Avonex, Rebif), ozanimod

Comparator (reference): Placebo

Outcome: QoL physical - MS related (MSQOL-54 PH; MSQoL-54 MH, MSIS29 Psychological)

Setting(s): Outpatient



Geometry of the Network*

Total studies: Total Participants:	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CrI)		Certainty of the evidence	Ranking	Interpretation of Findings
		With Placebo	*With* intervention			
Daclizumab Direct evidence; 1 RCT; 621 participants)	-	-	**SMD 0.22 SD higher** (0.05 higher to 0.38 higher)	⊕⊕⊕◯ Moderate Due to Imprecision[1]		
Interferon beta 1b (Betaferon) No direct evidence	-	-	**SMD 0.41 SD higher** (0.13 lower to 0.95 higher)	⊕◯◯◯ Very low Due to Imprecision[2]		
Interferon beta 1a (Avonex, Rebif) No direct evidence	-	-	**SMD 0.36 SD higher** (0.16 higher to 0.55 higher)	⊕⊕◯◯ Low Due to Imprecision[3]		
Ozanimod No direct evidence	-	-	**SMD 0.5 SD higher** (0.29 higher to 0.71 higher)	⊕⊕◯◯ Low Due to Imprecision[3]		
Placebo	Reference Comparator	No estimable	No estimable	Reference Comparator		

NMA-SoF table definitions
* Solid lines represent direct comparisons
** Network Meta-analysis estimates are reported as risk ratio. CI: confidence interval.
*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

GRADE Working Group grades of evidence (or certainty in the evidence)
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes
1 Absolute observed point estimate falls in the small positive effect, 95% CI range from trivial positive to small positive: downgraded one level.
2 Absolute observed point estimate falls in the small positive effect, 95% CI range from trivial negative to large positive: downgraded three levels.
3 Absolute observed point estimate falls in the small positive effect, 95% CI range from trivial positive to moderate positive: downgraded two levels.

Estimates of effects, credible intervals, and certainty of the evidence for comparison immunomodulators and immunosuppressants for relapsing multiple sclerosis

Frequentist NMA-SoF table

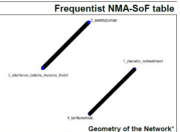
Patient or population: Patients with RMS

Interventions: teriflunomide

Comparator (reference): Placebo

Outcome: QoL mental Non-MS related (SF-36) (Lower scores indicate worse disability)

Setting(s): Outpatient



Geometry of the Network*

Total studies: Total Participants:	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CrI)		Certainty of the evidence	Ranking	Interpretation of Findings
		With Placebo	*With* intervention			
Teriflunomide Direct evidence; 1 RCT; 1169 participants)	-	-	SMD **0.1 SD higher** (0.02 lower to 0.22 higher)	⊕◯◯◯ Very Low Due to Impression and risk of bias[1]		-
Placebo	Reference Comparator	No estimable	No estimable	Reference Comparator		-

NMA-SoF table definitions
* Solid lines represent direct comparisons
** Network Meta-analysis estimates are reported as risk ratio. CI: confidence interval.
*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

GRADE Working Group grades of evidence (or certainty in the evidence)
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
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Explanatory Footnotes
1 Absolute observed point estimate falls in the trivial positive effect, 95% CI range from trivial negative to small positive: downgraded two levels. Further downgraded one level for risk of bias.

Estimates of effects, credible intervals, and certainty of the evidence for comparison immunomodulators and immunosuppressants for relapsing multiple sclerosis

Frequentist NMA-SoF table

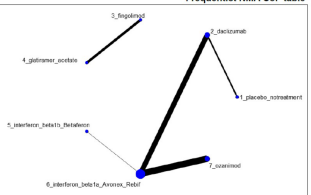
Patient or population: Patients with RMS

Interventions: Daclizumab, Interferon beta 1b (Betaferon), Interferon beta 1a (Avonex, Rebif), ozanimod

Comparator (reference): Placebo

Outcome: QoL mental - MS related (MSQOL-54 PH; MSQoL-54 MH, MSIS29 Psychological)

Setting(s): Outpatient



Geometry of the Network*

Total studies: Total Participants:	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CrI)		Certainty of the evidence	Ranking	Interpretation of Findings
		With Placebo	*With* intervention			
Daclizumab Direct evidence; 1 RCT; 621 participants)	-	-	**SMD 0.12 SD higher** (0.05 lower to 0.28 higher)	⊕⊕◯◯ Low Due to Imprecision[1]		
Interferon beta 1b (Betaferon) No direct evidence	-	-	**SMD 0.3 SD higher** (0.24 lower to 0.84 higher)	⊕◯◯◯ Very low Due to Imprecision[2]		
Interferon beta 1a (Avonex, Rebif) No direct evidence	-	-	**SMD 0.03 SD higher** (0.17 lower to 0.22 higher)	⊕⊕◯◯ Low Due to Imprecision[1]		
Ozanimod No direct evidence	-	-	**SMD 0.05 SD higher** (0.15 lower to 0.26 higher)	⊕⊕◯◯ Low Due to Imprecision[1]		
Placebo	Reference Comparator	No estimable	No estimable	Reference Comparator		

NMA-SoF table definitions
* Solid lines represent direct comparisons
** Network Meta-analysis estimates are reported as risk ratio. CI: confidence interval.
*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

GRADE Working Group grades of evidence (or certainty in the evidence)
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes
1 Absolute observed point estimate falls in the trivial positive effect, 95% CI range from trial negative to small positive: downgraded two levels.
2 Absolute observed point estimate falls in the small positive effect, 95% CI range from small negative to large positive: downgraded three levels.

Undesirable Effects

How substantial are the undesirable anticipated effects for each intervention?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Large: **Moderate:** **Small:** **Trivial:** Interferon beta 1a, Natalizumab, Dimethylfumarate, Alemtuzumab, Ocrelizumab, Cladribine, Mitoxantrone, Fingolimod, Interferon beta 1b, Glatiramer acetate **Varies:** **Don't know:**	**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 favour 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.	The panel noted that for some DMTs no serious adverse events were reported due to data extraction having specific inclusion criteria. It is important to distinguish 'no data' from 'no serious adverse events'. For example, azathioprine had a large amount of discontinuation events, but there were no data for serious adverse events. This is because a very specific definition of severe adverse events was used for the analysis, so for studies that did not use that classification, the data could not be extracted as severe adverse events. All but ponesimod, azathioprine and peg-interferon has combined undesirable effects judged as 'trivial'. Ponesimod, azathioprine and peg-interferon are rated as 'small'. Two issues were noted: (1) Only 'discontinuation due to any cause' were included in the net sum as also including 'serious adverse events' would have double-counted these events. (2) The panel noted there were concerns with post-marketing surveillance from a safety standpoint. Some of the DMTs have serious adverse effects, albeit rare, e.g. alemtuzumab risk of infections and of autoimmune adverse effects (0.4%), risk of PML for natalizumab, fingolimod risk of cardiac issues and infections. 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. The panel also highlighted discontinuation of DMTs as a risk of rebound effect that prompted a warning for S1P modulators (fingolimod) and natalizumab. Rebound phenomena can be as high as 10% with S1P modulators. The panel highligted that in the NMA only RCTs are considered, so post-marketing studies and surveillance are not included. There was not capacity within the scope of this project to systematically review all post-marketing studies for all the DMTs. The panel decided that post-marketing safety warnings will be used to contextualise the EtD. EMA safety warnings and label changes can be found here: http://www.msif.org/wp-content/uploads/2022/08/EMA-safety-warnings_RMS_020622.docx [https://www.msif.org/supporting-documents-memp-etd/] The panel noted that three of the DMTs did not pass or have been withdrawn marketing authorisation or regulatory approval by the major regulators, e.g. US FDA and EMA. Daclizumab has been withdrawn from the market in 2018, so not available and should not be considered further. Laquinimod has not received approval by EMA or US FDA, but it may have approval in some countries e.g. Russia. It is unknown if it has been withdrawn globally. Mitoxantrone has approval by the US FDA, but was never approved by the EMA. Since US FDA approval, there has been serious long-term safety concerns, with an updated label. The panel considered that mitoxantrone was currently very rarely used, if at all. The panel noted post-marketing surveillance considerations for dimethyl fumarate with PML. Summary of extra safety considerations: 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. 3. Natalizumab: updated PML risk for JCV positive patients identified in post-marketing safety studies. 4. Fingolimod: rebound effect and cardiovascular, liver and cancer risks identified in post-marketing safety studies.

Estimates of effects, credible intervals, and certainty of the evidence for comparison immunomodulators and immunosuppressants for relapsing multiple sclerosis

Frequentist NMA-SoF table

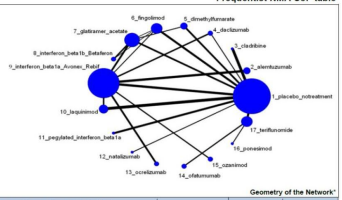
Patient or population: Patients with RMS

Interventions: Alemtuzumab, cladribine, daclizumab,dimethylfumarate, fingolimod, glatiramer acetate, interferon_beta1b_Betaferon, interferon_beta1a_Avonex_Rebif, laquinimod, pegylated interferon beta 1a, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, teriflunomide

Comparator (reference): Placebo

Outcome: Mortality

Setting(s): Outpatient



Geometry of the Network

Total studies: Total Participants:	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CrI)			Certainty of the evidence	Ranking	Interpretation of Findings
		With Placebo	*With* intervention	Difference			
Alemtuzumab No direct evidence	**OR 1.38** (0.16 to 12.14)	3 per 1,000	4 per 1,000	**1 more per 1,000** (from 2 fewer to 29 more)	⊕◯◯◯ Very Low Due to Imprecision and risk of bias[1]		-
Cladribine (Direct evidence; 1 RCT; 1326 participants)	**OR 0.98** (0.18 to 5.39)	3 per 1,000	4 per 1,000	**0 fewer per 1,000** (from 2 fewer to 12 more)	⊕⊕⊕◯ Moderate Due to Imprecision[2]		
Daclizumab (Direct evidence; 1 RCT; 623 participants)	**OR 0.32** (0.04 to 2.37)	3 per 1,000	1 per 1,000	**2 fewer per 1,000** (from 3 fewer to 4 more)	⊕⊕⊕◯ Moderate Due to Imprecision[2]		
Dimethylfumarate (Direct evidence; 2 RCT; 2309 participants)	**OR 0.75** (0.11 to 5.24)	3 per 1,000	2 per 1,000	**1 fewer per 1,000** (from 2 fewer to 11 more)	⊕⊕◯◯ Low Due to Imprecision and risk of bias[3]		
Fingolimod (Direct evidence; 2 RCT; 2357 participants)	**OR 0.38** (0.07 to 1.98)	3 per 1,000	1 per 1,000	**2 fewer per 1,000** (from 3 fewer to 3 more)	⊕⊕◯◯ Low Due to Imprecision and risk of bias[3]		
Glatiramer acetate (Direct evidence; 2 RCT; 2119 participants)	**OR 0.49** (0.10 to 2.38)	3 per 1,000	1 per 1,000	**1 fewer per 1,000** (from 2 fewer to 4 more)	⊕⊕◯◯ Low Due to Imprecision and risk of bias[3]		
Interferon beta 1b (Betaferon) No direct evidence	**OR 0.37** (0.02 to 5.81)	3 per 1,000	1 per 1,000	**2 fewer per 1,000** (from 3 fewer to 13 more)	⊕⊕◯◯ Low Due to Imprecision and risk of bias[3]		
Interferon beta 1a No direct evidence (Direct evidence; 3 RCT; 1588 participants)	**OR 0.63** (0.18 to 2.17)	3 per 1,000	2 per 1,000	**1 fewer per 1,000** (from 2 fewer to 3 more)	⊕⊕◯◯ Low Due to Imprecision and risk of bias[3]		
Laquinimod No direct evidence (Direct evidence; 3 RCT; 3461 participants)	**OR 0.51** (0.12 to 2.18)	3 per 1,000	1 per 1,000	**1 fewer per 1,000** (from 2 fewer to 3 more)	⊕⊕⊕◯ Moderate Due to Imprecision[2]		
Pegylated interferon beta 1a (Direct evidence; 1 RCT; 1512 participants)	**OR 0.49** (0.07 to 3.51)	3 per 1,000	1 per 1,000	**1 fewer per 1,000** (from 3 fewer to 7 more)	⊕⊕◯◯ Low Due to Imprecision and risk of bias[3]		
Natalizumab (Direct evidence; 1 RCT; 944 participants)	**OR 2.52** (0.12 to 52.69)	3 per 1,000	7 per 1,000	**4 more per 1,000** (from 2 fewer to 123 more)	⊕◯◯◯ Very Low Due to Imprecision[4]		
Ocrelizumab No direct evidence	**OR 0.39** (0.03 to 4.50)	3 per 1,000	1 per 1,000	**2 fewer per 1,000** (from 3 fewer to 9 more)	⊕⊕◯◯ Low Due to Imprecision and risk of bias[3]		
Ofatumumab No direct evidence	**OR 0.49** (0.01 to 24.94)	3 per 1,000	1 per 1,000	**1 fewer per 1,000** (from 3 fewer to 61 more)	⊕◯◯◯ Very Low Due to Imprecision and risk of bias[3]		
Ozanimod No direct evidence	**OR 0.96** (0.03 to 29.63)	3 per 1,000	3 per 1,000	**0 fewer per 1,000** (from 3 fewer to 72 more)	⊕◯◯◯ Very Low Due to Imprecision[4]		
Ponesimod No direct evidence	**OR 0.30** (0.01 to 13.20)	3 per 1,000	1 per 1,000	**2 fewer per 1,000** (from 3 fewer to 32 more)	⊕◯◯◯ Very Low Due to Imprecision and risk of bias[4]		
Teriflunomide (Direct evidence; 1 RCT; 1169 participants)	**OR 1.50** (0.16 to 14.45)	3 per 1,000	4 per 1,000	**1 more per 1,000** (from 2 fewer to 35 more)	⊕◯◯◯ Very Low Due to Imprecision and risk of bias[3]		
Placebo	Reference Comparator	No estimable	No estimable	No estimable	Reference Comparator		

NMA-SoF table definitions
* Solid lines represent direct comparisons
** Network Metaanalysis estimates are reported as risk ratio. CI: confidence interval.
*** Anticipated absolute effect: Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

GRADE Working Group grades of evidence (or certainty in the evidence)
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes
1 Absolute observed point estimate falls in the trivial negative effect: (below small effect threshold), 95% CI range from trivial positive effect to small negative effect: downgraded two levels. Further downgraded one level for risk of bias.
2 Absolute observed point estimate falls in the null effect, 95% CI range from trivial positive effect to trivial negative effect: downgraded one level.
3 Absolute observed point estimate falls in the trivial positive effect: (below small effect threshold), 95% CI range from trivial positive effect to trivial negative effect: downgraded one level.
4 Absolute observed point estimate falls in the trivial positive effect: (below small effect threshold), 95% CI range from trivial positive effect to trivial negative effect: downgraded one level. Further downgraded one level for risk of bias.
5 Absolute observed point estimate falls in the trivial positive effect: (below small effect threshold), 95% CI range from trivial positive effect to trivial negative effect: downgraded one level. Further downgraded one level for risk of bias.
6 Absolute observed point estimate falls in the trivial negative effect, 95% CI range from trivial positive effect to large negative effect: downgraded three levels
7 Absolute observed point estimate falls in the trivial positive effect: (below small effect threshold), 95% CI range from trivial positive effect to trivial negative effect: downgraded one level. Further downgraded one level for risk of bias.
8 Absolute observed point estimate falls in the trivial positive effect, 95% CI range from trivial positive effect to large negative effect: downgraded three levels. Further downgraded one level for risk of bias.
9 Absolute observed point estimate falls in the null effect, 95% CI range from trivial positive effect to large negative effect: downgraded three levels.
10 Absolute observed point estimate falls in the trivial positive effect: (below small effect threshold), 95% CI range from trivial positive effect to moderate negative effect: downgraded three levels. Further downgraded one level for risk of bias.

Estimates of effects, credible intervals, and certainty of the evidence for comparison immunomodulators and immunosuppressants for relapsing multiple sclerosis

Frequentist NMA-SoF table

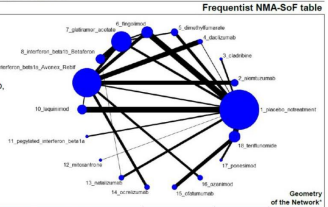
Patient or population: Patients with RMS

Interventions: Alemtuzumab, cladribine, daclizumab, dimethylfumarate, fingolimod, glatiramer acetate, interferon_beta1b_Betaferon, Interferon beta 1a (Avonex, Rebif), laquinimod, pegylated interferon beta1a, mitoxantrone, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, teriflunomide

Comparator (reference): Placebo

Outcome: Serious adverse events (SAEs)

Setting(s): Outpatient



Geometry of the Network*

Total studies: Total Participants:	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CrI)			Certainty of the evidence	Ranking	Interpretation of Findings
		With Placebo	*With intervention*	Difference			
Alemtuzumab No Direct evidence	**OR 1.52** (0.94 to 2.48)	**79 per 1,000**	**120 per 1,000**	**36 more per 1.000** (from 4 fewer to 96 more)	⊕◯◯◯ Very Low Due to Imprecision and Risk of Bias[1]		
Cladribine (Direct evidence; 1 RCTs; 1326 participants)	**OR 1.39** (0.80 to 2.40)	**79 per 1,000**	**106 per 1,000**	**27 more per 1.000** (from 15 fewer to 92 more)	⊕◯◯◯ Very Low Due to Imprecision[2]		
Daclizumab (Direct evidence; 1 RCTs; 600 participants)	**OR 1.90** (1.21 to 2.99)	**79 per 1,000**	**140 per 1,000**	**61 more per 1.000** (from 15 more to 125 more)	⊕⊕◯◯ Low Due to Imprecision[3]		
Dimethylfumarate (Direct evidence; 2 RCTs; 2300 participants)	**OR 1.04** (0.71 to 1.52)	**79 per 1,000**	**82 per 1,000**	**3 more per 1.000** (from 22 fewer to 36 more)	⊕⊕◯◯ Low Due to Imprecision and Risk of Bias[4]		
Fingolimod (Direct evidence; 2 RCTs; 2355 participants)	**OR 0.86** (0.64 to 1.13)	**79 per 1,000**	**69 per 1,000**	**10 fewer per 1.000** (from 27 fewer to 9 more)	⊕⊕◯◯ Low Due to Imprecision and Risk of Bias[5]		
Glatiramer acetate (Direct evidence; 3 RCTs; 2371 participants)	**OR 0.94** (0.68 to 1.28)	**79 per 1,000**	**75 per 1,000**	**4 fewer per 1.000** (from 24 fewer to 20 more)	⊕⊕◯◯ Low Due to Imprecision and Risk of Bias[6]		
Interferon beta 1b (Betaferon) No direct evidence	**OR 0.92** (0.55 to 1.54)	**79 per 1,000**	**73 per 1,000**	**6 fewer per 1,000** (from 34 fewer to 38 more)	⊕⊕⊕◯ Moderate Due to Imprecision[8]		
Interferon beta 1a (Rebif, Avonex) (Direct evidence; 1 RCTs; 897 participants)	**OR 1.21** (0.88 to 1.67)	**79 per 1,000**	**94 per 1,000**	**15 more per 1,000** (from 9 fewer to 46 more)	⊕◯◯◯ Very Low Due to Imprecision and risk of bias[7]		
Laquinimod (Direct evidence; 3 RCTs; 3457 participants)	**OR 1.25** (0.92 to 1.70)	**79 per 1,000**	**97 per 1,000**	**18 more per 1.000** (from 6 fewer to 48 more)	⊕◯◯◯ Very Low Due to Imprecision and risk of bias[9]		
Pegylated interferon beta1a (Direct evidence; 1 RCT; 1512 participants)	**OR 1.08** (0.59 to 1.96)	**79 per 1,000**	**85 per 1,000**	**6 more per 1,000** (from 31 fewer to 65 more)	⊕◯◯◯ Very Low Due to Imprecision and risk of bias[9]		
Mitoxantrone (Direct evidence; 1 RCT; 53 participants)	**OR 0.89** (0.02 to 47.22)	**79 per 1,000**	**71 per 1,000**	**8 fewer per 1,000** (from 77 fewer to 723 more)	⊕◯◯◯ Very Low Due to Imprecision and risk of bias[10]		
Natalizumab (Direct evidence; 1 RCT; 939 participants)	**OR 1.24** (0.73 to 2.09)	**79 per 1,000**	**96 per 1,000**	**17 more per 1,000** (from 20 fewer to 73 more)	⊕⊕◯◯ Low Due to Imprecision[11]		
Ocrelizumab No direct evidence	**OR 1.00** (0.58 to 1.72)	**79 per 1,000**	**79 per 1,000**	**0 fewer per 1,000** (from 32 fewer to 50 more)	⊕◯◯◯ Very Low Due to Imprecision and risk of bias[12]		
Ofatumumab No direct evidence	**OR 1.52** (0.89 to 2.57)	**79 per 1,000**	**115 per 1,000**	**36 more per 1,000** (from 8 fewer to 102 more)	⊕◯◯◯ Very Low Due to Imprecision and risk of bias[13]		
Ozanimod No direct evidence	**OR 1.50** (0.85 to 2.64)	**79 per 1,000**	**114 per 1,000**	**35 more per 1,000** (from 11 fewer to 106 more)	⊕◯◯◯ Very Low Due to Imprecision[14]		
Ponesimod No direct evidence	**OR 1.24** (0.66 to 2.35)	**79 per 1,000**	**96 per 1,000**	**17 more per 1,000** (from 25 fewer to 89 more)	⊕◯◯◯ Very Low Due to Imprecision and risk of bias[15]		
Teriflunomide (Direct evidence; 2 RCT; 2253 participants)	**OR 1.16** (0.81 to 1.64)	**79 per 1,000**	**90 per 1,000**	**11 more per 1,000** (from 14 fewer to 44 more)	⊕◯◯◯ Very Low Due to Imprecision and risk of bias[16]		
Placebo	Reference Comparator	No estimable	No estimable	No estimable	Reference Comparator		

NMA-SoF table definitions
* Solid lines represent direct comparisons
** Network Metanalysis estimates are reported as risk ratio. CI: confidence interval.
*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

GRADE Working Group grades of evidence (or certainty in the evidence)
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes
1 Absolute observed point estimate falls in the trivial negative effect: (below small effect threshold), 95% CI range from trivial positive effect to moderate negative effect: downgraded three levels. Further downgraded one level for risk of bias.
2 Absolute observed point estimate falls in the trivial negative effect: (below small effect threshold), 95% CI range from trivial positive effect to moderate negative effect: downgraded three levels.
3 Absolute observed point estimate falls in the small negative effect, 95% CI range from trivial negative effect to moderate negative effect: downgraded two levels.
4 Absolute observed point estimate falls in the trivial negative effect: (below small effect threshold), 95% CI range from trivial positive effect to trivial negative effect: downgraded one level. Further downgraded one level for risk of bias.
5 Absolute observed point estimate falls in the trivial positive effect: (below small effect threshold), 95% CI range from trivial positive effect to trivial negative effect: downgraded one level. Further downgraded one level for risk of bias.
6 Absolute observed point estimate falls in the trivial positive effect: (below small effect threshold), 95% CI range from trivial positive effect to trivial negative effect: downgraded one level.
7 Absolute observed point estimate falls in the trivial negative effect: (below small effect threshold), 95% CI range from trivial positive effect to small negative effect: downgraded two levels. Further downgraded one level for risk of bias.
8 Absolute observed point estimate falls in the trivial negative effect: (below small effect threshold), 95% CI range from trivial positive effect to small negative effect: downgraded two levels. Further downgraded one level for risk of bias.
9 Absolute observed point estimate falls in the trivial negative effect: (below small effect threshold), 95% CI range from trivial positive effect to small negative effect: downgraded two levels. Further downgraded one level for risk of bias.
10 Absolute observed point estimate falls in the trivial positive effect: (below small effect threshold), 95% CI range from moderate positive effect to large negative effect: downgraded three levels. Further downgraded one level for risk of bias.
11 Absolute observed point estimate falls in the trivial negative effect: (below small effect threshold), 95% CI range from trivial positive effect to small negative effect: downgraded two levels.
12 Absolute observed point estimate falls in the null effect, 95% CI range from trivial positive effect to small negative effect: downgraded two levels. Further downgraded one level for risk of bias.
13 Absolute observed point estimate falls in the trivial negative effect: (below small effect threshold), 95% CI range from trivial positive effect to moderate negative effect: downgraded three levels. Further downgraded one level for risk of bias.
14 Absolute observed point estimate falls in the trivial negative effect: (below small effect threshold), 95% CI range from trivial positive effect to moderate negative effect: downgraded three levels.
15 Absolute observed point estimate falls in the trivial negative effect: (below small effect threshold), 95% CI range from trivial positive effect to moderate negative effect: downgraded three levels. Further downgraded one level for risk of bias.
16 Absolute observed point estimate falls in the trivial negative effect: (below small effect threshold), 95% CI range from trivial positive effect to small negative effect: downgraded two levels. Further downgraded one level for risk of bias.

Estimates of effects, credible intervals, and certainty of the evidence for comparison immunomodulators and immunosuppressants for relapsing multiple sclerosis

Frequentist NMA-SoF table

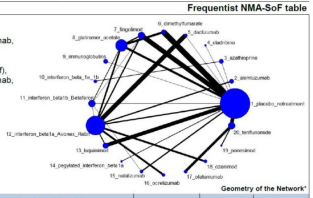
Patient or population: Patients with RMS

Interventions: Alemtuzumab, azathioprine, cladribine, daclizumab, dimethylfumarate, fingolimod, glatiramer acetate, immunoglobulins, interferon beta 1a 1b, interferon beta 1b (Betaferon), interferon beta 1a (Avonex, Rebif), laquinimod, pegylated interferon beta1a, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, terifunomide

Comparator (reference): Placebo

Outcome: Treatment discontinuation due to adverse events

Setting(s): Outpatient



Geometry of the Network*

Total studies: Total Participants:	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CrI)			Certainty of the evidence	Ranking	Interpretation of Findings
		With Placebo	*With intervention*	Difference			
Alemtuzumab No direct evidence	**OR 0.39** (0.19 to 0.79)	**50 per 1,000**	**20 per 1,000**	**30 fewer per 1,000** (from 40 fewer to 10 fewer)	⊕⊕⊕○ Moderate Due to risk of bias[1]		
Azathioprine (Direct evidence; 1 RCT; 54 participants)	**OR 6.26** (0.67 to 58.05)	**50 per 1,000**	**246 per 1,000**	**196 more per 1,000** (from 16 fewer to 702 more)	⊕○○○ Very Low Due to Imprecision[3]		
Cladribine (Direct evidence; 1 RCT; 1326 participants)	**OR 1.38** (0.46 to 4.15)	**50 per 1,000**	**67 per 1,000**	**18 more per 1,000** (from 26 fewer to 128 more)	⊕⊕○○ Low Due to Imprecision[3]		
Daclizumab (Direct evidence; 1 RCT; 600 participants)	**OR 2.55** (1.40 to 4.63)	**50 per 1,000**	**117 per 1,000**	**68 more per 1,000** (from 18 more to 145 more)	⊕⊕⊕○ Moderate Due to imprecision[4]		
Dimethylfumarate (Direct evidence; 2 RCTs; 2300 participants)	**OR 1.35** (0.94 to 1.95)	**50 per 1,000**	**66 per 1,000**	**16 more per 1,000** (from 3 fewer to 43 more)	⊕⊕○○ Low Due to Imprecision and risk of bias[5]		
Fingolimod (Direct evidence; 2 RCTs; 2355 participants)	**OR 1.84** (1.31 to 2.57)	**50 per 1,000**	**87 per 1,000**	**38 more per 1,000** (from 14 more to 69 more)	⊕⊕⊕○ Moderate Due to risk of bias[1]		
Glatiramer acetate (Direct evidence; 4 RCTs; 2419 participants)	**OR 1.48** (1.02 to 2.14)	**50 per 1,000**	**72 per 1,000**	**22 more per 1,000** (from 1 more to 51 more)	⊕⊕⊕○ Moderate Due to risk of bias[1]		
Immunoglobulins (Direct evidence; 3 RCTs; 243 participants)	**OR 2.49** (0.37 to 16.50)	**50 per 1,000**	**115 per 1,000**	**65 more per 1,000** (from 31 fewer to 413 more)	⊕○○○ Very Low Due to Imprecision[3]		
Interferon beta 1a 1b No direct evidence	**OR 3.02** (0.27 to 33.65)	**50 per 1,000**	**136 per 1,000**	**86 more per 1,000** (from 36 fewer to 587 more)	⊕○○○ Very Low Due to Imprecision[3]		
Interferon beta 1b (Direct evidence; 1 RCTs; 372 participants)	**OR 2.27** (1.05 to 4.91)	**50 per 1,000**	**106 per 1,000**	**56 more per 1,000** (from 2 more to 154 more)	⊕⊕○○ Low Due to Imprecision and risk of bias[1]		
Interferon beta 1a (Direct evidence; 2 RCTs; 1457 participants)	**OR 1.48** (0.99 to 2.20)	**50 per 1,000**	**72 per 1,000**	**22 more per 1,000** (from 0 fewer to 53 more)	⊕⊕⊕○ Moderate Due to risk of bias[1]		
Laquinimod (Direct evidence; 3 RCTs; 3457 participants)	**OR 1.46** (1.00 to 2.15)	**50 per 1,000**	**71 per 1,000**	**21 more per 1,000** (from 0 fewer to 51 more)	⊕⊕⊕○ Moderate Due to risk of bias[1]		
Pegylated interferon beta1a (Direct evidence; 1 RCT; 1512 participants)	**OR 3.58** (1.47 to 8.73)	**50 per 1,000**	**157 per 1,000**	**108 more per 1,000** (from 22 more to 263 more)	⊕○○○ Very Low Due to Imprecision and risk of bias[6]		
Natalizumab (Direct evidence; 1 RCT; 939 participants)	**OR 1.57** (0.81 to 3.05)	**50 per 1,000**	**76 per 1,000**	**26 more per 1,000** (from 9 fewer to 88 more)	⊕⊕⊕○ Moderate Due to imprecision[4]		
Ocrelizumab No direct evidence	**OR 0.82** (0.42 to 1.60)	**50 per 1,000**	**41 per 1,000**	**9 fewer per 1,000** (from 28 fewer to 27 more)	⊕⊕○○ Low Due to Imprecision and risk of bias[4]		
Ofatumumab No direct evidence	**OR 2.00** (1.05 to 3.81)	**50 per 1,000**	**94 per 1,000**	**45 more per 1,000** (from 2 more to 116 more)	⊕⊕○○ Low Due to Imprecision and risk of bias[1]		
Ozanimod No direct evidence	**OR 1.01** (0.52 to 1.95)	**50 per 1,000**	**50 per 1,000**	**0 fewer per 1,000** (from 23 fewer to 43 more)	⊕⊕○○ Low Due to Imprecision and risk of bias[1]		
Ponesimod No direct evidence	**OR 5.04** **(2.15 to 11.82)**	**50 per 1,000**	**208 per 1,000**	**158 more per 1,000** (from 51 more to 332 more)	⊕○○○ Very Low Due to Imprecision and risk of bias[1]		
Terifunomide (Direct evidence; 2 RCT; 2253 participants)	**OR 1.82** (1.19 to 2.79)	**50 per 1,000**	**87 per 1,000**	**37 more per 1,000** (from 9 more to 77 more)	⊕⊕⊕○ Moderate Due to risk of bias[1]		
Placebo	Reference Comparator	No estimable	No estimable	No estimable	Reference Comparator		

NMA-SoF table definitions
* Solid lines represent direct comparisons
** Network Metanalysis estimates are reported as risk ratio. CI: confidence interval.
*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

GRADE Working Group grades of evidence (or certainty in the evidence)
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Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes
1 Downgraded one level for risk of bias.
2 Absolute observed point estimate falls in the trivial negative effect, 95% CI range from trivial positive effect to large negative effect: downgraded three levels.
3 Absolute observed point estimate falls in the trivial negative effect, 95% CI range from trivial positive effect to small negative effect: downgraded two levels.
4 Absolute observed point estimate falls in the trivial negative effect, 95% CI range from trivial negative effect to small negative effect: downgraded one level.
5 Absolute observed point estimate falls in the trivial negative effect, 95% CI range from trivial positive effect to trivial negative effect: downgraded one level. Further downgraded one level for risk of bias.
6 Absolute observed point estimate falls in the trivial negative effect, 95% CI range from trivial positive effect to large negative effect: downgraded three levels.

Note: The trial with two interferons showed large harm, but it had methodological NMA issues due to imprecision associated with a large open loop, and so was excluded from the analysis.

Certainty of evidence

What is the overall certainty of the evidence of effects for each intervention?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Very low: Ocrelizumab, Mitoxantrone, Interferon beta 1b, Glatiramer acetate **Low:** Interferon beta 1a, Natalizumab, Dimethylfumarate, Alemtuzumab, Cladribine, Fingolimod **Moderate:** **High:** **No included studies:**	For all desirable and undesirable effects, the overall certainty in the evidence was often very low due to imprecision (given that the CIs of the point estimates crossed one or more thresholds among the different magnitudes of the effect pre-defined by MEMP) and in some cases also to risk of bias of included studies. When assessing **disability** at 24 months, the certainty ranged from moderate (only natalizumab) to very low (most DMTs), with downgrading always due to imprecision and in some cases for risk of bias. Relative to **relapse** at 12, 24 and 36 months, overall certainty was very low, ranging from high (natalizumab at 12 months and cladribine, natlizumab and alemtuzumab at 24 months) to very low. Certainty in quality of life estimates ranged from moderate to very low. Among MRI outcomes, **new gadolinium-enhancing positive T1-weighted lesions** at 12 months showed an overall moderate certainty (daclizumab) with high quality for natalizumab, while at 24 months overall certainty was very low, although estimates on natalizumab again showed a high certainty. Similarly, natalizumab estimates for **new or enlarging T2-weighted lesions** at 24 months showed high certainty, with low overall certainty	The panel raised concerns around the methodology of assessing the balance of effects. Firstly, there are limtations in the use of HSUVs, as these have not been well assesed for MS and also lack specific input by pwMS. Secondly, the addition of outcomes to derive a summary figure and nrt balance for the balance of effects is complex due to the heterogencity of the studies included. Studies that measure more desirable outcomes may look better than those that measure fewer outcomes. Most frequent reason for downgrading the certainty of evidence comes from imprecision (rather than risk of bias or indirectness) from very large confidence intervals that cross the thresholds of trivial, small, moderate and large effects. The overall certainty considers the lowest certainty evidence of the outcomes included. The panel noted that this has made most of the evidence very low certainty of evidence. This is making it challenging to differentiate between DMTs. If considering multiple outcomes and they are all in the same direction, e.g. showing benefit, this would decrease concern for certainty of evidence for imprecision. The panel decided to consider this approach to create more granularity in the assessment. The panel decided to adjust certainty of evidence in line with adjustments made to standard GRADE methodology with PMS

	(fingolimod), while at 12 month interferon beta 1 a showed high certainty estimates, with very low overall certainty. Among undesirable effects, for **serious adverse events** the certainty in the evidence was almost always very low due to imprecision and in some cases also to risk of bias of included studies. The only exceptions were dimehtyl fumarate, fingolimod, glatiramer acetate (low certainty) and interferon beta 1b (moderate certainty). Therefore the overall certainty was very low. For **discontinuation due to adverse events** and **mortality** - although according to the GRADE methodology the overall certainty should be rated as very low - compared to serious adverse events, the certainty was moderate for a relatively higher number of DMTs. Note on deviation from standard GRADE methodology: 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 on certainty levels and direction of the individual outcomes. The panel decided to downgrade less for imprecision for the overall assessment for natalizumab, fingolimod, alemtuzumab.	guidelines. For natalizumab the very low overall certainty is driven by the mortality outcome. The mortality estimate for natalizumab was downgraded three levels for imprecision (wide CIs crossing three thresholds, while point estimated fell in "trivial negative effect"). The panel decided to downgrade by two levels only, bringing natalizumab to 'low' certainty. For ocrelizumab the very low overall certainty is driven by the disability outcome. It was downgraded by two levels due to imprecision. The point estimate fell in the moderate positive effect. It was also downgraded one level for risk of bias. The downgrading for treatment discontinuation due to adverse events was one level due to imprecision and one for risk of bias. The point estimate falling in the trivial positive effect. The panel decided not to downgrade less for ocrelizumab. For fingolimod the very low overall certainty is driven by the outcome excluded by the analysis, so was downgraded only one level, moving level to 'low'. For mortality downgrading was one level due to imprecision and risk of bias, with the point estimate falling in the trivial positive effect. For alemtuzumab the very low overall certainty is driven by the outcomes disability and mortality. For mortality two levels downgraded for imprecision and one for risk of bias, the point estimate falling the trivial negative effect. For disability, downgraded three level for imprecision, point estimate falling in the moderate positive effect. The panel decided to only downgrade by one level imprecision, bringing the level to 'low'. Summary: adjustments of less downgrading for natalizumab, fingolimod and alemtuzumab.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Important uncertainty or variability: **Possibly important uncertainty or variability:** **Probably no important uncertainty or variability:** Interferon beta 1a, Natalizumab, Dimethylfumarate, Alemtuzumab, Ocrelizumab, Cladribine, Mitoxantrone, Fingolimod, Interferon beta 1b, Glatiramer acetate **No important uncertainty or variability:**	**Health State Utility Values** We conducted a scoping review to retrieve the available evidence on Health State Utility Values (HSUVs) for MS. Health utility is a summary index measure of health-related quality of life, usually obtained by means of surveys among people affected by a condition. HSUVs are used to assign a value to health states on a scale on which 1 is equivalent to full health and 0 is considered equivalent to being dead. Values can also be negative, representing health states values worse than being dead. We considered eligible any systematic review, overview, of reviews, HTA report. If such studies were not available, we searched for studies designed to specifically collect Health-Related Quality of Life data, or as part of an RCT or prospective observational study. The search was performed from January 2010 to February 2022 on MEDLINE, Embase, Web of Science Core Collection, the Health Technology Assessment Database, Epistemonikos databases. We retrieved 1,170 citations. After screening of titles and abstracts, detailed assessment of eligibility was performed on 8 reviews (including a report from the Institute for Clinical and Economic Review providing data on utility values based on previously published studies) and 11 primary studies. Data on HSUVs were extracted from four systematic reviews (Chataway 2021, Naci 2010, Zhou 2021, Prevolnik Rupel 2019) and one evidence report (ICER 2017). We also checked all the individual studies included in the 4 systematic reviews. After considering any generic QoL measures, only studies using the EQ-5D tool as the primary outcome measure were appraised to assess QoL among pwMS. This choice was based on the amount of work that has been done about the EQ-5D and its measurement properties. Moreover, it is a commonly used generic QoL instrument that allows for direct derivation of the value a person places on their life at the time the outcome is assessed. Therefore EQ-5D was considered as the most direct measure of QoL among PwMS. Three reviews (Wittenberg 2013, Ngorsuraches 2021, Milinis 2016) were excluded because the topic addressed was not relevant for our aim. Of the 11 individual studies retrieved, two (Hawton 2016, Erikkson 2019) were already included in one systematic review (Chataway 2021); five (Krokavcova 2019, Goodwin 2018, Ahmad 2020, Ahmad 2021, Ahmad 2017) used scales different from the EQ-5D and four (Hernandez 2021, Hawton 212, Hawton 2012 A, Goodwin 2019) addressed topics that were not pertinent. Our review identified published evidence only for some of the outcomes	The panel noted concerns around the accuracy and validity of the HSUVs used for the calculations. There is a lack of evidence for the prioritised HSUVs, especially from the perspective of MS and with input from pwMS. The panel considered there to be significant differences between MS and other disease areas, e.g. due to the young age of pwMS, cognitive decline may be valued very differently than it is among older people with Alzheimer Disease. For a number of HSUVs used in the analysis, the panel had to estimate an appropriate value, based on other MS outcomes. Whilst it was recognised that the methodology was useful as a tool, the panel also felt it should be interpreted with caution, especially in absolute terms. The panel noted the lack of evidence also for the systematic review on values and preferences for pwMS. The evidence suggested that the order of preference for mode of administration was oral, infusion, injections, and that frequency of administration was an important factor. The panel noted personal and anecdotal evidence of infrequent infusions sometimes being preferred over frequent oral medication. The panel judged whether there was important uncertainty in how much people valued the main outcomes **without consideration for the HSUVs and thresholds**. The panel decided to align with previous judgements for PMS, with all DMTs judged as 'probably no uncertainty or variability on the main outcomes'.

voted as critical or important by the panel, since most studies reported HSUVs related to being affected by MS in general. Some studies did not even report the type of MS (relapsing or progressive). Another limitation of the available evidence is that most studies were conducted in high-income countries (HICs) and none was conducted in lower-middle (LMICs) or lower income countries (LICs).

Namely, for the outcomes "QoL impairment" and "relapse" we found evidence in the Chataway 2021 review, including studies assessing the impact of such outcomes on QoL by means of the EQ-5D tool.

For the EDSS- based "Disability " outcome voted by the panel as critical, HSUVs were available for different EDSS scores (6, 7 and 8). Having to choose one utility value for this outcome, the panel agreed to consider the HSUVs related to an EDSS score of 6, based on the following considerations:
- "disability worsening" is a dichotomous outcome (N of patients with the outcome) and the adopted definition of it is: "an increase of 1 EDSS point in participants with a baseline score up to 5, or of 0.5 points for participants with a baseline EDSS ofover 5.5". Therefore, the former includes all cases where the worsening was up to 6. The latter, 6 or higher.
- the EDSS is highly centered on walking ability (EDSS 5.5= Able to walk without aid or rest for 100m ; EDSS 6.0= Requires a walking aid – cane, crutch, etc. – to walk about 100m with or without resting)
- the numerical difference between the HSUVs of EDSS 6 and 7 is small
- An EDSS score of 8 refers to people " Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms". Some of such patients may not have been eligible for inclusion on pivotal trials on DMTs that we are evaluating.
As per the outcomes "New gadolinium-enhancing positive T1 weighted MRI lesions", "New or enlarging T2 weighted MRI lesions", "Serious Adverse Events" and "Discontinuation of treatment due to adverse events (tolerability)", no evidence was retrieved, and the panel agreed on adopting assumed utility values.
We did not find any RCT assessing the outcome "cognitive decline". Also "Mortality" was voted as a critical outcome by the panel, and its utility value - as mentioned above - is zero.

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Preferences and values

We conducted a systematic search and we found two systematic reviews and 5 observational studies (cross-sectional, surveys) reported results on preferences and values.

CONSIDERATIONS FOR PEOPLE AFFECTED BY MS

Webb 2018 did a systematic review of discrete choice experiments and conjoint analysis studies in people with RRMS. Among the 16 studies reviewed, most common attributes were effect on relapse (13, 76.5%), effect on progression (12, 70.6%), as well as severe side effects (12, 70.6%) and mild side effects (13, 76.5%). Also common were route (10, 58.8%) and frequency of administration (13, 76.5%). Only four (23.5%) looked at monitoring of treatment, and another four (23.4%) included further miscellaneous aspects of administration. Six studies (35.3%) explored attributes related to the alleviation of MS symptoms. Three (17.6%) included attributes explicitly related to quality of life, one of which looked specifically at patients' valuation of health-related quality of life. Four (23.5%) included attributes related to MRI scans. Two (11.8%) include an attribute relating to reproduction (male and female) and two (11.8%) had miscellaneous attributes that fitted into no other category.
Visser 2020 reviewed studies which used various methods to identify attributes, such as a literature review, current clinical literature, consultation with clinical experts, DMT trials and interviews or focus groups with patients. The study reports that patients prefer a DMT that decreases relapse rate. Also, patients prefer oral DMTs over injection or infusion therapy. A higher risk of severe side effects was associated with a reduced preference, while minor side effects had no significant impact on patient preferences.

Moreover, naïve patients and patients not using treatment at the time of survey administration (though had prior DMT experience) preferred a treatment with lower duration, type and severity of side effects than patients with treatment experience. Patients with previous DMT use preferred a treatment with high efficacy. At least, patients using first-line DMTs are more averse to fatal risks than those taking a second-line DMTs.

Frost 2019, a survey that analysed barriers and facilitators to the determine patients' preferences and their willingness-to-pay (WTP) that reflected their value of DMTs for MS. Based on clinical literature, economic evaluation and patient preference studies the authors obtained the DMT attributes and their levels. Patients preferred DMTs with a lower relapse rate, lower disability progression, lower severe adverse events, lower frequency. For the route of administration, intuitively, the results showed that the patients preferred oral DMTs. Their next preference was intravenous DMTs, followed by subcutaneous and intramuscular DMTs.

Visser 2021: An online survey to elicit patient preferences for attributes of MS therapies in three Western European countries (the Netherlands, France, and the United Kingdom). Some attributes and attribute levels concerning MS treatment were derived from systematic literature reviews and were verified during two focus group sessions with MS patients.

Respondents had to repeatedly choose between various treatment scenarios with four treatment characteristics: risk of relapse, reduction of disease progression, risk of side effects and mode of administration. Based on the preferences of 753 MS patients, two latent classes (1 and 2) were identified (class probability of 74% vs 26%)

Patients in class 1 generally preferred:

• any treatment over no treatment.

• A treatment to provide less risk of relapse and less disease progression.

• Rare severe side effects were less desirable than very common mild side effects. Moderate side effects were perceived not statistically different from very common mild side effects (p = 0.427).

• one pill per day was most preferred followed by an implant replaced every year, an implant replaced every three years, two pills per day, and injections once per week.

Patients in class 2- preferred:

• no treatment.

• A lower risk of relapse and reducing disease progression

• rare severe side effects were less desirable than very common mild side effects.

• indifferent between common moderate side effects and very common mild side effects (p = 0.169).

• pills twice per day vs implants, whereas injections once per week were not statistically different from the reference level injections three times per week (p = 0.396)

In general, in both classes' patients preferred their treatment to reduce risk of relapse and disease progression, and the presence of rare severe side effects had a negative effect on treatment choice as compared to very common mild side effects.

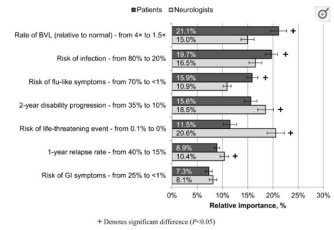
Preferences for modes of administration differed per class, but it was observed that patients generally would be open to having an implant as a mode of administration. Patients were willing to accept an increase in risk of relapse and some disease progression to get their treatment via an implant rather than via injections. Furthermore, the mean predicted uptake was the highest for the implant, followed by pills, injections, and no treatment.

CONSIDERATIONS FOR PATIENTS AND HEALTH PROFESSIONAL

Kumar 2021 conducted a cross-sectional survey using a "discrete choice experiment" approach to assess patient (with non-highly active RRMS) and neurologist treatment preferences.

Among patients, the most important treatment attribute was reducing the rate of BVL, followed by the risk of infection and risk of flu-like symptoms. Reducing the rate of BVL was approximately twice as important to patients as reducing the risk of a life-threatening event, the 1-year relapse rate, and the risk of gastrointestinal symptoms. In contrast, the most important treatment attribute among neurologists was reducing the risk of a life-threatening event, followed by slowing the rate of 2-year disability progression and reducing the risk of infection. Reducing the risk of a life-threatening event was approximately twice as important to neurologists as reducing the risk of flu-like symptoms, the risk of gastrointestinal symptoms, and the 1-year relapse rate.

Figure 1 reports relative importance of treatment attributes among patients and physicians. (Source: Kumar 2021)



Day 2018 selected 2056 participants from the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry and 18 members of the American Academy of Neurology MS DMT guideline development panel to complete a brief survey prioritizing outcomes of importance to MS DMT selection.
Reduced disability progression was identified as a priority outcome by the majority of persons with MS and guideline panelists. More guideline panelists prioritized relapse rate reduction when selecting an MS DMT. No significant differences were observed between respondents concerning other outcomes. Of interest, 46.9% of persons with MS and 33.3% of guideline panelists identified the selection of therapies most likely to lead to improvements in quality of life, MS symptoms, or preservation of cognition, as priority outcomes in DMT selection.
Martinez-Lopez 2020 conducted a multicenter, cross-sectional, web-based study to assess pharmacists´ preferences for DMT efficacy attributes. Treatment efficacy attributes and levels were selected through a review of RRMS clinical trials and patient preferences literature and, finally, were confirmed in a focus group formed by six hospital pharmacists with expertise in MS. Then eight hypothetical treatment scenarios containing unique combinations of attributes and levels were developed. Participants placed the greatest relative importance on delaying disease progression (35.7%), followed by preserving HRQoL (21.6%) and cognition (21.6%). On the base of the number of years of experience managing DMTs (less than 5 years [n = 19], between 5 and 10 years [n = 18], and more than 10 years [n = 28]), was conducted. Overall, no relevant differences were observed between different groups.

CONSIDERATIONS FOR PAYERS
No evidence found

CONSIDERATIONS FOR HEALTH SYSTEM
No evidence found

KEY FINDINGS

- **Patients prefer DMTs that decrease relapse rate, have positive effect on progression, have less severe side effects; minor side effects have no significant impact on preferences;**
- **Patients prefer oral DMTs over injection or infusion therapy and lower frequency of administration;**
- **For clinicians, the most important treatment attribute is reducing the risk of a life-threatening event, followed by slowing the rate of 2-year disability progression and reducing the risk of infection**
- **For pharmacists, the most important treatment attribute is delaying disease progression, followed by preserving quality of life and cognition.**
- **For guideline panelists', reduced disability progression and relapse rate are identified as a priority outcomes.**

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Protocol: https://osf.io/5edjf

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison for each intervention?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Favors the comparison: **Probably favors the comparison:** **Does not favor either the intervention or the comparison:** **Probably favors the intervention:** Ocrelizumab, Mitoxantrone, Interferon beta 1b, Glatiramer acetate **Favors the intervention:** Interferon beta 1a, Natalizumab, Dimethylfumarate, Alemtuzumab, Cladribine, Fingolimod **Varies:** **Don't know:**	Assessing the balance of effects implies judgement. In order to make this process transparent, and noting the complexity generated by a considerable number of outcomes and of interventions to assess, MEMP attributed to each outcome a numerical value (health state utility value (HSUV)) ranging from 0 to 1, where 0=death and 1=full health. Values lower than zero indicate a health state that is considered as worse than being dead. A set of outcome-specific HSUVs, one for each of the critical and important outcomes identified by MEMP, was developed through the following steps: - the evidence review team performed a scoping review of the literature, retrieving 8 reviews (including an evidence report from the Institute for Clinical and Economic Review, ICER, providing data on utility values based on previously published studies) and 11 primary studies. on quality of life (QoL) of people with MS expressed as HSUVs. Detailed assessment was performed on four systematic reviews (Chataway 2021, Naci 2010, Prevolnik Rupel 2019, Zhou 2021) and one evidence report (ICER 2017) measuring QoL by means of the EQ-5D scale, that was considered as the most direct measure of QoL to assess quality of life among persons with MS and it is a commonly used generic QoL instrument allowing for direct derivation of the value a person places on their life at the time the outcome is assessed. (more details about evidence retrieval and selection can be found in the above section "Values"). - each study included in the retrieved systematic reviews was assessed and HSUVs were extracted and shared with MEMP. Unfortunately, most studies provided non-outcome-specific HSUVs, generally related to being affected by MS, therefore - to obtain a list of outcome-specific HSUVs - most values were assumed by the panel. - each outcome-specific HSUV was combined with the point estimate of the absolute risk reduction per 1,000 (and its 95% confidence intervals (CIs)) for that outcome reported in the clinical trials on efficacy and safety of DMTs included in the network metanalysis that MEMP referred to as the evidence base. Such combination of HSUVs and absolute risk reduction (or increase, in case of undesirable effect) estimate was performed by means of a formula based on an international stakeholder survey of thresholds according to disease conditions & HSUVs (Morgano et al., in preparation), according to a new method being implemented by the GRADE Working Group. - the resulting point value (and its 95% CIs) was contextualised within a range of magnitude of effects structured as "trivial", "small", "moderate" and "large", separated by specific thresholds. - the imprecision of such point value was determined by the width of its	The panel decided to take the same approach to avoid duplication between outcomes in HSUV calculations as for PMS. If two time-points are measured, only the one with higher certainty is used. If the certainty is the same, the longer time-frame is used. If both serious adverse events and discontinuation due to adverse events are measured, only discontinuation due to adverse events is used. MRI lesion outcomes are aggregated where there is more than one outcome measured, such as T1 and T2 weighted lesions. The panel noted that the methods suppress the certainty of most DMTs to 'very low'. However, within the 'very low' there are still different levels of certainty. Please note certainty rating adjustments for natalizumab, fingolimod and alemtuzumab. Imprecision is a challenge in the field with small studies and outcomes with high variability or 'soft' (e.g. EDSS) outcomes. More research is needed. Other DMTs with more certainty dimethyl fumarate, cladribine, interferon beta 1a. Previously highlighted issues around the accuracy of the summary value were noted by the panel. Due to feasibility of the EtD methodology, the panel was recommended to shortlist 8-10 medicines for full analysis. <u>Shortlisting</u> The exact ranking of the DMTs should be analysed with caution, because the panel noted that certain medicines had a greater number of prioritized outcomes measured. For medicines with more outcomes this may increase the certainty, but also results in a larger contribution to the net balance than medicines that do not have as many outcomes reported. It was noted that this sum of benefits does not include any benefit for ocrelizumab in relapse reduction, as the outcome measure used in the two trials for relapsing MS (OPERA I and II) used Annualised Relapse Rate (ARR), which was not a measure selected for this analysis. The panel noted that rituximab was not included in the analysis, despite being among the list of treatments considered in both PMS and RMS. There were two trials identified for rituximab. One study (Honce 2019) was deemed not usable because it assessed rituximab in induction before treatment with GA. The other (Hauser 2008) is a small phase II rituximab vs placebo trial for RMS: https://www.nejm.org/doi/10.1056/NEJMoa0706383?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200www.ncbi.nlm.nih.gov but its follow up lasted only 48 weeks. The panel agreed at the outset to consider a minimum timepoint of 52 weeks for the outcomes, therefore Hauser was initially included but it had no data to be extracted given its short follow-up.

95% CIs: one level downgrading for each threshold crossed by the CIs. Downgrading for imprecision was possible up to three levels (e.g. from "high" to "very low").

The table shows the net balance of effects for disease modifying drugs in RMS, resulting from combining desirable and undesirable effects of each drug. Details about thresholds between the four magnitudes of effect ("trivial", "small", "moderate" and "large") can be found here: https://www.msif.org/wp-content/uploads/2022/09/Balance-of-effects-calculations-net-balance.xlsx [https://www.msif.org/supporting-documents-memp-etd/]

The column "Number of outcomes" reports how many outcomes were considered by MEMP to calculate the net balance of effects, among those available for each drug in the RCTs retrieved through the systematic review and NMA that served as the evidence base.

In order to obtain pooled network estimates allowing comparisons among the available treatment alternatives, for each outcome only one measure of effect was necessarily chosen (e.g., the predefined outcome measure for "relapse" was dichotomous: "number of patients with a relapse"). As a consequence, for some of the drugs, not all the data relative to the reported outcomes were extractable and usable for analysis (e.g. trials were relapses were expressed as "annualized relapse rate" - continuous outcome measure - were not extractable and are not reported in the table).

Therefore, the number of important or critical outcomes differed by different intervention due to varying outcomes included in trials (e.g. Drug A had 8 included outcomes, Drug B had 3 included outcomes). The panel noted that this impacted the quantitative benefits and harms across outcomes, but the plain number of outcomes for each drug per-se was not considered as informative for the MEMP decisions. The ranking provided a starting point for discussion when considering the balance of effects, but the approach and limitations needed to be considered carefully when contextualising the information for making recommendations.

To illustrate this point, see interferon 1a and pegylated interferon. From the range of outcomes included, 1a has a sum of desirable effects more than double that of pegylated interferon. Yet if the sum only included outcomes common to both DMTs (relapses), 1a would only have moderate benefit, whilst pegylated interferon would still show large benefit. The reason 1a achieves the large benefit overall is through having data for additional important outcomes, for quality of life, disability and MRI lesions.

Table - Summary net balance of effects with net health state utility values (HSUVs) of disease modifying treatments in RMS

Summary of quantified desirable and undesirable effects – relapsing forms of MS

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	Dimethyl fumarate	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

Note: Use with caution, noting variability of quantified outcomes for different DMTs, e.g. relapse reduction effect for ocrelizumab, ofatumumab and ozanimod not included

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- Chataway 2021 - Chataway J, Murphy N, Khurana V, Schofield H, Findlay J, Adlard N. Secondary progressive multiple sclerosis: a systematic review of costs and health state utilities. Curr Med Res Opin. 2021 Jun;37(6):995-1004. doi:

There are other guidelines for off-label azathioprine and rituximab, by the MOLT panel. These considered randomised and non-randomised controlled trials for the two DMTs: https://www.msif.org/molt-guidelines-azathioprine-rituximab/

The associated rituximab Cochrane review: https://www.cochrane.org/CD013874/MS_rituximab-people-multiple-sclerosis

Rituximab cannot be included in the MEMP list due to lack of RCTs meeting the inclusion criteria. The lack of rituximab in this analysis was noted as an important omission of DMTs widely used in clinical practice.

The panel considered whether azathioprine should be shortlisted even though it ranks number 16. It has large benefit, low cost and is widely available. The panel decided not to include azathioprine, as it has very low certainty of evidence, there was only one RCT (comparing azathioprine with placebo, i.e. direct evidence) with only 59 trial participants, and it was well below a number of other DMTs ranked ahead of it. There is very little systematically collected clinical evidence.

Panel noted post-marketing safety updates for alemtuzumab, natalizumab and fingolimod: http://www.msif.org/wp-content/uploads/2022/08/EMA-safety-warnings_RMS_020622.docx [https://www.msif.org/supporting-documents-memp-etd/]

Daclizumab has been withdrawn from the market, and was therefore not shortlisted.

Mitoxantrone only has regulatory approval by the US FDA, not the EMA, and is now rarely used in high-income countries. It might be an accessible high-efficacy option in low-to-middle income countries.

The panel considered whether only one of the interferon products should be included in the short-list, but decided to keep both products due to their different profiles.

The cut-off for the PMS short-list is 0.029, so the DMTs for RMS are more effective as cut-off at 0.1160.

The panel considered whether to include ponesimod or GA. They decided to include GA, due to good safety in pregnancy and breastfeeding and little monitoring while treating, making it more feasible in low-resource settings. However, GA is not unique for safety in pregnancy but has good profile. The panel decided not to include ponesimod in the short-list. Ponesimod has a similar indication and side effect profile as fingolimod. Fingolimod has other benefits, e.g. follow-on products and currently more available. Fingolimod could represent the S1P modulator class.

The panel noted that the method of estimating the net value by adding up all the outcomes, gives an advantage those RCTs and DMTs that simply measured more outcomes. In practice the effect of this on the ranking is that it gives extra advantage to interferon beta 1a, interferon beta 1b and daclizumab, which measured two QoL outcomes that most of the other DMTs did not measure. This makes the ranking of these two products seem to be more effective than the other DMTs, not because the magnitude of effect is greater, but because they used more outcomes to measure the effect. These QoL measures are therefore additive to the other measures such as disability and relapses.

The ranking is determined by the HSUVs, incorporating several outcomes in addition to those considered in the ocrelizumab vs interferon OPERA trials. In addition, in the two OPERA trials their primary outcome was relapses but these were measured as annual relapse rate (ARR), and not as number of pwMS with relapses, so could not be included in the data extraction and therefore do not count towards the net score for ocrelizumab. In the head-to-head trials, the outcomes of relapse and disability, which were secondary outcomes and therefore not powered to measure differences, were pooled to get the head-to-head results. In pooled relapses and disability of both OPERA trials ocrelizumab is significantly more effective than interferon beta 1a. This is contrast to our ranking in the NMA results.

The panel noted that we are not comparing the relative efficacy and safety risks, but combining this with HSUVs and the other outcomes, including the number of outcomes.

The panel decided to short-list for consideration natalizumab, fingolimod, alemtuzumab, mitoxantrone, interferon beta 1b, dimethyl fumarate, cladribine, interferon beta 1a, ocrelizumab and glatiramer acetate.

Judgements on shortlisted DMTs:

	10.1080/03007995.2021.1904860 • Naci 2010 - Naci H, Fleurence R, Birt J, Duhig A. The impact of increasing neurological disability of multiple sclerosis on health utilities: a systematic review of the literature. J Med Econ. 2010 Mar;13(1):78-89. doi: 10.3111/13696990903543085 • Prevolnik Rupel 2019 - Prevolnik Rupel V, Divjak M, Zrubka Z, Rencz F, Gulácsi L, Golicki D, Mirowska-Guzel D, Simon J, Brodszky V, Baji P, Závada J, Petrova G, Rotar A, Péntek M. EQ-5D studies in nervous system diseases in eight Central and East European countries: a systematic literature review. Eur J Health Econ. 2019 Jun;20(Suppl 1):109-117. doi: 10.1007/s10198-019-01068-9 • Zhou 2021 - Zhou T, Guan H, Wang L, Zhang Y, Rui M, Ma A. Health-Related Quality of Life in Patients With Different Diseases Measured With the EQ-5D-5L: A Systematic Review. Front Public Health. 2021 Jun 29;9:675523. doi: 10.3389/fpubh.2021.675523	This judgement should take into account desirable health effects, all judged as large, undesirable health effects, all judged as trivial, and certainty of evidence. The panel decided to align with the approach taken with PMS and judged all interventions with very low certainty as 'probably favours the intervention' and those with low certainty as 'favours the intervention', i.e. interferon beta 1a, natalizumab, dimethyl fumarate, alemtuzumab, cladribine, fingolimod.

Resources required

How large are the resource requirements (costs) for each intervention?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Large costs: Interferon beta 1a, Natalizumab, Dimethylfumarate, Alemtuzumab, Ocrelizumab, Cladribine, Mitoxantrone, Fingolimod, Interferon beta 1b, Glatiramer acetate **Moderate costs:** **Negligible costs and savings:** **Moderate savings:** **Large savings:** **Varies:** **Don't know:**	Long-term resource requirements are influenced by the DMTs patent status around the world. Patent landscape of DMTs available here: http://www.msif.org/wp-content/uploads/2022/03/DMTs-patent-overview-March-22.pdf Evidence on cost of DMTs for PMS was retrieved from manual search of grey literature (publicly available price databases, non-commercial, governmental agencies, HTA reports). We collected the prices of DMTs used in RMS considering both originators and generics/biosimilars, when available, with registered indication for RMS as well as off-label. Whenever an alternative was available we chose the lowest price. Prices are compared by means of their yearly cost per patient. This was calculated from the cost of one drug unit (tablet, pre-filled syringe, etc.) multiplied by the number of units administered yearly, according to the recommended dosage. Whenever available, ex-factory ("ex-work") price was reported, without taxes and duties/fees for distribution by the pharmacies. All prices are expressed in US Dollars by conversion from the original currency. Prices are structured by country income, according to the World Bank classification Most data are available from HICs that also show a wider availability of DMTs. Since MEMP has a particular interest for low-resource settings in lower income countries, we reported only three HICs (one from southern and one from northern Europe, and the US) and focused mainly in searching information from UMICs, LMICs and LICs. We found no data from the latter. Ex-factory (ex-work) price was retrieved whenever available. Such price does not include taxes and distribution/procurement expenses. In order to make prices comparable across countries, local currencies were converted into US Dollars (currency exchange updated on **June 6 2022**). Whenever different dosages for the same drug were avbialble, we separately reported their price. In case of individualized dosage (e.g. mg per Kg, or per square meter of body surface) we averaged a dose by getting input from clinical MEMP experts or from the dose used in the trial(s). Table 1 reports the price and Divided Daily Dose (DDD) of DMDs used in MS already included in the WHO EML. Table 2 summarizes median prices of each DMT for each patient per year across country incomes. Tables 3 to 4 show details about the drug price in each country and the cost per-unit and the price per patient per year (unit price multiplied by the number of units administered yearly), together with the source of each information. Prices from years before 2020 are not adjusted for inflation to 2022 values. The lowest reported price of each drug across each country income class is in bold green color; the highest in bold red. Abbreviations are listed below after the tables.	Affordability of the different DMTs is a complex topic as drug prices are not always publicly available or transparent. Pathways to affordability: We are aware that tiered pricing has been used in some countries, where substantially lower prices can be negotiated for specific countries or health systems relative to income levels. For example, we are aware of a LMIC with 10 on-label DMTs fully reimbursed by their national health system. The price reductions from listed prices can be at least as high as 75%. If an MS medicine is listed on the EML, a number of avenues to tackle availability and affordability of MS medicines can start through working with our key stakeholders. We can also further develop our relationships with other international organisations such as: 1. The Clinton Health Access Initiative, who are willing to work with the WHO to improve drug access and delivery by resolving the various barriers that are impeding progress. 2. The Medicines Patent Pool is interested to work closely with us to identify opportunities to use voluntary licensing for any patented small molecules for MS, particularly if they are added to the WHO EML. MSIF has also created a theoretical framework for pooled price negotiations for the African region, which would need to be triggered by the listing of DMTs onto the WHO EML. Panel discussion: Drug cost is the major driver of resource requirements, but the panel identified the following additional resource requirements: lab-based diagnostics/monitoring (e.g. JCV testing for natalizumab, monthly blood and urine tests for alemtuzumab, and and complex monitoring for fingolimod), pre-screening and vaccinations (not implemented everywhere yet, but recommended for natalizumab, ocrelizumab, alemtuzumab, fingolimod), costs related to storage (e.g continuous electricity supply to maintain cold chain for GA, IFNs, natalizumab, ocrelizumab, alemtuzumab), management and disposal, pre-infusion preparation and human resources for administration (infusion: natalizumab, ocrelizumab, alemtuzumab) and travel costs by patients to clinics and associated costs for medication to manage side effects. JCV testing needed in particular for natalizumab was considered a considerable issue, although this was sometimes covered by the pharmaceutical company and may be more relevant for feasibility. S1P receptor modulators (fingolimod,) require dermatology screening and opthalmology, otherwise age-appropriate cancer screening with all DMTs. The panel used the same thresholds for costs as for PMS: Large: >$1000/year/patient Moderate costs: >$100/year/patient Negligible/cost-savings: less than $100 To make the final judgements on resource requirements, the panel considered whether the additional considerations would change the judgements. It was concluded that they would only add more cost onto the 'large' costs, so the judgments remained the same.

The following drugs, originally included in the MEMP PICO questions, are not included in the cost comparison tables: **leflunomide, diroximel fumarate, fludarabine, minocycline, mycophenolate mofetil, monomethyl fumarate** (no evidence from RCTs was retrieved); **laquinimod** (no price information was retrieved).
Prices from years before 2020 are not adjusted for inflation to 2022 values.

All terms are compliant with the Glossary of the WHO CC for Pharmaceutical Pricing and Reimbursement Policies of the GÖG / Austrian National Public Health Institute (https://ppri.goeg.at/about_translations).

If comparing drug prices for relapsing and progressive MS in the "Resources Required" domain, please note that price assessment for progressive MS was based on currency exchange rates of April 12, 2022, while price assessment for relapsing MS was performed on **June 6, 2022**. Therefore some differences may be appreciable.

General considerations
Data from price databases suggests that DMT prices are generally higher in HICs, particularly in the US, where they often are multiples of the prices in other HICs.
In UMICs, and particularly in LMICs, they are on average lower, although with notable variability.
The DMT with the lowest median price/year/patient in the considered countries, regardless of their income, is methotrexate, while the highest are immunoglobulins.
Generally, older, out-of-patent drugs show lower prices and also lower price variability, while branded drugs often show a remarkable variability, the highest prices being in the US among the HICs.
Such variability may be in part explained by the healthcare system organisation (insurance-based rather than universal coverage) and by negotiations between the local government and the producers, that are usually confidential and may result in a substantial reduction of prices, sometimes > 50%. Discounts may have various determinants, such as price-volume agreements, presence on the market of short expiry products creating competition, and others.
The only countries for which we reported a negotiated price are Turkey (that adopted a negotiation based on a fixed currency exchange with EUR) and one [LMIC] remaining confidential.
Some drugs may be much less expensive in specific countries because they can be produced locally (e.g. Xacrel, the brand name of ocrelizumab produced in Iran by CinnaGen. An equivalence trial vs Ocrevus® in RRMS is ongoing)
One more determinant of variation in prices may be different timings in patent expiry (e.g. fingolimod, still branded in the EU but generic in other extra-EU countries).
Transparency and consistency should be mandated – if not for confidential agreements – at least in the implementation of policies for local production of drugs and in the application of patent expiry, in order to warrant equity.

Table 1 - International Drug Price Indicator Guide: price of azathioprine, rituximab, methotrexate, methylprednisolone and immunoglobulin

Drug	DDD	High/Low Ratio	Price (US $)	Price DDD (US $)	WHO EML
Azathioprine 50 mg TAB-CAP (PO)	0.15g				C
Supplier Number of Prices=1			0.1741/TAB-CAP	0.523	
Buyer Number of Prices=3		2.37	0.1463/TAB-CAP (median)	0.439	
Rituximab 10 mg/ml AMP (INJ)	N/A**				C
Supplier Number of Prices=0					
Buyer Number of Prices=4		1.77	13.6721/ML (median)	N/A	
Methotrexate sodium 2,5 mg TAB-CAP (PO)	2.5 mg				C
Supplier Number of Prices=4		3.63	0.1573/TAB-CAP	0.1573	
Buyer Number of Prices=3		2.12	0.0629/TAB-CAP (median)	0.0629	
Methylprednisolone (sodium succinate) 1g VIAL (INJ)	20 mg				C, P
Buyer Number of Prices=2		1.62	10.3808/VIAL	0.207	
Immunoglobulin, Human 5% VIAL (1 VIAL=100 ML) **(INJ)**					
Buyer Number of Prices=1	N/A		188.43	N/A	N

NOTES, ABBREVIATIONS

Rituximab = 13. 6721 x 50 ml= 683.60 $
Category C of the WHO International Medical products Price Guide=drug included in the complementary list of the WHO EML in the same dosage form and strength
Category P of the WHO International Medical products Price Guide=drug included in the list of WHO EML but in a different presentation (different dosage form and/or strength)
Category N= Not present in EML

Azathioprine and methotrexate are currently included in the Essential Medicines List (EML) as Disease-Modifying Anti-Rheumatic Drugs (DMARDs) (29.2) and azathioprine only, also among Immunomodulators for Non-Malignant Disease (8.1).
Rituximab is included in the EML in the Antineoplastics and Supportive Medicines list, among Targeted Therapies (8.2.2).
Methylprednisolone is included in the EML as Hormones and Antihormones (8.2.4).
Intravenous immunoglobulin is included as Plasma-derived Medicines for Primary Immune Deficiency and Kawasaki Disease. (11.2.1)

While all medicines were assessed as large costs, the panel noted that some medicines had an order of magnitude higher costs: alemtuzumab, cladribine, natalizumab and ocrelizumab.

Note: Cladribine prices are for oral on-label cladribine, off-label cladribine prices were not considered.

The panel noted that the costs for alemtuzumab and cladribine show the cost for the years of treatment (year 1 and 2), but these DMTs are not taken continuously and are effective for a number of years after the first two years. Other DMTs are taken continuously. Cost per person per year is much lower if considered over the time of effectiveness and the cost-effectiveness data supports this. However, there are patients who require subsequent treatment cycles.

Mitoxantrone had lower costs, but considerable long-term monitoring and safety risks.

The panel commented on the substantially lower prices mainly seen in LMICs rather than UMICs. However, there are some exceptions, e.g. fingolimod and natalizumab which are substantially discounted in UMIC as well. This may be due to follow-on products becoming more available.

Table 2 - Median price (cost per-patient per-year in USD) and price range of DMDs for RRMS in a sample of HICs, UMICs and LMICs.

DMTs shortlisted by MEMP are highlighted in yellow

Drug, formulation	HIC *[range]*	UMIC *[range]*	LMIC *[range]*
Alemtuzumab (Lemtrada ®) 12mg INJ	42,635 *[34,090-96,374]*	35,831 *[32,570-42,375]*	36,385 * (India)
Azathioprine 50mg TAB **	209 *[4,303 - 120]*	361 *[350 -1,632]*	329 *[142 - 548]*
Cladribine (Mavenclad ®) 10mg TAB	26,298 *[24,684 – 62,628]*	23,834 *[9,480-31,104]*	6,602 * (LMIC)
Cyclophosphamide 1 g POW **	195 *[153 -6,121]*	118 *[114 -132]*	13 * (India)
Dimethylfumarate (Tecfidera ®) 240mg TAB	13,140 *[13,140 – 1,000]*	10,685 *[1,405 -16,286]*	1,028 *[523 – 2,688]*
Fingolimod (Gylenia®) 0,5 mg TAB	22,692 *[21,736 – 80,782]*	9,998 *[3,106 – 16,706]*	3,560 *[960 – 20,294]*
Glatiramer acetate 40 mg/ml INJ	8,511 *[6,355 -12,566]*	6,618 *[1,987 – 11,797]*	960 * (Iran)
Immunoglobulin 10 g INJ **	46,020 * Italy	44,772	-
Immunoglobulin 30 g INJ **	78,677 § *[102,132 -55,224]*	55,497 * Brazil	-
Interferon beta 1a (Avonex ®) 0.03 mg/0,5 ml INJ	9,932 *[8,164 -68,536]*	10,452 *[2,341 – 14,144]*	3,440 *[600 – 10,452]*
Interferon beta 1b (Rebif ®) 0.022 mg/0,5 ml INJ	9,516 *[9,268 -69,108]*	7,961 *[4,872 – 9,717]*	7,675 §
Interferon beta 1b (Rebif ®) 0.044 mg/0,5 ml INJ	12,879 *[10,664 – 68,640]*	9,729 *[2,488 – 12,429]*	10,684 *[3,594 – 14,664]*
Interferon beta 1b (Betaferon ®) (Extavia ®) 0.250 mg/ml INJ	9,951 *[6,491 -35,126]*	9,250 *[1,981 -13,362]*	3,670 *[720 – 11,076]*
Methotrexate 7,5 mg TAB **	20 § *[19 – 21]*	27 *[20 – 43]*	8 * (India)
Methylprednisolone 1g INJ **	302 *[216 – 334]*	280 § *[220 – 340]*	60 * (India)
Mitoxantrone 2mg/ml INJ	1,307 *[1,079 -2,668]*	1,896 *[1,569 – 2,979]*	-
Natalizumab (Tysabri®) 300 mcg/15 ml INJ	22,633 *[18,460 - 56,633]*	16,783 *[10,946 – 21,645]*	4,603 *[3,600 -24,141]*
Ocrelizumab (Ocrevus ®) 300 mg/10 ml INJ	24,192 *[24,090 - 66,681]*	17,928 *[6,790 - 25,296]*	4,600 *[1,200 – 22,580]*
Ofatumumab (Kesimpta ®) 20mg INJ	22,032 *[15,864 – 62,490]*	12,732 *[11,376 – 17,796]*	-
Ozanimod (Zeposia ®) 0.92mg TAB	23,623 *[16,042 – 66,120]*	-	-
Peg-Interferon beta 1a (Plegridy ®) 0.125mg INJ	11,195 *[11,195 – 68,692]*	5,817 *[2,304 – 11,717]*	2,751 * (India)
Ponesimod (Ponvory ®) 20mg TAB	21,542 *[21-535 – 73,055]*	-	-
Rituximab 500 mg, 10 mg/ml INJ **	4,298 *[3,912 – 8,813]*	3,089 *[2,899 – 4,596]*	2,330 *[120 – 7,184]*
Siponimod (Mayzent ®) 2 mg TAB	25,159 *[23,867 – 72,215]*	14,731 *[7,402 – 30,503]*	-
Teriflunomide (Aubagio ®) 14mg TAB	12,914 *[10,461 – 71,190]*	8,698 *[1,693 – 10,585]*	2,004 *[431 – 11,326]*

Abbreviations: HIC=high income countries, INJ=injectable, LMIC= lower-middle income countries, POW=Powder for Injection; TAB=tablets, UMIC=upper-middle income countries

Decimals are rounded

* Price available in only one country** for RRMS and PMS

§ Mean (only two values available)

Currency exchange rates as of June 6, 2022

TABLE 3 - Prices of disease modifying treatments for RMS in a sample of High Income Countries (HIC)

Prices are **ex-factory**, unless otherwise indicated and do not include VAT and duties/fees for distribution by the pharmacies
Currency: USD. When three or more values where available, green color indicates the least expensive and red color the most expensive within the category of country income.
Currency conversion: www.xe.com (accessed 06/06/2022). 1 EUR = 1,07225 USD, 1 USD = 0.932615 EUR

Drug, formulation	Italy*				Norway^^				VA U.S. DEPARTMENT OF VETERANS AFFAIRS (Office of Procurement, Acquisition and Logistics (OPAL)**			
	NPP	*NPP CPY*	BUP	*BUP CPY*	NPP	*NPP CPY*	BUP	*BUP CPY*	NPP	*NPP CPY*	BUP	*BUP CPY*
Alemtuzumab (Lemtrada ®) 12mg INJ	-	-	8,527	*42,635*	-	-	*6,818*	***34,090***	-	-	19,274.79	***96,373***
Azathioprine 50mg TAB	0.19	*208.05*	-	-	-	-	*0.11 #*	***120.45 #***	3.93	***4,303***		
Cladribine (Mavenclad ®) 10mg TAB	-	-	2,057	***24,684***	-	-	*2,191*	*26,298*	-	-	5,219.01	***62,628***
Cyclophosphamide 1 g POW	-	-	11.79	***153.27***	-	-	15.00	*195.00*	470.87	***6,121***	-	-
Dimethylfumarate (Tecfidera ®) 240mg TAB	-	-	20.37	***14,870***	-	-	18.00	*13,140*	-	-	1.37	***1,000***
Fingolimod (Gylenia ®) 0,5 mg TAB	-	-	62.17	22,692	-	-	59.55	***21,735***	-	-	221.32	***80,781***
Glatiramer acetate 40 mg/ml INJ	40.74	***6,355***	-	-	54.56	*8,511*	-	-	80.49	***12,556***		
Immunoglobulin 10 g INJ*	590.00	*46,020*	-	-	-	-	-	-	-	-		
Immunoglobulin 30 g INJ^^	-	-	-	-	2,124.00	***55,224***	-	-	-	-	1,964.07	***102,131***
Interferon beta 1a (Avonex ®) 0.03 mg/0,5 ml INJ	-	-	191	*9,932*	-	-	157	***8,160***	-	-	1,318	***68,536***
Interferon beta 1a (Rebif ®) 0.022 mg/0,5 ml INJ	-	-	61	*9,516*	-	-	59.41	***9,267***	-	-	443	***69,108***
Interferon beta 1a (Rebif ®) 0.044 mg/0,5 ml INJ	-	-	82.56	*12,879*	-	-	68.36	***10,664***	-	-	440	***68,640***
Interferon beta 1b (Betaferon ®) (Extavia ®) 0.250 mg/ml INJ	-	-	54.68	*9,951*	-	-	35.67	***6,491***			193	***35,126***
Methotrexate 7,5 mg TAB	0.13	***20.28***	-	-	0.12	***18.72***	-	-	-	-	-	-
Methylprednisolone 1g INJ	16.60	***215.80***	-	-	23.23	*301.99*	-	-	-	-	25.72	***334.36***
Mitoxantrone 2mg/ml INJ	89.96	***1,079***	-	-	222.36	***2,668***	-	-	108.94	1,307		
Natalizumab (Tysabri ®) 300 mcg/15 ml INJ	-	-	1,741	*22,633*	-	-	1,420	***18,460***	-	-	4,356	***56,633***
Ocrelizumab (Ocrevus ®) 300 mg/10 ml INJ	-	-	6,048	*24,192*	-	-	6,022	***24,089***	-	-	16,670	***66,680***
Ofatumumab (Kesimpta ®) 20mg INJ	-	-	1,322	***15,864***	-	-	1,836	*22,032*	-	-	5,207	***62,489***
Ozanimod (Zeposia ®) 0.92mg TAB	-	-	43.95	***16,041***	-	-	64.72	*23,622.80*	-	-	181.15	***66,119***
Peg-Interferon beta 1 a (Plegridy ®) 0.125mg INJ	-	-	430.57	*11,194*	-	-	474.00	***12,324***	-	-	2,642	***68,692***
Ponesimod (Ponvory ®) 20mg TAB	-	-	59	***21,535***	-	-	59.02	*21,542*	-	-	200.15	***73,054***
Rituximab 500 mg, 10 mg/ml INJ	1,074	4,297	-	-	978	***3,912***	-	-	2,203.13§	***8,812 §***	-	-
Siponimod (MayzentR) 2 mg TAB	-	-	65.39	***23,867***	-	-	68.93	*25,159*	-	-	197.85	***72,215***
Teriflunomide (Aubagio ®) 14mg TAB	-		35.38	*12,913*	-	-	28.66	***10,460***	-	-	195.04	***71,189***

* Ex-factory price from: http://www.farmadati.it/ (accessed 07.04.2022)
^^ Norway https://legemiddelverket.no/english/public-funding-and-pricing/maximum-price#list-of-products-with-maximum-prices (accessed 01.04.2022).
** VA U.S. https://www.va.gov/opal/nac/fss/pharmprices.asp (accessed 01.04.2022)
# Imurel ®
§ Truxima

TABLE 4 - Prices of disease modifying treatments for RMS in a sample of Upper-Middle Income Countries (UMIC)

Prices are **ex-factory**, unless otherwise indicated and do not include VAT and duties/fees for distribution by the pharmacies
Currency: USD
When three or more values are available, green color indicates the least expensive and red color the most expensive within the category of country income.
Currency conversion: www.xe.com (accessed 06/06/2022, unless otherwise specified); 1 EUR = 1.07225 USD, 1 USD = 0.932515 EUR; 1 ZAR = 0.0652688 USD, 1 USD = 15,3213 ZAR, 1 BRL = 0.209160 USD, 1 USD = 4,78103 BRL; 1 MYR = 0,227702 USD, 1 USD = 4,35171 MYR; 1 COP = 0,000263059 USD, 1 USD = 3.801,42 COP, 1 LBP = 0,000663350 USD, 1 USD = 1.507,50 LBP

Drug, formulation	Serbia ‡				South Africa§				Brazil*			
	NPP	*NPP CPY*	BUP	*BUP CPY*	NPP	*NPP CPY*	BUP	*BUP CPY*	NPP	*NPP CPY*	BUP	*BUP CPY*
Alemtuzumab (Lemtrada ®) 12mg INJ	--	-	8,475	***42,375***	-	-	6,529	*32,645*	-	-	6,761	*33,808*
Azathioprine 50mg TAB	-	-	-	-	-	-	0.33	*361.35*	0.32	***350.40***	-	-
Cladribine (Mavenclad ®) 10mg TAB	-	-	1,549	*18,588*	-	-	-	-	-	-	*1,948*	*23,376*
Cyclophosphamide 1 g POW	-	-	-	-	-	-	8.77	***114***	-	-	10.17	***132.21***
Dimethylfumarate (Tecfidera ®) 240mg TAB	-	-	-	-	-	-	7.24	*5,285*	10.70	*7,811*	-	-
Fingolimod (Gylenia ®) 0.5 mg TAB	-	-	-	-	-	-	13.38	*4,883*	18.85	*6,880*	-	-
Glatiramer acetate 40 mg/ml INJ	-	-	-	-	-	-	8.74	*2,727*	-	-	69.39	*10,824.84*
Immunoglobulin 10 g INJ^	-	-	-	-	-	-	323 #	***21,005 #***	-	-	--	-
Immunoglobulin 30 g INJ^^	-	-	-	-	-	-	-	-	-	-	1,423	*55,497*
Interferon beta 1a (Avonex ®) 0.03 mg/0.5 ml INJ	-	-	-	-	-	-	102	*5,304*	-	-	272	***14,144***
Interferon beta 1b (Rebif ®) 0.022 mg/0.5 ml INJ	-	-	-	-	-	-	31.23	***4,872***	51.03 §§	*7,960* §§	-	-
Interferon beta 1b (Rebif ®) 0.044 mg/0.5 ml INJ	-	-	-	-	-	-	34.79	*5,427*	57.74 §§	*9,007.44* §§	-	-
Interferon beta 1b (Betaferon ®) (Extavia ®) 0.250 mg/ml INJ	-	-	-	-	-	-	27	*4,914*	-	-	73.42	***13,362***
Methotrexate 7.5 mg TAB	-	-	-	-	0.13	***20.28***	-	-	0.17	*26.52*	-	-
Methylprednisolone 1g INJ	-	-	-	-	-	-	26.18	***340.34***	-	-	-	-
Mitoxantrone 2mg/ml INJ	-	-	-	-	158	*1,896*	-	-	248	***2,978***	-	-
Natalizumab (Tysabri ®) 300 mcg/15 ml INJ	-	-	1,515	*19,695*	-	-	842	***10,946***	-	-	1,049	*13,643*
Ocrelizumab (Ocrevus ®) 300 mg/10 ml INJ	-	-	5,384	*21,536*	-	-	1,697	***6,790***	-	-	5,189	*20,756*
Ofatumumab (Kesimpta ®) 20mg INJ	-	-	-	-	-	-	-	-	-	-	1,483	***17,796***
Peg-Interferon beta 1 a (Plegridy ®) 0.125mg INJ	-	-	-	-	-	-	204	*5,304*	-	-	243.49	*6,330*
Rituximab 500 mg, 10 mg/ml INJ	-	-	-	-	725	***2,899***	-	-	-	-	769	*3,076*
Siponimod (Mayzent ®) 2 mg TAB	-	-	-	-	-	-	20.28	***7,402***	-	-	30.08	*10,979*
Teriflunomide (Aubagio ®) 14mg TAB	-	-	23.83	*8,698*	-	-	13.90	*5,073*	-	-	21.31	*7,778*

* Remunet ®
‡ Expert input (personal communication)
§ South Africa http://www.mpr.gov.za/Published/Documents.aspx#DocCatId=21 (accessed 06.04.2022)
* Brazil https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/cmed/precos/capa-listas-de-precos (accessed 04.03.2022)
# *12 g by IG*
0.440,22 mg generic IFN beta 1a

Table 4 – (continued)

Drug, formulation	Lebanon*^				Colombia ‡				Malaysia ‡				Turkey‡			
	NPP	*NPP CPY*	BUP	*BUP CPY*	NPP	*NPP CPY*	BUP	*BUP CPY*	NPP	*NPP CPY*	BUP	*BUP CPY*	NPP	*NPP CPY*	BUP	*BUP CPY*
Alemtuzumab (Lemtrada ®) 12mg INJ	-	-	7,571	*37,855*	-	-	*NA*	***32,570***	-	-	8,088	40,440	-	-	-	-
Azathioprine 50mg TAB	-	-	1.49 *	***1,632 ***	-	-	-	-	-	-	-	-	-	-	-	-
Cladribine (Mavenclad ®) 10mg TAB	-	-	2,256	*27,072*	-	-	*NA*	***31,104***	-	-	2,024	*24,293*	-	-	*NA*	***788***
Cyclophosphamide 1 g POW	-	-	9.11	*118*	-	-	-	-	-	-	-	-	-	-	-	-
Dimethylfumarate (Tecfidera ®) 240mg TAB	-	-	18.91	*13,804*	-	-	*NA*	*13,560 ‡*	-	-	22.31	***16,286***	-	-	*NA*	***1,405***
Fingolimod (Gylenia ®) 0.5 mg TAB	44.08	*16,089*	-	-	-	-	*NA*	*13,116*	-	-	45.77	***16,706***	*NA*	***3,106***	-	-
Glatiramer acetate 40 mg/ml INJ			75.62	***11,797***	-	-	*NA*	*6,618*		-	-	-	-	-	*NA*	***1,987***
Immunoglobulin 10 g INJ	574	***44,772***	-	-	-	-	-	-	-	-	117.72^	*36,729^*	-	-	-	-
Immunoglobulin 30 g INJ	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Interferon beta 1a (Avonex ®) 0.03 mg/0.5 ml INJ	-	-	226.74	*11,790*	-	-	-	-	-	-	-	-	-	-	*NA*	***2,341***
Interferon beta 1b (Rebif ®) 0.022 mg/0.5 ml INJ	-	-	62.29	***9,717***	-	-	-	-	-	-	-	-	-	-	-	-
Interferon beta 1b (Rebif ®) 0.044 mg/0.5 ml INJ	-	-	79.67	***12,429***	-	-	*NA*	*10,860*	-	-	*67*	*10,452*	-	-	*NA*	***2,488***
Interferon beta 1b (Betaferon ®) (Extavia ®) 0.250 mg/ml INJ	--	-	51.79	*9,426*	-	-	*NA*	*11,184*	-	-	49.86	*9,075*	-	-	*NA*	***1,981***
Methotrexate 7.5 mg TAB	0.55	***43***	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Methylprednisolone 1g INJ	-	-	16.90	***220***	-	-	-	-	-	-	-	-	-	-	-	-
Mitoxantrone 2mg/ml INJ	130.72	***1,569***														
Natalizumab (Tysabri ®) 300 mcg/15 ml INJ	-	-	1,665	***21,645***	-	-	*NA*	*17,760*	-	-	*1,291*	*16,783*	-	-	*NA*	*12,215*
Ocrelizumab (Ocrevus ®) 300 mg/10 ml INJ	-	-	6,324	***25,296***	-	-	*NA*	*17,928*	-	-	*2,583*	*10,332*	-	-	*NA*	*7,484*
Ofatumumab (Kesimpta ®) 20mg INJ	-	-	1,102	*13,224*	-	-	*NA*	***11,386***	-	-	*1,020*	*12,240*	-	-	-	-
Peg-Interferon beta 1 a (Plegridy ®) 0.125mg INJ	-	-	450.64	***11,717***	-	-	-	-	-	-	-	-	-	-	*NA*	***2,304***
Rituximab 500 mg, 10 mg/ml INJ	726.30	*2,905*	1,149	***4,596***	-	-	*NA*	*4,370*	-	-	*775.57*	*3,102*	-	-	-	-
Siponimod (Mayzent®) 2 mg TAB	-	-	50.64	*18,484*	-	-	-	-	-	-	*83.57*	***30,503***	-	-	-	-
Teriflunomide (Aubagio ®) 14mg TAB	-	-	29	***10,585***	-	-	*NA*	*10,444*	-	-	*26.87*	*9,808*	-	-	*NA*	***1,693***

NA Not available
‡ Expert input (personal communication)
*^ Lebanon https://www.moph.gov.lb/en/Drugs/index/34948/lebanon-national-drug-index (accessed 08.04.2022)
* Imuran ®
^ Xanax ®

TABLE 5 - Prices of disease modifying treatments for RMS in a sample of Lower-Middle Income Countries (LMIC)

Prices are **ex-factory**, unless otherwise indicated and do not include VAT and duties/fees for distribution by the pharmacies
Currency: USD
Exchange rates: www.xe.com (accessed 06/06/2022 unless otherwise specified). 1 INR = 0,0128775 USD, 1 USD = 77,6547 INR; 1 NGN = 0,00240890 USD, 1 USD = 415,127 NGN; 1 GHS = 0,126559 USD, 1 USD = 7,89519 GHS, 1 KES = 0,00854762 USD, USD = 116,992 KES

Drug, formulation	Nigeria‡				Ghana‡				Morocco‡				India*‡			
	NPP	*NPP CPY*	BUP	*BUP CPY*	NPP	*NPP CPY*	BUP	*BUP CPY*	NPP	*NPP CPY*	BUP	*BUP CPY*	NPP	*NPP CPY*	BUP	*BUP CPY*
Alemtuzumab (Lemtrada ®) 12mg INJ	-	-	-	-	-	-	-	-	-	-	-	-	-	-	7,277	*36,385*
Azathioprine 50mg TAB	0.16	*350*	-	-	0.50	***548***	-	-	-	-	0.30 *	*329* *	0.13	***142.35***	-	-
Cyclophosphamide 1 g POW	-	-	-	-	-	-	-	-	-	-	-	-	1.02	*13.26*	-	-
Dimethylfumarate (Tecfidera ®) 240mg TAB	-	-	-	-	-	-	-	-	-	-	-	-	NA	*523.44*	NA	***2,688***
Fingolimod (Gylenia ®) 0.5 mg TAB	-	-	-	-	-	-	-	-	--	-	55.60	***20,294***	-	-	-	-
Interferon beta 1a (Avonex ®) 0.03 mg/0.5 ml INJ	-	-	-	-	-	-	-	-	-	-	201	***10,452***	-	-	-	*1,325.08*
Interferon beta 1a(Rebif ®) 0.022 mg/0.5 ml INJ	-	-	-	-	-	-	-	-	-	-	51.40	***8,018***	-	-	-	-
Interferon beta 1a (Rebif ®) 0.044 mg/0.5 ml INJ	-	-	-	-	-	-	-	-	-	-	68.49	10,684	-	-	-	-
Interferon beta 1b (Betaferon ®) 0.250 mg/ml INJ	-	-	-	-	-	-	-	-	-	-	213	***11,076***	-	-	-	-
Methotrexate 7.5 mg TAB	-	-	-	-	-	-	-	-	-	-	-	-	0.15	*7,80*	-	-
Methylprednisolone 1g INJ	-	-	-	-	-	-	-	-	-	-	-	-	4.59	*59.67*	-	-
Natalizumab (Tysabri ®) 300 mcg/15 ml INJ	-	-	-	-	-	-	-	-	-	-	1,857	***24,141***	-	-	NA	*12,792*
Ocrelizumab (Ocrevus ®) 300 mg/10 ml INJ	-	-	-	-	-	-	876	*3,504*	-	-	5,645	***22,580***	-	-	-	-
Peg-Interferon beta 1 a (Plegridy ®) 0.125mg INJ	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NA	*2,750.64*
Rituximab 500 mg, 10 mg/ml INJ	394.59	*1,578*	-	-	-	-	-	-	-	-	1,215	*4,860*	141.68	*566.72*	-	-
Teriflunomide (Aubagio ®) 14mg TAB	-	-	-	-	-	-	-	-	-	-	31.03	*11,326*	NA	***431***	NA	*2,004*

NA=Not available
* India https://www.nppaindia.nic.in/wp-content/uploads/2020/10/Ceiling-Price-List-F.pdf (accessed 31.03.2022)
‡ Expert input (personal communication)
# Imurel ®

TABLE 5 (continued)

Drug, formulation	Sri Lanka §				[LMIC]^ **				Kenya *				Iran *			
	NPP	*NPP CPY*	BUP	*BUP CPY*	NPP	*NPP CPY*	BUP	*BUP CPY*	NPP	*NPP CPY*	BUP	*BUP CPY*	NPP	*NPP CPY*	BUP	*BUP CPY*
Azathioprine 50mg TAB	-	-	-	-	-	-	-	-	*0.17*	*186*	-	-	-	-	-	-
Cladribine (Mavenclad ®) 10mg TAB	-	-	-	-	-	-	*NA*	*6,602*	-	-	-	-	-	-	-	-
Dimethylfumarate (Tecfidera ®) 240mg TAB	-	-	-	-	-	-	*NA*	*1,533*	-	-	-	-	-	-	*NA*	***840***
Fingolimod (Gylenia ®) 0.5 mg TAB	*7.50*	*2,738*	-	-	-	-	*NA*	*4,380*	-	-	-	-	*NA*	***960***	-	-
Glatiramer acetate 40 mg/ml INJ	-	-	-	-		-	-	-	-	-	-	-	-	-	*NA*	*960*
Interferon beta 1a (Avonex ®) 0.03 mg/0.5 ml INJ	-	-	-	-	-	-	*NA*	*3,280*	*171*	*8,892*	-	-	*NA*	***600***	*NA*	*3,600*
Interferon beta 1a (Rebif ®) 0.022 mg/0.5 ml INJ	-	-	47	***7,332***	-	-	-	-	-	-	-	-	-	-	-	-
Interferon beta 1a (Rebif ®) 0.044 mg/0.5 ml INJ	-	-	94	***14,664***	-	-	*NA*	***3,594***	-	-	-	-	-	-	-	-
Interferon beta 1b (Betaferon ®) 0.250 mg/ml INJ	-	-	-	-	-	-	*NA*	*3,739*	-	-	-	-	*NA*	***720***	*NA*	*3,600*
Natalizumab (Tysabri ®) 300 mcg/15 ml INJ	-	-	-	-	-	-	*NA*	*5,607*	-	-	-	-	-	-	*NA*	***3,600***
Ocrelizumab (Ocrevus ®) 300 mg/10 ml INJ	-	-	-	-	-	-	*1,423.25*	*5,693*	-	-	-	-	*NA*	***1,200***	-	-
Rituximab 500 mg, 10 mg/ml INJ	-	-	-	-	-	-	*582.48*	*2,329*	*1,026*	*4,104*	*1,796*	***7,184***	*NA*	***120***	-	-
Teriflunomide (Aubagio ®) 14mg TAB	-	-	-	-	-	-	*NA*	***3,427***	-	-	-	-	-	-	*NA*	*840*

NA Not available
* Expert input (personal communication)
** Negotiated price
^ Confidential expert input from LMIC
§ Expert input (personal communication). Wholesale price

ABBREVIATIONS
BUP=Brand Unit Price; **CAP=**capsule; **CPY**=cost per-patient-per-year; **INJ**=injectable; **NPP**=Non-Proprietary Name Unit Price; **POW**=powder for injection; **TAB**=tablet

ASSUMED DMT DOSAGE

· ***Alemtuzumab****: one 12mg vial/day i.v. in 5 consecutive days per year = 5 12mg vials per year*
· ***Azathioprine****: (average dose) one 50mg tablet x 3/day (target dose 2.5mg/Kg/day) = 1,095 50mg tablets/year*
· ***Cladribine****: one 10mg tablet/day for two weeks (2 one-week cycles); 1.75mg/Kg = twelve 10mg tablets per cycle (body weight range 60 to 70kg)*
· ***Cyclophosphamide****: 750mg/square meter (900mg)/4 weeks i.v. = 13 vials per year*
· ***Dimethylfumarate****: one 240mg tablet bid = 730 240mg tab per year*
· ***Fingolimod****: one 0.5mg cap/day = 365 0.5mg caps per year*
· ***Glatiramer acetate****: one 40mg vial x 3/week s.c. = 156 40mg vials per year*
· ***Interferon beta 1a (Avonex ®)****: one 0.03mg vial/week i.m. = 52 0.03mg vials per year*
· ***Interferon beta 1a (Rebif ®)****: one 0.22mg - 0.044 mg vial x 3/week s.c. = 156 0.22 mg vials per year*
· ***Interferon beta 1b****: one 0.250 mg vial every other day s.c. = 182 0.250 mg vials per year*
· ***IvIG****: 1,000mg/Kg/4 weeks (60Kg) i.v. = 60g/4 weeks i.v.= 780g/year (dosage as in Hommes 2004)*
· ***Methotrexate****: 7.5mg (3 2.5mg tablets)/week = 156 tablets per year*
· ***Methylprednisolone****: one 1,000mg vial/4 weeks i.v. = 13 1,000mg vials per year (although it has been tested in trials as DMT, methylprednisolone is an acute treatment)*
· ***Mitoxantrone****: 8 mg/square meter/month i.v. =12 2mg/ml vials 10 ml per year*
· ***Natalizumab****: one 300mg vial/4 weeks i.v. = 13 300mg vials per year*
· ***Ocrelizumab****: one 600mg vial/6 months i.v.= four 300mg vials per year*
· ***Ofatumumab****: one 20mg vial/month s.c.= twelve 20mg vials per year*
· ***Ozanimod****: one 0.92 mg cap/day = 365 0.92mg caps per year*
· ***Peg-Interferon beta 1a****: one 125mcg vial/2 week s.c. or i.m.= 26 125mcg vials per year*
· ***Ponesimod****: one 20mg tablet/day (maintenance dose) = 365 20mg tablets per year*
· ***Rituximab****: four 500mg vials i.v. in one session per year (starting dose*

1,000mg i.v. twice two weeks apart; retreatment 1,000mg (two vials) i.v. after 6-9 months

· ***Siponimod**: one 2mg tablet/day = 365 2mg tablets per year*

· ***Teriflunomide**: one 14mg tablet/day = 365 14mg tablets per year*

Drug	Drug Unit
Alemtuzumab (Lemtrada ®)	One 12 MG vial
Azathioprine	One 50mg tab
Cladribine (Mavenclad ®)	One 10 mg tab
Cyclophosphamide	One 1 g VIAL POW
Dimethylfumarate (Tecfidera ®)	One 240mg tab
Fingolimod (Gylenia ®)	One 0.5mg tab
Glatiramer acetate	One 40mg /1ml pre-filled syringe
Immunoglobulin	One 10g dose
Immunoglobuilin	One 12g dose
Immunoglobulin	One20g dose
Immunoglobulin	One30g dose
Interferon beta 1a (Avonex ®)	One 0.03mg/0.5ml pre-filled syringe
Interferon beta 1b (Rebif ®)	One 0.044mg/0.5ml pre-filled syringe
	One 0.022mg/0.5ml pre-filled syringe
Interferon beta 1b (Betaferon ®)	One 0.0250mg/1ml vial
Methotrexate	One 7.5mg tab
Methylprednisolone	One 1000mg vial
Mitoxantrone	One 2 mg/ml vial
Natalizumab (Tysabri ®)	One 300 mcg/15 ml vial
Ocrelizumab (Ocrevus ®)	One 10ml/300mg vial
Ofatumumab (Kesimpta ®)	One 20 mg pen
Ozanimod (Zeposia ®)	One 0.92mg cap
Ponesimod (Panvory ®)	One 20 mg tab
Peg-Interferon beta 1a 125 mcg	One 125 mcg vial
Rituximab 500 mg,	One 50ml/500mg vial
Siponimod (Mayzent ®)	One 2mg tab
Teriflunomide (Aubagio ®)	One 14mg tab

ABBREVIATIONS

CAP=capsule**; POW**=powder for injection; **TAB**=tablet

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Very low: **Low:** **Moderate:** **High:** **No included studies:**		

Cost effectiveness

Which intervention does the cost effectiveness favor?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Favors the comparison: **Probably favors the comparison:** **Does not favor either the intervention or the comparison:** **Probably favors the intervention:** Alemtuzumab, Cladribine **Favors the intervention:** **Varies:** Interferon beta 1a, Natalizumab, Dimethylfumarate, Ocrelizumab, Fingolimod, Interferon beta 1b, Glatiramer acetate **No included studies:** Mitoxantrone	Cost-effectiveness is influenced by resource requirements, which are influenced by the medicines patent status. Patent landscape of DMTs available here: http://www.msif.org/wp-content/uploads/2022/03/DMTs-patent-overview-March-22.pdf 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. All types of economic analysis were considered, conducted in model-based or trial-based frameworks. Searches adopting filters specific to economic evidence were performed on February 17, 2022, from inception, on the following databases: MEDLINE, EMBASE and SCOPUS. The search retrieved 5,235 references. Only studies published in 2012 or later were considered, to warrant directness and interpretability of their findings, considering that in such time window several new DMTs became available, and therefore prices, cost-effectiveness and place-in-therapy changed substantially. Fifty-one studies were selected through a two-step screening process by pairs of researchers independently assessing the retrieved references. Thirty-six studies were funded by the company producing the DMT assessed in the economic analysis and results invariably favor the drug.	Alemtuzumab has a higher number of comparisons vs other DMTs, where it proved to be always cost effective. The evidence includes several independent studies. Cladribine, GA, interferon beta 1b, natalizumab, ocrelizumab: cost-effective vs other DMTs in several studies, all funded by the company producing the drug, i.e. with risk of bias. One recent independent study in Iran (LMIC) shows that rituximab is cost-effective when compared to natalizumab. In general, the results are conflicting and most studies are from HICs, where willingness-to-pay thresholds are associated with country GDP. Cost-effectiveness varies between settings. This is partly due to income level, the price of the medicine, what is included in cost calculations (e.g. some supportive interventions like rehabilitation may or may not be available), and also depending on which other DMTs are available. For alemtuzumab and cladribine, the treatment schedules are only for two years, but some people require maintenance therapy. For alemtuzumab after the two years, 20% of people require a third course of treatment and a small fraction a

Only eight studies were performed in countries other than HIC: 6 in Iran (LMIC) (1, 10, 12, 19, 40, 45) one in Colombia (7) and one in China (8) (UMIC). (Table 3).

NOTES

Health effects are usually measured as life-years gained (LYGs) or quality-adjusted life-years (QALYs), accounting also for quality-of-life outcomes. Cost-effectiveness analysis (CEA) is usually performed by means of LYGs, and the parameter of interest is the incremental cost-effectiveness ratio (ICER). In cost-utility analysis (CUA) QALYs are commonly used and the parameter of interest is called incremental cost-utility ratio (ICUR). The terms ICER and ICUR are sometimes not distinguished and whether the result is expressed in LYGs or QALYs depends on the context. The ICER or ICUR is compared with the (official or approximate) willingness to pay for each unit of effect (LYG or QALY) gained. The per-QALY gained willingness-to-pay threshold is usually based on per capita Gross Domestic Product (GDP). For developing countries WHO recommends a threshold 1 to 3 times the GDP (Bertram 2016, doi: 10.2471/BLT.15.164418) .

Direct costs *are usually referred to cost of drug, its acquisition, administration, monitoring, natural disease management, relapse treatment, and adverse event management.*

Indirect costs *are usually referred to loss of productivity, absenteeism, early retirement, travelling cost to reach healthcare facilities.*

Interpretation

- Alemtuzumab shows the higher number of comparisons vs other DMTs where it proved to be cost-effective. Such comparisons include several independent studies.
- Several studies suggest a superiority of cladribine over other DMDs in terms of cost-effectiveness, but they are 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.
- Results of economic analyses on individual DMDs often offer conflicting results (see Table 2)
- One recent independent study in Iran (LMIC) shows that rituximab is cost-effective when compared to natalizumab
- Of the six studies assessing the cost-effectiveness of **treatment strategies**, four are independent. Their results are inconsistent. Oral agents are cost-effective according to one study (48) but not according to another study (50). One recent independent study (47) assessed the cost-effectiveness of different escalation strategies, with inconclusive results since cost and health outcomes were overlapping among different escalation sequences.

The economic evidence on cost-effectiveness of DMDs in RMS shows the following main **limitations**:

- most studies are performed in HICs and their results may not be transferable to countries with different income level.
- generally, more economic analysis studies are available on recently marketed drugs
- most studies are funded by the company producing the DMD assessed in the economic analysis and their results should be interpreted with caution, especially because the willingness-to-pay threshold is associated with the country gross domestic product. Moreover, the methological quality of economic analysis studies is harder to assess due to the lack of established criteria, and their results can not be quantitatively pooled ina metanalysis.
- parameters used by the authors to assess clinical effectiveness and cost vary substantially. This may in part explain the general inconsistency in results, that in some cases are conflicting.

Table 1 - Summary of cost-effectiveness comparisons among DMDs for RRMS (references in brackets refer to studies reported in the tables 2, 3 and 4)

Studies **without risk of bias** from funding by pharmaceutical industry are highlighted in **yellow**.
Studies assessing the cost-effectiveness of people with RRMS **after a previous treatment failure** are in **red color**.

fourth. For cladribine the clinical trials were based on two cycles within the two years, but a third cycle can be needed.

The cost-effectiveness studies are modelled on known parameters from the registration trials, or results from meta-analyses, and these are projected into the timeframe. The assumption is often based on the initial dosing expected to be required rather than reflect on real-world data on doses required.

Judgements:
1. Mitoxantrone had no included studies.
2. Alemtuzumab 'probably favours intervention' due to the number of studies and two independent studies.
2. Cladribine had a large number of studies, but all were sponsored by the pharmaceutical company. Cladribine judged as ‘probably favours the intervention’ with a note on industry sponsors of all the studies. Cost-effectiveness of sub-cutaneous off-label cladribine was not assessed, and it may be much cheaper than the on-label cladribine.
3. All the other DMTs were judged as 'varies'.

ALE better than
- FIN (9, 11, 15, 16, 17)
- IFN β1b (9, 16)
- IFN β1a (9, 11, 16)
- Peg IFN β1a (9, 16)
- NAT (9, 10, 11, 15, 16, 17)
- OCR (15)A (15, 16)
- DMF (16)
- TER (16)
- BSC (16)

CLA better than
- OCR (3)
- ALE (3, 13, 18)
- NAT (3, 6, 18)
- FIN (4, 5, 6, 13)

DMF better than
- FIN (31, 33, 35)
- GA (28, 29, 31, 33)
- IFN β1a (29, 35)
- IFN β1b (33)
- TER (33, 35)

FIN better than
- DMF (37)
- IFN β1a (46)
- NAT (12, 23)
- ALE (23)

GA better than
- FIN (42)
- IFN β1a (39, 41)
- IFN β1b (41)
- BSC (14)

IFN β-1a better than
- FIN (33, 44)
- GA (33, 38)
- IFN β1b (33, 38)
- TER (33)
- BSC (45)

IFN β-1b better than
- BSC (43)

NAT better than
- FIN (2, 7, 28, 36)

OCR better than
- IFN β1a (21, 26)

PegIFN β1a better than
- GA (20, 25, 27, 32)
- IFN β1a (19, 2, 25, 27, 28, 32)
- IFN β1b (20, 25, 28)

RTX better than
- NAT (1)

TER better than
- DFM (22)
- GA (22)
- IFN β1a (22, 35)
- IFN β1b (8, 22)
- BSC (22)

ABBREVIATIONS
ALE=alemtuzumab, BSC=best supportve care, CLA=cladribine, DMF=dimethylfumarate, FIN=fingolimod, GA=glatiramer acetate, IFN=interferon, NAT=natalizumab, OCR=ocrelizumab, Peg IFN=pegylated interferon, RTX=rituximab, TER=teriflunomide, USD=US dollars

Table 2 - Studies on specific DMDs for RRMS in High Income Countries

Studies **without risk of bias** from funding by pharmaceutical industry are highlighted in **yellow**.
Studies assessing the cost-effectiveness of people with RRMS **after a previous treatment failure** are in **red color**.

Study	study type	Type of MS	Country	Interventions	Time horizon	Perspective	Currency	type of cost	Summary results	Potential CoI
2. Spelman 2021	CEA	RMS after treatment failure with IFN, GA, DMF, TFM	UK	NAT, FIN	Lifetime	Public health system	2019 GBP	Direct	Clinical benefit for therapy escalation to NAT vs FIN, translating to higher QALYs and lower costs for UK patients inadequately responding to IFN, GA, DMF, TFM.	YES Biogen, producer of NAT
3. Espinoza 2021	CEA	Highly active RRMS	Chile	CLA, OCR, ALE, NAT	45 y	Public health system	2019 USD 2018 USD (resources) 2017 USD (price of OCR, ALE, NAT)	Direct	**CLA** is expected to produce higher QALYs than all evaluated alternatives. CLA cannot be considered cost effective for the Chilean health care public sector using a 1 GDP per capita threshold. However, under reasonable discount scenarios, it becomes an attractive alternative.	YES Merck, producer of CLA
4. Poveda 2020	CEA	Highly active RRMS	Spain	CLA, FIN	50 y	Public health system	2018 EURO	Direct	**CLA** is a cost-effective treatment, compared to FIN, for the treatment of RMS with high disease activity.	YES Merck, producer of CLA
5. Pinheiro 2020	CEA	Highly active RRMS	Portugal	CLA, FIN	50 y	Payer	2015/2016 (resources) 2014 (drug) EURO	Direct	Treatment of highly active RRMS with **CLA** was less costly and more effective than treatment with FIN in the Portuguese setting.	YES Merck, producer of CLA
6. Mankinen 2020	Cost assessment modelling	Highly active RRMS	Finland	CLA, FIN, NAT, FIN+NAT	4 y	Partially societal	2019 EURO	Direct, indirect	**CLA** robustly saves modelled drug-associated costs in comparison to FIN, NAT and their mix.	YES Merck, producer of CLA
9. Walter 2019	CUA	RRMS	Austria	ALE, FIN, NAT, IFN β1a, IFN β1b, Peg IFN β1a	10 y	Payer	2017 EURO	Direct	**ALE** is a cost-saving alternative to treat RRMS in pre-treated and therapy naïve patients. From the patient perspective, alemtuzumab improves quality-of-life.	YES Sanofi, producer of ALE
11. Stasinic 2019	CEA	RRMS	Italy	ALE, IFN β1a, NAT, FIN	Lifetime	Public health system	2017 EURO	Direct	**ALE** is likely to be cost-effective versus IFN β-1a, NAT and FIN in the treatment of RRMS in Italy	NO
13. Michels 2019	CEA	Highly active and rapidly evolving RMS	Netherlan ds	CLA, ALE, FIN	50 y	Public health system	2016 EURO		Treatment of RRMS with **CLA** is cost effective vs ALE and FIN in persons with highly active RMS, and cost effective versus natalizumab in rapidly evolving RMS, at a threshold of €50.000, driven by the lower costs. Outcomes are based on indirect comparisons and post hoc subgroup analysis, these results should be interpreted with caution	YES Merck, producer of CLA
14. Giovannoni 2019	CEA Risk sharing scheme	RMS	UK	GA, BSC	10 y	Public health system	2015/16 GBP	Direct	**GA** had a beneficial effect on long-term disability and was a cost-effective treatment for RRMS.	YES Teva, producer of GA
15. Chirikov 2019	CEA	RMS	US	ALE, OCR, NAT, FIN, GA	20 y	Societal	2016 USD	Direct, indirect	**ALE** was cost-effective in RMS treatment.	YES Sanofi, producer of ALE
16. Zimmermann 2018	CUA	RRMS PPMS	US	OCR (PPMS), DMF, FIN, GA, NAT, IFN β1a, IFN β1b, TFM, PegIFN β1a, BSC	Lifetime	Payer	2017 USD	Direct	**OCR** would likely be cost effective as a first-line treatment for RRMS with a discounted price but was not cost effective for PPMS. **ALE** dominated other options for second-line treatment of RRMS. Other DMTs were generally similar in terms of costs and health outcomes, providing health benefits compared to BSC but with significant added costs. If drug prices were lowered, more DMTs could be cost effective.	NO
17. Piena 2018	CMA	Active RRMS	Netherlan ds	ALE, FIN, NAT	5 y	Public health system	2015 EURO	Direct	From the Dutch healthcare perspective, treating active RRMS patients with **ALE** results in cost savings compared to second-line alternatives FIN and NAT from ~3 years since treatment initiation onwards. After 5 years, alemtuzumab's cost savings are estimated at €30k compared to fingolimod and €43k compared to natalizumab.	YES Genzyme, producer of ALE
18. Hettle 2018	CEA	Highly active RRMS	England	CLA, ALE, NAT	Lifetime	Societal		Direct	**CLA** is a cost-effective alternative to ALE and NAT in the treatment of highly active RRMS from the perspective of the NHS in England	YES Seroso, producer of CLA
20. Centonze 2017	CEA BIA	RRMS	Italy	PegIFN β1a, GA, IFN β1a, IFN β1b	Lifetime 3 y	Public health system	2014 EURO	Direct, indirect	**PegIFN β1a** for the treatment of RRMS is not only clinically effective, but also economically efficient and financially sustainable from the Italian NHS perspective.	YES Biogen, producer of PegIFN β1a
21. Yang 2017	CEA	RRMS, SPMS	US	OCR, IFN β1a	20 y	Payer	2016 USD		**OCR** is more cost-effective than s.c IFN β1a for the treatment of RMS.	YES Genentech, producer of OCR
22. Soini 2017	CEA	RRMS	Finland	DMF, GA, IFN β1a, IFN β1b, TFN, BSC	15 y	Payer	2016 EUR (drugs) 2013-2014 EUR (health care cost)	Direct	**TFN** cost-effective as BSC or DMF with the common threshold values, was dominant versus other first-line RRMS treatments, and provided the greatest impact on investment. TFN is potentially the most cost-effective option among first-line treatments of RRMS in Finland	YES Sanofi, producer of TFM
23. Montgomery, Kusel 2017	CEA	Highly active RRMS, SPMS	UK	ALE, FIN	Lifetime	Public health system	2015 GBP	Direct	Considering in the model retreatment with ALT and long term adverse event decrements, **FIN** is cost effective compared to ALT, assuming application of only a modest level of confidential patient access scheme discount	YES Novartis, producer of FIN
24. Montgomery, Manuszczak 2017	CEA	Rapidly evolving RRMS, SPMS	UK	NAT, FIN	Lifetime	Public health system	2014-2015 GBP	Direct	A modest discount to the UK FIN list price is required to make **FIN** a more cost-effective option than NAT in rapidly evolving RRMS	YES Novartis, producer of FIN
25. Hernandez 2017	CEA	RRMS, SPMS	Scotland	GA, PegIFN β1a, IFN β1a, IFN β1b	30 y	Public health system	2015 GBP	Direct	Long-term treatment with **PegIFN β1a** improves clinical outcomes, while its cost profile makes it either dominant or cost-effective compared with other self-injectable DMTs for the treatment of RRMS in Scotland	YES Biogen, producer of PegIFN β1a
26. Frasco 2017	CEA	RRMS	US	OCR, IFN β1a	30 years	Societal	2016 USD	Direct, indirect	**OCR** provides greater value to RRMS patients compared with IFN β1a s.c. with a higher incremental monetary benefit	YES Genentech, producer of OCR
27. Dashputre 2017	CEA	RRMS	US	GA, DMF, NAT, FIN, Peg IFN β1a, IFN β1a, IFN β1b	2 y	Payer	2015 USD		**PegIFN** dominated on IFN β1a and GA. Compared with FIN, NAT and DMF, PegIFN was less expensive and less effective. PegIFN is a viable alternative when compared with the other DMTs in the model. ALT had an ICER of $25,276 cost per relapse avoided relative to IFN beta-1a 44 ug.	NO
28. Bozkaya 2017	CEA	RRMS, SPMS	US	GA, FIN, DMF, NAT, Peg IFN β1a, IFN β1a	10 y	Payer	2016 USD	Direct	**NAT**, **DMF**, and **PegIFN β1a** are cost-effective DMT choices compared to FIN, GA, and IFN, respectively.	YES Biogen, producer of DMF and PegIFN β1a
29. Su 2016	CEA	RRMS, SPMS	Canada	GA, DMF, IFN β1a	20 y	Public health system	2013 CAD	Direct	**DMF** cost-effective compared to GA and IFN β1a.	YES Biogen, producer of DMF
30. Pucholt 2016	Cost comparison	RRMS previous treatment failure (Ado-EDSS ≥4)	Italy	NAT	6-30 months	Societal, Public health system	2014 EURO	Direct, indirect	In Italy, cost of management of patients with RRMS developing anti- IFN-β antibodies is higher for the society than for the national health service	NO
31. Mausskopf 2016	CEA	RRMS, SPMS	US	GA, delayed-release DMF, FIN	20 y	Payer	2015 USD	Direct, indirect	Delayed-release **DMF** is likely to increase QALYs for patients with RMS and be cost-effective compared with FIN and GA.	YES Biogen, producer of DMF
32. Hernandez 2016	CEA	RRMS, SPMS	US	GA, PegIFN β1a, IFN β1a	10 y	Payer	2014 USD	Direct	Long-term treatment with **PegIFN β1a** improves clinical outcomes at reduced costs compared with IFN β1a 44 mcg and GA 20 mg	YES Biogen, producer of IFN β1b
33. Chevalier 2016	CEA	RRMS, SPMS	France	GA, DMF, FIN, TER, IFN β1a, IFN β1b	30 y	Societal	2015 EURO (drugs) 2013 EURO (other direct and indirect costs)	Direct, indirect	**DMF** and **IFN β1a** 44mcg were the two optimal treatments, as the other treatments (IFN β1a 30mcg, IFN β1b 250mcg, TFM, GA, FIN) were dominated on the efficiency frontier. Despite no reference threshold for France, DMF can be considered as a cost-effective option.	YES Biogen, producer of DMF
34. Dorman 2015	Budget impact analysis	RRMS	Canada	Delayed release DMF	3 y	Public health system	2013 CAD	Direct	The acquisition costs of **DMF** for treatment of RRMS are predicted to be partially offset by reduced costs of relapses in the Canadian healthcare system.	YES Biogen, producer of DMF
35. Zhang 2015	CEA	RRMS, SPMS	US	DMF, FIN, TER, IFN β1a	5 y	Societal	2012 USD	Direct	**DMF** was a dominant therapy to manage RRMS. Apart from DMF, **TER** was the most cost-effective therapy compared with IM IFN β-1a.	NO
36. O'Day 2015	CEA	RRMS, rapid evolving RRMS	Sweden	FIN, NAT	2 y	Public health system	2011 Kr	Direct	Treatment with FIN costs less, but treatment with NAT results in more relapses avoided. **NAT** is a cost-effective treatment option for patients with MS in Sweden. In the rapidly evolving RRMS population NAT dominates FIN	YES Biogen, producer of NAT
37. Manuszczak 2015	CEA	Highly active RRMS, SPMS	England	DMF, FIN	Lifetime	Public health system	2013-2014 GBP	Direct	**FIN** is cost-effective in highly active RRMS in UK.	YES Novartis, producer of FIN
38. Dembek 2014	CEA	RRMS Treatment naive	Spain	GA, IFN β1a , IFN β1b, BSC	30 y	Societal	2010 EURO	Direct, indirect	i.m. **IFN b-1a** more cost-effective than SC IFN β1a, IFN β1b or GA	YES Biogen, producer of IFN β1a (Avonex ®)
39. Darbà 2014	CEA	RRMS	Spain	GA, IFN β1a, GA+IFN β1a	10 y	Public health system	2013 EURO		**GA** is a cost-effective treatment option for the prevention of relapses in Spanish patients diagnosed with RRMS. GA in monotherapy compared with IFN in monotherapy and IFNβ+GA combined. GA is the dominant strategy.	YES. TEVA, producer of GA
41. Sanchez-De La Rosa, JMedEcon 2012	CEA	RRMS	Spain	GA, IFN β1a, IFN β1b	10 y	Societal	2010 EURO	Direct, indirect	First-line treatment with **GA** is the less costly strategy for the treatment of patients with RRMS. Treatment with IM IFN -1a is a dominant strategy (lower cost and higher QALY) compared with s.c. IFN β -1a and s.c. IFN β -1b. However, i.m. IFN β -1a is not a cost-effective [illegible]	YES. TEVA, producer of GA
42. Sanchez-De La Rosa, HealthEconRev 2013	CEA	RRMS	Spain	GA, FIN	1 y	Payer	2012 EURO	Direct	FIN therapy requires twice the investment as **GA** that shows to be a more sustainable treatment strategy	YES. TEVA, producer of GA
43. Pan 2012	CEA	RRMS	US	IFN β1b, BSC	Lifetime	Societal	2011 USD	Direct, indirect	Treatment with **IFN β-1b** during the earlier disease phase of patients with MS significantly increased patient life-years and QALYs. IFN β-1b is likely to be a cost-effective strategy	YES. Bayer, producer of IFN β1b
44. Lee 2012	CEA	RRMS, SPMS	US	FIN, IFN β1a	10 y	Societal	2011 USD	Direct, indirect	FIN use is not likely to be cost-effective compared to **IFN β -1a** unless its cost falls < $3475 per month or a higher than normal willingness-to-pay threshold is accepted by decision makers.	NO
46. Agashivala 2012	CEA	RRMS	US	early FIN, FIN after 1 y of IFN β1a	2 y	Payer	2012 USD	Direct	Continuous treatment with **FIN** for 2 years resulted in a lower cost per relapse avoided compared with treatment with IM IFN-β1a for the first year and then switching to FIN therapy. Delaying FIN therapy does not seem to be cost effective.	YES Novartis, producer of FIN

ABBREVIATIONS

ALE=alemtuzumab, BIA=budget impact analysis, CMA=cost minimization analysis, BSC=best supportive care, C-U=cost-utility analysis, CEA=cost-effectiveness analysis, CAD=Canadian dollars, CLA=cladribine, CNY=Chinese yen (¥), DMD=disease modifying treatment, DMF=dimethylfumarate, FIN=fingolimod, GA=glatiramer acetate, HIC=high income country, Kr=Swedish Kronor, LMIC=low-middle income country, IFN=interferon, NAT=natalizumab, OCR=ocrelizumab, Peg IFN=pegylated interferon, RRMS=relapsing-remitting multiple sclerosis, RTX=rituximab, SM=symptom management, SPMS=secondary progressive multiple sclerosis, TER=teriflunomide, USD=US dollars

Table 3 - Studies on specific DMDs for RRMS in Lower- and Upper-Middle Income Countries (LMIC, UMIC)

Studies **without risk of bias** from funding by pharmaceutical industry are highlighted in **yellow**.
Studies assessing the cost-effectiveness of people with RRMS **after a previous treatment failure** are in **red color**.

Study	study type	Type of MS	Country	Interventions	Time horizon	Perspective	Currency	type of cost	Summary results	Potential CoI
1. Rezaee 2021	CEA	RRMS	Iran (LMIC)	RTX, NAT	Lifetime	Societal	2019 USD	Direct, indirect	**RTX** had higher cost-effectiveness than NAT and could be a priority for RRMS patients compared to NAT.	NO
7. Lasalvia 2020	CEA	Highly active RRMS	Colombia (UMIC)	NAT, FIN	5 y	Payer	USD	Direct	**NAT** dominated FIN with lower costs and higher QALYs.	YES Sterdhal Pharma, producer of NAT
8. Xu 2019	CEA	RRMS	China (LMIC)	TFM, IFN β1b	Lifetime	Public health system	2018 USD and CNY	Direct	**TFM** is a cost-effective therapy compared to IFN β1b in the treatment of RMS patients in China. Results should be interpreted with caution as head-to-head comparisons are not available.	YES Sanofi, producer of TFM
10. Tahiri 2019	CUA	RRMS	Iran (LMIC)	ALE, NAT	20 y	Societal, Public health system	2018 USD	Direct, indirect	**ALE** was dominant in the treatment of RRMS compared with natalizumab in both societal and healthcare service perspective due to lower total cost, greater efficacy and slowing of disease progression, and lower rate of relapses. Comparative head-to-head trials and long term follow-up are needed to confirm those results.	YES Sanofi, producer of ALE
12. Rezaee 2019	CEA CUA	RRMS	Iran (LMIC)	FIN, NAT	Lifetime	Societal	2016 USD	Direct, indirect	Cost-effectiveness and cost-utility of FIN were higher than those of NAT. It is recommended that treatment with FIN be the first priority of second-line treatment for MS patients	NO
19. Hashemi Meshkini 2018	CEA	RRMS	Iran (LMIC)	Peg IFN β1a, IFN β1a	10 y	Payer	2015 USD	Direct	**PegIFN β1a** is cost-effective in Iran	NO
40. Nabil 2013	CEA	RRMS, SPMS	Iran (LMIC)	BSC, BSC+IFN β1a, BSC+ IFN β1a+ IFN β1b	Lifetime	Societal	2012 USD	Direct, indirect	All kinds of available branded, copied biopharmaceuticals or biosimilar IFN β in Iran are cost-effective except Avonex ® 3 m. IFN β1a	NO
45. Imani 2012	CUA	RRMS	Iran (LMIC)	Symptom management , IFN β1a, IFN β1b	Lifetime	Public health system	2011 USD	Direct	Treatment with DMDs in RRMS patients was associated with increased benefits compared with symptom management, albeit at higher costs. Patients receiving **IFN β1a Avonex** incurred slightly higher QALYs than patients receiving other DMDs. treatment with Avonex dominates other DMDs in Iran.	NO

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Table 4 - Studies on treatment strategies

Studies **without risk of bias** from funding by pharmaceutical industry are highlighted in **yellow**.
Studies assessing the cost-effectiveness of people with RRMS **after a previous treatment failure** are in **red color**.

Study	study type	Type of MS	Country	Interventions	Time horizon	Perspective	Currency	type of cost	Summary results	Potential CoI
47. Vermeegh 2021	CEA	RRMS (treatment naive)	Netherlan ds	Escalation sequences	Lifetime	Societal	2015 (EURO)	Direct, indirect	Sequences ranked by net health benefit Most effective: PegIFN - DMF - OCR - NAT - ALE Most cost-effective: PegIFN - GA - OCR - CLA - ALE Costs and health outcomes were overlapping among different treatment escalation sequences. The most cost-effective sequence yielded numerically worse health outcomes per patient, while the sequence that yields most QALYs is not the most cost-effective option	NO
48. Alrothia 2021	single-centered retrospective chart review (no modelling)	RRMS	Saudi Arabia	Oral treatments (FIN, DMF, TER), IFN-based treatments, Monoclonal antibodies (RTX, NAT)	n.a.	n.a.	USD	Direct	Orally administered agents were associated with the lowest direct medical cost in comparison to IFN-based therapy (e.g., Rebif-8) and MABs (e.g., NAT, RTX). Oral showed better effectiveness, and were dominant in comparison to Rebif-8	NO
49. Furnari 2019	CEA	RRMS with failure to first-line injectable DMDs	Italy	Early treatment with NAT ("escalation strategy"); Switching among IFN/GA	Lifetime	Societal	2015 (EURO)	Direct, indirect	Early escalation to NAT is dominant vs. switching among immunomodulators, in RRMS patients who do not respond adequately to conventional immunomodulators	YES Biogen, producer of NAT
50. Alsaqabi 2017	CEA	RRMS treatment naive	Saudi Arabia	Oral DMDs (FIN, TFM, DMF), IFN-based treatments	20 y	Payer	2015 USD	Direct	**None of the DMDs** were found to be cost-effective in the treatment of RRMS at a willingness to pay threshold of $100,000. The DMDs would only be cost-effective at a WTP above $300,000	NO
51. Suwad 2017	CEA	RRMS	US	1) SM; 2) SM->IFN β1a ->SM; 3) SM-> IFN β1a ->NAT-> SM; 4) SM->IFN β1a ->NAT ->ALE->SM	20 y	Payer	2014 USD	Direct, indirect	**Symptom management** alone was the most cost-effective therapy for RRMS. All the ICERs for the different treatment strategies evaluated were above the USD100,000 willingness to pay threshold per QALY	NO

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Equity

If recommended, which intervention would reduce health inequities the most?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Reduced: Alemtuzumab, Mitoxantrone **Probably reduced:** Natalizumab, Ocrelizumab, Cladribine, Fingolimod **Probably no impact:** Interferon beta 1a, Interferon beta 1b, Glatiramer acetate **Probably increased:** Dimethylfumarate **Increased:** **Varies:** **Don't know:**	We conducted a systematic search and we found three systematic reviews, 7 observational studies (cross-sectional, surveys) and 7 additional studies (comment, editorial/letter) reported results on the impact of DMTs on equity. **Population-level** **Access to DMTs in disadvantaged groups** ***Race*** **Onuorah 2022** performed a systematic review of RCTs to assess the representation of minority patients in DMTs trials. Among 44 phase 3 trials reviewed, 37.8% did not report race, 31,1% reported race as proportion of white participants only, and only 31.1% reported detailed information on race. In the selected studies with information on racial and ethnic representation, the median percentage of White participants was 93.8% (range 78.5–99.6% across 28 studies), 1.9% for Black participants (range 0.1–8.1% across 14 studies), and 0.5% for Asian participants (range 0.1–14.5% across 11 studies). No patient- or health care provider -facing DMT websites reported data on race and ethnicity in pivotal trials. These findings are consistent with the hypothesis that ethnic minority populations are consistently underrepresented in clinical trials of multiple sclerosis, leading to limited data on the effectiveness of treatments in these groups of patients and lack of an evidence-based approach to treatment. **Additional evidence** suggested by panel members that confirm the	The panel noted the lack of evidence considering the equity issues between the specific DMTs. Atlas of MS shows unequal access to DMTs between LMICs and HICs. 'High efficacy' DMTs (natalizumab, ocrelizumab, alemtuzumab) are even less available. The panel noted the following factors affecting equity: cost/income, route of administration, access to healthcare facilities, storage, e.g. cold-chain requirements. Important to consider actual care delivery. For many patients who are poor/unhoused/have other barriers to adherence, a twice-year infusion is often preferable and easier, even if there are considerable costs to getting to an infusion centre, versus a self-injectable that they may have to carry with them and keep refrigerated. Important to note when we rate the relative impact of equity of self-injectables vs infusions. The panel discussed the difference between **health equity** vs **financial equity**. Health equity would increase more if a moderate cost but higher efficacy DMT was available than if a very inexpensive but less effective DMT was recommended. Health equity considerations if MS is not treated include direct costs of disability progression, unemployment, caring responsibilities for family, equipment and living arrangement modifications, not just cost of medicine. Cost of medicine is also potentially modifiable. This guideline's primary purpose

above results:
Avasarala 2014: Evidence highlight that as compared with white Americans; African Americans are thought to have a lower risk for developing MS but a greater risk of disability. Compared with white Americans with MS, African Americans with MS have a more aggressive disease course and a greater risk of early second relapse. Hence, differences in MS susceptibility, disability outcomes, and clinical course may have biologic origins related to race/ethnicity. Nevertheless, the most important clinical trials on drug treatment for MS show that the percentage of white American patients was prevalent while other races/ethnicities have been little investigated, for that it is difficult to categorize treatment options for African American patients due the different characteristics of the disease in this population. The study notes also that African American patients probably seek help at referral centers only after severe disability ensues, which introduces selection bias.
Avasarala 2019: The study reports lack of recruitment of non-Caucasian patients with MS in clinical trials with no data compared how drugs performs in African American versus Caucasian American. MS drugs approved by the FDA do not contain efficacy data for minorities and therefore clinicians are unable to discuss the efficacy data of any MS drug with their non-Caucasian patients. The lack of any drug data in non-Caucasian patients with MS in published clinical trials is troublesome. The authors state that reporting baseline patient demographic data characteristics in the published literature must be made mandatory.
Avasarala 2021: The study confirms what already seen in the previous ones (Avasaral 2014 and 2019) and conclude that the disease characteristics and phenotype of MS among Blacks and Hispanics are typically aggressive and for this reason alone, if not for any other metric, there needs to a radical shift in allotment of funds devoted to promoting drug research in minority population
Below a table summarizes the results.

Table 1. Panels A and B Showing Distribution of Patients in MS and NMOSD Pivotal Clinical Trials, Respectively

Racial Distribution of MS Patients Who Received Investigational Drug (Panel A)				
	Asian Participants	Hispanic Participants	White Participants	Black Participants
Siponimod	31	74	1,050	7
OPERA 1/2		0	743	40
ORATORIO		32	454	9
Ozanimod	1	16	876	5
Racial Distribution of NMOSD Trial Patients Who Received Investigational Drug (Panel B)				
	Black Participants	Asian Participants	Hispanic Participants	White Participants
Satralizumab	0	21	0	31
Inebilizumab	14	37	25	86

Raw numbers are shown.
Abbreviations: MS, multiple sclerosis; NMOSD, neuromyelitis spectrum disorder.

Gender
Alonso-Moreno 2021 performed a systematic review of clinical trials of 4 monoclonal antibodies for MS (natalizumab, rituximab, ocrelizumab or alemtuzumab) analysing the presence of gender bias. They found 55 trials, published from 2000 to 2019. Of all patients included in these trials, 64.6% were women, with a range of 18.3% to 85.0%. Only 8 articles discussed the results separately for men and for women. They concluded that clinical trials present a significant gender bias, as the endpoints were not analysed according to patients' gender. The presence of gender bias entails the possibility of a differential effect of medications by gender and therefore less generalisable results.

Khayambashi 2020: evaluated health care utilization in transgender and non-heterosexual persons with MS using data from the North American. Research Committee on Multiple Sclerosis (NARCOMS) Registry. Outcomes of interest were any emergency room visits (ER) in the prior six months; (ii) any hospital admissions in the prior six months; and (iii) any DMT use in the prior six months.
The frequency of any ER visits, any hospital admissions, and DMT use did not differ according to gender identity and sexual orientation. This finding should be interpreted cautiously given the small number of transgender participants, and the short, 6-month reference study period.

Place
Chen 2021 using data from the Australian Multiple Sclerosis Longitudinal Study (AMSLS), examined whether people with MS living in regional or remote areas have higher disability, greater severity of symptoms, lower HRQoL, worse employment outcomes and receive different DMT treatment compared to those living in major cities in

is to help inform an application to the WHO EML, which is meant to impact availability and costs for medicines that are efficacious.

Other considerations relevant for equity:
1. Access to electricity and refrigeration (maintain cold-chain and storage) and access to healthcare facilities (to access infusion suites). These considerations would seem to favour oral treatments.
2. Pregnancy and breastfeeding, as disease onset is normally at this stage and women 2-3x more affected than men. GA, interferons can be used. While contraindicated, natalizumab, ocrelizumab and alemtuzumab, cladribine can be used with careful timing of the dosing for planned pregnancies. Dimethyl fumarate can potentially be used with very careful dosing and monitoring. Fingolimod, and mitoxantrone have a contraindications and cannot be used during pregnancy.

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 log-term health outcomes in addition to 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 required JCV testing for PML.

Cladribine and fingolimod were also judged as 'probably reduced' even though they are oral medications due to contradictions in pregnancy. The monitoring and risk of rebound for fingolimod made it less equitable to DMF. Despite high cost similar to alemtuzumab, the monitoring requirements are considerably lower for cladribine then alemtuzumab.

Interferon beta 1a, Interferon beta 1b, glatiramer acetate were considered to have 'probably no impact' due to safety in pregnancy, although they required regular injections and cold-chain.

Dimethyl fumarate was judged as 'probably increased' as oral, no cold-chain, requires relatively little monitoring, category B risk for pregnancy, indication for paediatrics.

Australia. They found that those living in inner regional areas were less likely to use high efficacy DMTs (natalizumab, fingolimod and alemtuzumab) and more likely to use moderate efficacy DMTs (teriflunomide, dimethyl fumarate). These associations remained after taking age, disease duration and education level into account.

Socio-economic status

Roddam 2019 performed a systematic review investigating differences in access to prevention services, healthcare services, treatments and social care between inequality groups. They found evidence of inequalities in access to services with a trend for worse access among men, older age groups, those from lower socio-economic groups, the least educated, non-Caucasians, those with mental health problems and those from rural areas. In the studies on access to disease modifying treatments, older age and lower socioeconomic status were consistently associated with a lower rate of uptake, while race and gender were not.

Carnero Contentti 2021 conducted a web-survey in Argentina to investigate the barriers and utilization of MS care services in Latin America. They found that between 65.7% (Uruguay) and 95.8% (Paraguay) of patients with MS in the region reported DMT treatment prescribed immediately after MS Diagnosis.
Between 2.8% and 21.9% reported having problems obtaining medications because these were not covered by their insurance plan. Nevertheless, over 80% (except for Ecuador (64%) and Honduras (60%)) indicated taking DMT as prescribed by their clinicians during the last year.
Examining DMT use in greater detail, they found significant level of innovator DMT replacement by generic or biosimilar compounds in Argentina (68%) and much less in Chile, Colombia, Honduras, and Mexico.
Lack of health insurance and longer duration of MS were associated with inadequate treatment, while higher level of education and retaining employment improved treatment delivery.
Lack of health insurance was associated with problems obtaining DMT whereas having a high level of education made access to DMT easier (first prescription or follow- up medication).

Gomez-Figueroa 2021 reported the results of retrospective study conducted in Mexico.
The study includes a mixed population (84.5% RRMS, 11.6 SPMS, 3.9% PMS). When comparing the lower versus higher level of Socio-Economic Status (SES), a significant association was found on the percentage of patients with a higher level of disability (EDSS >6) at arrival.
A greater proportion of patients with very low SES did not have access to a DMT compared to higher level. Conversely, patients with high SES had more access to high efficacy therapies compared to lower level of SES (35.7% vs 14.8%, $p<0.001$). Lower SES had an association with the proportion of patients not receiving any DMT, and a higher proportion of secondary-progressive.

Hartung 2020: retrospectively compared MS among all U.S. Medicare beneficiaries with and without Low Income Subsidy (LIS) benefits to estimate the effect of cost-sharing on time to self-administered DMT initiation. Beneficiaries were predominately White (36,447, 91.9%) and female (29,406, 74.1%). The time until DMT initiation was significantly lower in those with LIS benefits relative to those without. Of those who initiated, the full LIS recipients initiated on average 22 days sooner than non-full LIS recipients (114.9 days ± 95.8 days vs 137.0 days ± 106.6 days, $p<0.0001$). Even after adjusted for a broad spectrum of possible demographic and co-morbid condition confounders, those receiving LIS benefits remained 40% more likely to initiate a DMT. The effect of reduced cost-sharing on DMT initiation was consistent across a variety of demographic subgroups.

Reyes 2020 examined the association between SES and DMT prescribing patterns in pwRRMS treated at the Royal London Hospital in London.
Based on their efficacy, DMTs were categorized as moderate efficacy (Glatiramer Acetate and Beta-Interferons), high efficacy (Cladribine, Fingolimod and Dimethyl Fumarate) and very-high efficacy therapies (Natalizumab and Alemtuzumab. Data related patient demographics (age, sex and race), SES, disease characteristics and measure of deprivation that may influence prescribing practices in MS were collected. No association were found in DMT prescribing patterns with respect to income or education, even after adjuster for age, years on current DMT, prior use of DMTs, adverse events to prior DMTs and

pregnancy or plan to become pregnant.

Calocer 2016 evaluted the influence of SES on the delay between first and second line DMTs in RRMS patients. The second-line DMTs selected for the analysis were cyclophosphamide, mitoxantrone, natalizumab and fingolimod. No significant influence of SES was observed on delay to access a second line DMT if first line DMT exposure time was less than 5 years. After 5 years of first line DMT exposure, risk to access a second line DMT was 3 times higher for RRMS patients with the lowest European Deprivation Index (EDI) (socially favoured patients) compared to patients with higher EDIs.

Mode of administration, frequency of administration, storage
No evidence was found

GLOBAL PERSPECTIVE

Cost

Laurson-Doube 2020: Access to treatment and treatment choice are dictated by available resources, and resource allocation in many world regions is influenced by the WHO EML. Resource-poor regions cannot afford highly priced therapeutics and available guidelines do not consider regional safety and efficacy issues that are likely to differ markedly from those in resource-rich countries. Editorial highlight the necessity of guidelines for multiple sclerosis management in low-resource environments in which evidence should be integrated into proposals for sustainable improvement of care. Calculations of cost-effectiveness from high-income areas are often meaningless to low-resource areas where the financial burden of a disease is unknown.

Laurson-Doube 2021 reported data on the use of off-label DMTs: a total of 89 countries (87%) use at least one off-label DMT to treat MS. The authors discussed the difference between availability and affordability of off-label vs on-label MS DMTs in high income and low- and middle-income countries. An ethical use of off-label DMTs should be provided if: a) on-label DMTs are not tolerated, unsuitable for the best clinical outcome, unavailable or unaffordable; b) evidence of efficacy and safety on off-label DMTs is available; c) information on balance between health benefits and risks by health care professionals is available; d) clinical outcomes and adverse events when using off-label DMTs is monitored. The development of guidelines and recommendations, evidence-based and following a structured and transparent approach, are crucial for supporting the standardisation and improvement of care, and to inform policy and reimbursement decisions for the use of off-label DMTs.

Availability

Atlas of MS clinical management 2021. A global survey on the availability of resources and services for people with MS in different regions of the world found a widening gap between high- and low-income countries in the access to DMTs. They found that:
-14% of countries surveyed report having no licensed DMTs available for people with MS. In the African region this figure is 60%, and 70% of low income nations report no access to licensed DMTs;
-the use of off-label DMTs is common, reported by experts in 87% of countries worldwide. Lack of availability of similar licensed DMTs in the country or unaffordability of licensed DMTs are some of factors that can drive off-label DMT use;
-globally, 11% of countries do not use moderate efficacy licensed DMTs, and 20% of countries do not use good efficacy licensed DMTs. In particular, 25% of countries report that they do not use high efficacy licensed DMTs. This strongly correlates with income, with 50% of lower middle income countries and 100% of low income nations not using high efficacy DMTs.
Among barriers to DMT administration they identified:
-the cost to the government, healthcare system or insurance provider;
- concern about the side effects by people with MS
-lack of healthcare professionals and a lack of knowledge of DMTs amongst professionals
-bureaucracy, inefficiency or complexity within the healthcare system.

Lekha Pandit 2021: For chronic disorders such as multiple sclerosis (MS), personal funding of therapy is a strain on poor family resources and limits access to care, particularly for the uninsured majority living in countries with deficient national health care programs. In such situations, treatment needs of patients living with MS in LMICs need to be addressed pragmatically. The MSIF's recent atlas of MS survey which showed that 87% of countries use at least one off-label therapy to treat MS. Access to therapy was restricted in the majority of countries surveyed with 70% of low-income countries (LICs) having no on-label

MS DMTs. Mandating the requirement of phase 3 trials or head to-head comparator studies before accepting an affordable off-label drug (repositioned generic or bio similar) as standard for MS therapy is impractical. Treatment guidelines should look beyond therapies advocated in high-resource settings and rely on availability and affordability of other safe alternatives.

-Mode of administration, frequency of administration, storage
No evidence was found

KEY FINDINGS

- Under-representation of ethnic minority populations and women in clinical trials leading to limited data on the effectiveness of treatments in these groups
- Inequalities in access to services with a trend for worse access among men, older age groups, those from lower socio-economic groups, the least educated, non-Caucasians, those with mental health problems and those from rural areas;
- Lack of health insurance and longer duration of MS were associated with inadequate treatment, while higher level of education and retaining employment improved treatment delivery
- Lack of health insurance was associated also with problems obtaining access to DMTs whereas having a high level of education made access to DMT easier. One study conducted in UK did not difference in DMT prescribing patterns with respect to income or education
- High SES may facilitate access to a second-line DMT a few years after first-line DMT exposure;
- People with MS living in regional or remote areas have higher disability, greater severity of symptoms, lower HRQoL, worse employment outcomes and receive different DMT treatment compared to those living in major cities
- The frequency of any ER visits, any hospital admissions, and DMT use did not differ according to gender identity and sexual orientation
- Access to treatment and treatment choice are dictated by available resources. Cost and availability of DMTs are barriers both at population-level and at global-level
- The availability of DMTs is not equally distributed. In the African region most low income nations report no access to licensed DMTs

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Protocol: https://osf.io/5edjf

Acceptability

Which intervention is more acceptable to key stakeholders?

JUDGEMENT

No:
Probably no: Mitoxantrone
Probably yes: Interferon beta 1a, Natalizumab, Dimethylfumarate, Alemtuzumab, Fingolimod, Interferon beta 1b, Glatiramer acetate
Yes: Ocrelizumab, Cladribine
Varies:
Don't know:

RESEARCH EVIDENCE

We found four systematic reviews, 44 RCTs, 12 observational studies (cross-sectional, surveys) and one additional studies (comment, editorial/letter) reported results on the acceptability of DMTs in terms of dropouts due to any cause, adherence to treatment, patient satisfaction. No studies on acceptability from other stakeholders were found.

CONSIDERATION FOR PEOPLE AFFECTED BY MS

Dropouts due to any cause, DMT versus placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Dropouts due to any cause				
Dropouts due	Study population		**RR 1.24** (0.53	59 (1 RCT)	⨁⨁◯◯	

ADDITIONAL CONSIDERATIONS

On-label/off-label status may be relevant to acceptability, e.g. clinicians being comfortable to prescribe off-label and pwMS making informed decisions.

Key stakeholders to be considered include: patients, healthcare providers, policy makers/decision makers and payers.

Acceptability by health systems is affected by resource requirements. MSIF has provided several pathways for affordability in criteria 7 'resource requirements'.

Dropout due to any cause summary:
Dropout due to any cause of DMT vs placebo statistically significant results in favour of mitoxantrone (moderate certainty of evidence) and interferon beta 1a (very low certainty of evidence).

These comparisons also favour these DMTs, but these are not statistically significant: alemtuzumab vs interferon beta 1a, fingolimod vs GA, fingolimod vs interferon beta 1b, ocrelizumab vs interferon beta 1a.

Mode of administration:
Oral and infusion therapies score higher than injections. Injections are not preferred but still considered acceptable. Interferons and GA judged to be 'probably yes'.

Infusions could be judged as 'yes' but also need to consider post-marketing studies and serious safety issues.

Significant safety warning since approval:

to any cause - Azathioprine versus placebo	241 per 1.000	**299 per 1.000** (128 to 700)	to 2.90)	[1]	Moderate [a, b]	
Dropouts due to any cause - Daclizumab versus placebo	Study population		**RR 0.98** (0.57 to 1.68)	621 (1 RCT) [2]	⊕⊕⊕◯ Moderate [a, c]	
	88 per 1.000	**86 per 1.000** (50 to 148)				
Dropouts due to any cause - Dimethyl fumarate versus placebo	Study population		**RR 0.97** (0.82 to 1.13)	2307 (2 RCTs) [3,4]	⊕⊕◯◯ Low [d]	
	228 per 1.000	**221 per 1.000** (187 to 257)				
Dropouts due to any cause - Fingolimod versus placebo	Study population		**RR 0.96** (0.81 to 1.15)	2355 (2 RCTs) [5,6]	⊕⊕◯◯ Low [e]	
	270 per 1.000	**260 per 1.000** (219 to 311)				
Dropouts due to any cause - Glatiramer acetate versus placebo	Study population		**RR 0.96** (0.64 to 1.44)	2428 (4 RCTs) [3,7,8,9]	⊕◯◯◯ Very low [f, g]	
	141 per 1.000	**135 per 1.000** (90 to 202)				
Dropouts due to any cause - Immunoglobulins versus placebo	Study population		**RR 0.74** (0.11 to 5.01)	91 (2 RCTs) [10,11]	⊕◯◯◯ Very low [h, i]	
	53 per 1.000	**39 per 1.000** (6 to 264)				
Dropouts due to	Study population		**RR 0.41** (0.11 to	1758 (3 RCTs) [12,13,	⊕◯◯◯ Very [b,	
	169	**69**				

Article 20 safety warnings from EMA for natalizumab, alemtuzumab and fingolimod. US FSA safety warnings from US FDA: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/mitoxantrone-hydrochloride-marketed-novantrone-and-generics-healthcare-professional-sheet-text

There was been some significant safety warnings introduced since regulatory approval, notably to alemtuzumab, natalizumab (PML risk with JCV) and fingolimod. Dimethyl fumarate has also had a warning relating to risk of PML. The incidence of PML with dimethyl fumarate is lower than for natalizumab, but probably similar to fingolimod. However, unlike for fingolimod, there is a potential prognostic marker – sustained lymphopenia.

http://www.msif.org/wp-content/uploads/2022/08/EMA-safety-warnings_RMS_020622.docx
[https://www.msif.org/supporting-documents-memp-etd/]

The lack of capacity (e.g. MRI) or access to laboratory tests available (e.g. JCV testing) for required monitoring may be problematic. JCV testing is sometimes provided by the pharmaceutical company, but this is not always the case and follow-on products are becoming available, where this service may not be implemented.

Evidence shows risk of PML in JCV positive patients with natalizumab is extremely low during first 1-2 years of treatment (Ho PR, Koendgen H, Campbell N, Haddock B, Richman S, Chang I. Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies. Lancet Neurol. 2017 Nov;16(11):925-933. doi: 10.1016/S1474-4422(17)30282-X. Epub 2017 Sep 29. PMID: 28969984.).

Panel noted the catastrophic rebound risk if access is suddenly limited for natalizumab and fingolimod.

Judgements:
Natalizumab, fingolimod and dimethyl fumarate judged 'probably yes' due to monitoring and side-effects causing people having to switch.

Alemtuzumab 'probably yes' due to post-marketing safety warnings.

Ocrelizumab and cladribine both 'yes'. Ocrelizumab and fingolimod has more effect in RMS than PMS, making them more acceptable by pwMS. In PMS, ocrelizumab was judged as probably yes, but panel decided on 'yes' for RMS as the effect is 'large' in RMS and 'moderate' in PMS.

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 HICs due to post-marketing safety issues with cardiac toxicity and secondary cancers and leukaemia's. This may still be acceptable if other options are not available, but if other options exist, it is not used. Yearly cardiac ECHO 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 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.

any cause - Interferon beta-1a (Avonex/Rebif) versus placebo	per 1.000	**per 1.000** (19 to 247)	1.46)	14	low [j,k]	
Dropouts due to any cause - Interferon beta-1a (Pegylated) versus placebo	Study population		**RR 1.53** (1.11 to 2.11)	1512 (1 RCT) [15]	⊕⊕⊕◯ Moderate [a,l]	
	88 per 1.000	**135 per 1.000** (98 to 186)				
Dropouts due to any cause - Interferon beta 1b (betaferon) versus placebo	Study population		**RR 0.45** (0.14 to 1.40)	403 (2 RCTs) [16,17]	⊕◯◯◯ Very low [i,m,n]	
	346 per 1.000	**156 per 1.000** (48 to 485)				
Dropouts due to any cause - Laquinimod versus placebo	Study population		**RR 0.90** (0.76 to 1.07)	1990 (2 RCTs) [12,18]	⊕⊕⊕◯ Moderate [o]	
	219 per 1.000	**197 per 1.000** (166 to 234)				
Dropouts due to any cause - Mitoxantrone versus placebo	Study population		**RR 0.40** (0.21 to 0.74)	51 (1 RCT) [19]	⊕⊕◯◯ Low [a,o,p]	
	750 per 1.000	**300 per 1.000** (158 to 555)				
Dropouts due to any cause - Teriflunomide	Study population		**RR 0.97** (0.84 to 1.12)	2257 (2 RCTs) [20,21]	⊕⊕◯◯ Low [q]	
	305 per 1.000	**295 per 1.000** (256 to 341)				

versus placebo						

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a. not possible to assess: only one study
b. downgraded of one level for wide CI
c. downgraded of one level for selectionand attrition bias at unclear risk and high risk for other bias
d. downgraded of two levels for performance bias at high risk in one study and unclear in the other, both studies at high for attrition, reporting and other bias
e. downgraded of two levels for both studies at unclear risk for selection bias, one study at unclear ris of performance bias, both studies at high risk for attrition and other bias
f. downgraded of two levels for selection bias unclear in 2 studies, performance bias high risk in 2 studies, attrition bias at high risk in one study, reporting bias high risk in one study, other bias high risk in 3 studies
g. downgraded of one level for I2=59%
h. downgraded of one level for unclear risk of selection bias in both studies , one study at unclear risk of detection and performance bias, high risk of other bias in both studies
i. downgraded of two levels for small sample size and wide CI
j. downgraded of one level for 2 studies at unclear risk of selection and performance bias, one study at high risk for performance bias, one study at unclear risk of detection bias and 3 studies at high risk for other bias
k. downgraded of two levels for I2=94%
l. downgraded of one level for high risk of attrition and other bias and unclear risk for detection bias
m. downgraded of two levels for both studies at unclear risk for selection, performance and detection bias, one study at unclear risk for attrition bias and both at high risk for other bais
n. downgraded of two levels for I2=77%
o. downgraded of one level for selection bias unclear in 1 study, performance bias high risk in 1 study, attrition bias at high risk in 1 study, both at high risk for other bias
p. downgraded of one level for small sample size
q. downgraded of two levels for detection bias at unclear in one study and high in another study, attrition bias at unclear in one study and high in another study, high risk for reporting bias in one study and both at high risk for other bias

Dropouts due to any cause, DMT versus other DMT

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with other DMT	Risk with Dropouts due				

		to any cause				
Dropouts due to any cause - Alemtuzumab versus interferon beta-1a (Rebif)	Study population		**RR 0.35** (0.26 to 0.48)	1582 (3 RCTs) [1,2,3]	⊕⊕◯◯ Low [a]	
	277 per 1.000	**97 per 1.000** (72 to 133)				
Dropouts due to any cause - Azathioprine versus interferons beta (Avonex, Rebif or Betaseron)	Study population		**RR 1.45** (0.92 to 2.28)	244 (2 RCTs) [4,5]	⊕◯◯◯ Very low [b,c]	
	183 per 1.000	**266 per 1.000** (169 to 418)				
Dropouts due to any cause - Dimethyl fumarate versus glatiramer acetate	Study population		**RR 0.88** (0.70 to 1.11)	1067 (1 RCT) [6]	⊕⊕◯◯ Low [d,e]	
	236 per 1.000	**208 per 1.000** (165 to 262)				
Dropouts due to any cause - Fingolimod versus glatiramer acetate	Study population		**RR 0.60** (0.47 to 0.77)	1064 (1 RCT) [7]	⊕⊕⊕◯ Moderate [e,f]	
	257 per 1.000	**154 per 1.000** (121 to 198)				
Dropouts due to any cause - Fingolimod versus	Study population		**RR 0.92** (0.66 to 1.31)	1292 (1 RCT) [8]	⊕⊕⊕◯ Moderate [e,g]	
	103 per 1.000	**95 per 1.000** (68 to 136)				

interferon beta-1a (Avonex)						
Dropouts due to any cause - Fingolimod versus Interferon beta1b	Study population 412 per 1.000	**86 per 1.000** (41 to 173)	**RR 0.21** (0.10 to 0.42)	157 (1 RCT) [9]	⊕◯◯◯ Very low [e,h,i]	
Dropouts due to any cause - Glatiramer acetate versus interferon beta-1b (Betaseron)	Study population 162 per 1.000	**160 per 1.000** (123 to 209)	**RR 0.99** (0.76 to 1.29)	2319 (2 RCTs) [10,11]	⊕⊕⊕◯ Moderate [j]	
Dropouts due to any cause - Interferon beta 1a/Avonex/Rebif) versus Glatiramer acetate	Study population 143 per 1.000	**220 per 1.000** (161 to 300)	**RR 1.54** (1.13 to 2.10)	764 (1 RCT) [12]	⊕⊕⊕◯ Moderate [e,k]	
Dropouts due to any cause - Interferon beta 1b (Betaferon) vesrus Interferon beta 1 a (Avonex/Rebif)	Study population 203 per 1.000	**197 per 1.000** (110 to 355)	**RR 0.97** (0.54 to 1.75)	558 (3 RCTs) [13,14,15]	⊕◯◯◯ Very low [l,m,n]	
Dropouts due to	Study population 100	**222**	**RR 2.22** (0.24 to	19 (1 RCT) [16]	⊕◯◯◯ Very	

any cause - Interferon beta1b versus Natalizumab	per 1.000	**per 1.000** (24 to 1.000)	20.57)		low [c,e,o]	
Dropouts due to any cause - Ocrelizumab versus Interferon beta 1 a (Anonex/Rebif)	Study population		**RR 0.60** (0.48 to 0.75)	1656 (2 RCTs) [17,18]	⊕⊕⊕◯ Moderate [p]	
	204 per 1.000	**122 per 1.000** (98 to 153)				
Dropouts due to any cause - Ofatumumab versus sTerifl unomide	Study population		**RR 0.76** (0.47 to 1.25)	1882 (2 RCTs) [19,20]	⊕⊕◯◯ Low [q]	
	176 per 1.000	**134 per 1.000** (83 to 220)				
Dropouts due to any cause - Ozanimod versus Interferon beta1a (Avonex/Rebif)	Study population		**RR 0.47** (0.18 to 1.19)	2666 (2 RCTs) [21,22]	⊕⊕◯◯ Low [r]	
	169 per 1.000	**80 per 1.000** (31 to 202)				
Dropouts due to any cause - Ponesimod versus Terifl unomide	Study population		**RR 1.01** (0.78 to 1.31)	1133 (1 RCT) [23]	⊕⊕⊕⊕ High [e]	
	164 per 1.000	**166 per 1.000** (128 to 215)				

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a. downgraded of two levels for all studies at high risk for detection, performance, attrition and other bias
b. downgraded of one level for one study at unclear risk of selection bias, 2 studies at high risk for performance bias, one study at high risk of detection bias
c. downgraded of two levels for small sample size and wide CI
d. downgraded of two levels for high risk of bias for performance, attrition, reporting and other bias
e. not possible to assess: only one study
f. downgraded of one level for high risk of performance and other bias
g. downgraded of one level for high risk for detection and other bias
h. downgraded of two levels for unclear risk of selection bias, high risk of performance, attrition and other bias,
i. downgraded of one level for small sample size
j. downgraded of one level for both studies at unclear risk of selection bias, high risk of performance and other bias in both studies, one study at unclear risk of detection bias
k. downgraded of one level for high risk of performance and other bias and unclear risk for selection and attrition bias
l. downgraded of two levels for one study at unclear risk for selection, two studies at high risk of performance and detection bias, and unclear risk for attrition bias one study at high risk and one at unclear risk for other bias
m. downgraded of one level for I2=53%
n. downgraded of one level for wide CI
o. downgraded of two levels for unclear risk of selection bias, high risk of performance, and reporting bias
p. Downgraded of one level for one study at unclear and one at high rik of attrition bias and botth at high risk for other bias
q. downgraded of two levels for I2=81%
r. downgraded of two levels for I2=93%

Visser 2020 found the percentage of patients' discontinuing treatment

with DMTs ranged from 12.8–50.0%. The most commonly reported reason for discontinuation was the occurrence of adverse events (n = 12, range 6–48%), followed by the voluntary decision by the patient (n = 7, range 4–38%), and perceived lack of efficacy (n = 6, range 2–34%). On the other hand, reasons to choose the treatment included lower relapse rate, lower disability progression, lower severe adverse event, lower frequency of administration, oral administration, and lower cost. The study also reported four common reasons why patients switched treatment: the switch was initiated by the healthcare provider for not known reasons, poor tolerability, occurrence of adverse events and requested by the patient. Reasons for patients to switch to oral DMTs included the newly availability of oral formulations, intolerance to injections and increased disease activity.

Mode and frequency of administration

DMTs oral vs injectable

Mardan 20212 performed a systematic review to measure adherence and discontinuation rates of oral and injectable DMTs using: medication possession ratio (MPR); proportion of days covered (PDC); binary adherence cut-off score, reported at least 80% adherence unless otherwise specified, or effect size and standard error. Among 61 observational studies adherence varies across studies and is suboptimal. When compared with injectable DMTs and measured using mean adherence a significant improvement in 12-month medication adherence for oral DMTs was found.

The improvement contrasted with a 12-month oral and injectable adherence using a cut-off score of at least 80% to determine adherence, which showed no significant difference. Furthermore, there was no appreciable difference in 12-month discontinuation rates between oral and injectable DMTs.

Washington 2021: performed a systematic review to evaluate the factors associated with adherence to oral or self-injectable DMTs in the treatment of multiple sclerosis. 24 studies were included, 8 studies did not specify the participants' MS subtype, the remaining were RRMS. The adherence rates of the studies range from 52 to 92.8%. For the six studies which used pharmacy-based claims to measure adherence, either through the MPR or POC calculation, the mean rate of adherence was approximately 76.9%. The four studies which used an objective adherence measurement had a mean adherence rate of 80.55%. Finally, the mean rate of adherence of the self-reported studies was 74.0%. The review found that male gender, older age, depression, cognition, treatment satisfaction, and treatment side effects, injection-site reactions, and injection anxiety were the most prevalent factors associated with adherence to treatment. Contradictory evidence for disability in association with treatment adherence.

Nicholas 2020: a systematic literature review to assess the availability and variability of oral DMD adherence and/or persistence rates for once- and twice-daily oral DMDs in patients with MS using real-world data. Adherence was measured differently across studies.

Approximately one in five patients with MS do not adhere to, and one in four discontinue, daily oral DMT before 1 year. No differences between US- and no-US-based studies and between Black patients and Hispanic and Latin patients.

Alhazzani 2019: cross-sectional study; found more adherence with higher levels of education (i.e., secondary or university than lower educational levels (i.e., illiterate, primary, or intermediate levels), highest adherence in patients with oral treatment (fingolimod capsules), followed by beta interferons which is injected intramuscularly, as well as interferon beta-1b and interferon beta-1a, which are injected subcutaneously. No difference in adherence based on other characteristics (i.e., age, gender, region, marital status, age at disease onset, duration of disease, number of hospital admissions, number of attacks within the last 2 years, duration of used medications in years, or disease severity.

Morillo Verdugo 2019: cross-sectional study examined patients 'satisfaction with their treatment and reasons for changing treatment. Patient satisfaction for the type of administration was higher with oral route than with injectable treatment but no differences in adherence based on the administration route (oral [63%] vs injectable [77%]. Among oral treatments, the highest non-compliance rate appeared in patients receiving dimethyl fumarate (65%), followed by fingolimod (29%) and teriflunomide (7%). Among injectable drugs, the highest non-compliance rate was observed in patients who were treated with interferon beta-1b (47%), followed by interferon beta-1a (30%) and glatiramer acetate (26%).

Older age, more treatments received, time to diagnosis 5–10 years, better cognitive and memory status, being married/in a union, having received clear information about the treatment and higher satisfaction

with the current administration route are associated to treatment adherence.

Fernandez 2017, a retrospective study conducted in the neurology departments of 35 hospitals throughout Spain, assessed the degree of satisfaction of patients with RRMS regarding personal impressions of treatment benefits, tolerability, convenience of use and general satisfaction with the treatments with injectable DMTs using TSQM. By individual treatment, highest overall satisfaction was reported for interferon beta-1a SC and the lowest for interferon beta-1b SC. For side effects subscale, the highest score was reported for glatiramer acetate SC and the lowest for interferon beta-1a IM. For the effectiveness, patients were most satisfied with interferon beta-1a SC and least satisfied with (interferon beta-1b SC). Finally, in the case of convenience, interferon beta-1a SC scored highest and interferon beta-1b SC scored lowest.

Eagle 2017: prospective observational cohort study, examined treatment satisfaction (effectiveness, side effects, convenience and overall satisfaction) in MS with TSQM by comparing patients' satisfaction with oral, injectable and infusion therapies. The three injectable treatments were interferon beta-1a intramuscular (IFNβ 1a IM), interferon beta-1a subcutaneous (IFNβ 1a SC), and glatiramer acetate (GA). The infusion treatment was natalizumab (NTZ). The oral treatments were fingolimod (FTY) and dimethyl fumarate (DMF). The most consistent differences among the groups were related to the convenience of the medication, with oral medications have the highest scores and infusion medications the second highest.

In terms of side effects, significant differences between all groups in terms of the presence of side effects were found, with the infusion medication having the lowest rate of side effects and the injectable medications having the highest. At the same time, the side effects of the injectable medications had a significantly smaller effect on mental function than the other two treatment groups among the subjects who had side effects.

In terms of overall satisfaction subscale, the oral medication group reported significantly higher satisfaction compared to the injectable group in the total score, and the same relationship was seen in the question related to satisfaction with the medication. Table 2 reports the treatment satisfaction outcomes compared across the treatment groups for the routes of administration (From Eagle 2017)

Table 2
Treatment satisfaction comparison based on mode of administration.

	Injectable	Infusion	Oral	p-value	Adjusted p-value‡
Effectiveness	74.8+/−19.8	73.4+/−20.5	72.1+/−19.6	0.53	0.1011
Q1. Ability to treat or prevent condition	5.6+/−1.3	5.5+/−1.3	5.5+/−1.3	0.65	0.1992
Q2. Ability to relieve symptoms	5.4+/−1.3	5.2+/−1.5	5.1+/−1.3	0.24	0.2579
Q3. Time it takes medication to start working	5.4+/−1.2	5.5+/−1.2	5.3+/−1.2	0.79	0.0463
Number (%) who report side effects*	112 (55.2)	9 (20.5)	35 (31.8)	< 0.001	< 0.001
Side effects	80+/−15.8	72.9+/−15.6	74.7+/−20.6	0.16	0.3838
Q5. Bothersomeness of side effects	3.7+/−0.8	3.8+/−0.7	3.7+/−1.0	0.90	0.0367
Q6. Side effects interfere with physical function	4.4+/−0.8	3.7+/−0.9	4.0+/−1.0	0.017	0.0736
Q7. Side effects interfere with mental function	4.6+/−0.7	4.0+/−1.1	4.3+/−1.0	0.017	0.0241
Q8. Side effects impact overall satisfaction	4.2+/−0.9	4.2+/−0.8	4.0+/−0.9	0.53	0.6845
Convenience	68.4+/−17.8	70.7+/−20.6	88.1+/−16.8	< 0.001	< 0.001
Q9. Ease/difficulty to use	5.0+/−1.2	5.2+/−1.4	6.4+/−1.0	< 0.001	< 0.001
Q10. Ease/difficulty of planning to use	5.3+/−1.1	5.5+/−1.3	6.2+/−1.0	< 0.001	< 0.001
Q11. Convenience of taking as instructed	5.0+/−1.2	5.0+/−1.5	6.2+/−1.2	< 0.001	< 0.001
Overall satisfaction	76.5+/−20.8	74.1+/−20.2	75.5+/−23	0.78	0.0276
Q12. Confidence that taking medication is good	4.1+/−0.9	4.1+/−0.9	4.0+/−1.0	0.59	0.1137
Q13. Certainty that good things about medication outweigh bad	4.1+/−0.9	3.9+/−1	4.1+/−1	0.25	0.062
Q14. Satisfaction with medication	5.7+/−1.1	5.8+/−1	5.8+/−1.3	0.95	0.0033

Injectable medications were glatiramer acetate, interferon beta-1a intramuscular and interferon beta-1a subcutaneous, infusion medication was natalizumab, and oral medications were dimethyl fumarate and fingolimod.
‡ : p-value for three group comparison controlling for age, gender, EDSS and time on treatment.
* : For the comparison of the % who report side effects, multivariable logistic regression was used.

Mortensen 2017, a qualitative focus group interviews to aimed to explore which specific DMTs may be preferable from MS patient perspectives regarding efficacy, side effects, and mode of administration. Efficacy was decisive but it could be moderated by side effects or mode of administration. For instance, some had fear of needles leading to them reject any type of injectable DMT; others opted for the monthly natalizumab infusions due to its lack of daily administration and side effects, despite the risk of developing progressive multifocal leukoencephal¬opathy, a viral and often fatal brain disease.

With regard to mode of administration, almost all participants preferred oral DMT to injections. Tablets were easy to take and recurrently described as less likely to making the person feel "pathologized" than injections. The negative feeling of "pathologization" might also be caused by severe side effects or hospital visits (natalizumab infusions). Frequency of administration affected the participants' preferences only in so far as they suffered from side effects or needle phobia.

Fragoso 2016: survey that assessed the degree of satisfaction of patients with MS regarding treatments with DMTs prescribed at five different Brazilian MS Units. Questions related to personal impressions of treatment benefits, tolerability, convenience of use and general satisfaction with the treatment was assessed by individual interview. For

all DMTs, over 80% of the patients perceived that they were beneficial. The convenience of oral drugs was higher than that of injectable medications, but the difference was less than 10%. Tolerability was the aspect scoring lesser values, ranging from 40 to 50% for all treatments.
Ting 2015 (abstract): conducted a systematic review of clinical studies that reported MS patient satisfaction with their disease-modifying therapies (DMTs) using the Treatment Satisfaction Questionnaire for Medication (TSQM) (score range 0-100). The DMTs studied included interferon beta-1b, glatiramer acetate, fingolimod, teriflunomide, and natalizumab. TSQM assesses four key dimensions of treatment satisfaction: Effectiveness; Side Effects; Convenience; and Global Satisfaction. Change from baseline (CFB) at 6 months on the effectiveness subscale ranged from 1.8 to 26.9, convenience subscale from 3.6 to 41.2, and global satisfaction subscale from 2.9 to 20.4. CFB at 6 months was generally higher for natalizumab and fingolimod compared with injectable platform DMTs, although this finding may be confounded by the differences in study design and patient characteristics.
Turcani 2021 reports the results of a non-interventional real-world study that mapped the treatment patterns of disease-modifying therapy (DMT) and assessed treatment satisfaction with DMT in patients with RRMS from 10 multiple sclerosis centers across Slovakia. Three parameters of TSQM-9, effectiveness, convenience and global satisfaction, were analyzed separately for
all DMTs in total, for DMTs by the route of administration and separately for each DMT. When assessing all DMTs in total, the highest score (mean; 95% CI) was reported for convenience (75.05; 73.49–76.61), followed by effectiveness (68.15; 66.56–69.75), with the lowest for global satisfaction (66.94; 65.26–68.62). When assessing DMTs by route of administration, infusions rated best for effectiveness and global satisfaction in comparison to oral dosage and injections. For convenience (mean; 95% CI), oral forms were appraised highly (82.66; 80.59–84.73), followed by infusions (74.40, 70.12–78.69), while injections were rated as the worst (66.92; 64.81–69.04).

Fingolimod vs placebo or other DMTs
Wu 2021 summarized the evidence on the efficacy and safety of different doses of fingolimod for the treatment of RRMS. Among outcomes of the efficacy the authors reported data on treatment satisfaction measured by questionnaire (TSQM). The results showed that, compared with control group (placebo or other DMT), fingolimod 0.5 mg/d and 0.25 mg/d could improve patient treatment satisfaction (MD = 13.03 (8.20, 17.85) and MD=11.10 (4.81, 17.39) respectively) score.

Injectable subcutaneous vs Peg-IFNbeta-1a (125 µg SC every 2 weeks)
Centonze 2019, a multicenter, open-label study conducted in 32 Italian centers to evaluate the impact of switching to Peginterferon beta-1a in patients with RRMS unsatisfied with other SC interferons. Self-reported effectiveness, convenience, global satisfaction, side effects, and injection-system satisfaction were analyzed using TSQM-9 and the Multiple Sclerosis International Quality of Life questionnaire. Patients switching to Peg-IFN from other subcutaneous interferons reported a statistically significant improvement of the Convenience Score of the TSQM at 12 and 24 weeks, also considering social-demographic factors (age, sex) and clinical characteristics (EDSS, time since MS diagnosis, treatment duration). A significant improvement was achieved also in the other TSQM domains (effectiveness and global satisfaction) and MusiQoL total scores.at 12 and 24 weeks.

Tolerability
Perez 2021: retrospective review of electronic medical records considering a multi-ethnic cohort of MS patients in treatment with DMTs. Data showed a differential response to therapeutic intervention by race and ethnicity in terms of tolerability profiles: Blacks had poor tolerability to first-line treatment with interferons respect to Hispanics and Whites. While white patients tolerated glatiramer acetate less frequently, teriflunomide, fumarates, S1P inhibitors and the monoclonal antibodies were relatively well tolerated across ethnic groups, with a less than 20% discontinuation rate due to adverse events

Cost
Frost 2019 determine patients' preferences and their willingness-to-pay (WTP) that reflected their value of DMTs for MS. Satisfaction with the treatment is related to monthly out-of-pocket costs associated with DMTs. Indeed, out-of-pocket costs are a key factor patients' decision making regarding their interest in trying a DMT. Also found that drug administration route and frequency are of great importance to patients when considering a new product.

Type of side effects

Atlas of MS clinical management 2021. A global survey on the availability of resources and services for people with MS in different regions of the world reported that the second most common barrier in access DMTs, reported by experts from 41 participating countries (39%), is that people with MS do not take DMTs when offered them, often due to expense or concern about the side effects.

Requirement to attend a healthcare facility for administration and/or follow up monitoring

No evidence was identified

CONSIDERATIONS FOR PAYERS

No evidence found

CONSIDERATIONS FOR CLINICIANS

No evidence found

CONSIDERATIONS FOR HEALTH SYSTEM

No evidence found

KEY FINDINGS

- In the comparison DMTs vs placebo, results are in favor (SS) of: mitoxantrone (moderate certainty of evidence) and Interferon beta-1a (Avonex/Rebif (very low certainty of evidence). The majority of comparisons are in favour of drugs but not significant. In the comparison DMTs vs other DMTs, results are in favor (SS) of alemtuzumab versus interferon beta-1a (Rebif) (low certainty of evidence); fingolimod versus glatiramer acetate (moderate certainty of evidence), fingolimod versus Interferon beta1b (very low certainty of evidence), Ocrelizumab versus Interferon beta 1 a (Anonex/Rebif) (low certainty of evidence).
- Adherence varies differently across studies (range 52 to 92.8%). The most commonly reported reason for discontinuation is occurrence of adverse events, followed by the voluntary decision by the patient and perceived lack of efficacy
- Patient satisfaction for the type of administration is higher with oral route than with injectable treatment but no differences in adherence based on the administration route
- The most prevalent factors associated with adherence to treatment are: Male gender, older age, marital status, depression, cognition, treatment satisfaction, treatment side effects, injection-site reactions, and injection anxiety were
- Among oral treatments, the highest non-compliance rate appear in patients receiving dimethyl fumarate, followed by fingolimod and teriflunomide.
- Among injectable drugs, the highest non-compliance rate appear in patients treated with interferon beta-1b, followed by interferon beta-1a and glatiramer acetate.
- Tablets are easy to take and less likely to making the person feel “pathologized” than injections.
- Reasons for patients to switch to oral DMTs included the newly availability of oral formulations, intolerance to injections and increased disease activity.
- Considering overall satisfaction, oral medication group report significantly higher satisfaction compared to the injectable group. Considering side effect, infusion medication have the lowest rate of side effects and the injectable medications have the highest rate
- Patients in treatment with injectable DMTs show the highest overall satisfaction for interferon beta-1a SC and the lowest for interferon beta-1b SC. When assessing DMTs by route of administration, infusions rated best for effectiveness and global satisfaction in comparison to oral dosage and injections
- In terms of side effects, patients reported a lowest rate of side effects with infusion medication and highest side effects for the injectable medications
- Patients preferred DMT with an easy level of preparation for injection, a home infusion to hospital-based infusion, mostly women and those with long travel distances
- Adherence to biochemical liver testing while on treatment varied across the oral DMTs. For people filling a prescription for dimethyl fumarate, the proportion who were adherent was high. For fingolimod and teriflunomide, for which the testing requirements were more frequent, on-treatment adherence to biochemical liver tests decreased over time.
- MS treated with ocrelizumab experience lower work and

activity impairment than patients treated with other DMTs. Overall, patients initiating oral DMTs had less than half the number of days on long-term disability than patients initiating injectable DMTs.

- From a clinician and payers perspective, the availability of high efficacy DMTs with a positive risk/benefit profile and a reasonable price positively impact affordability, health care sustainability and cost savings.
- From a clinician point of view, drug-related problems is a barrier to prescribing MS medications
- Reasons reported by neurologists for not using DMTs on some patients with confirmed SPMS included: funding/reimbursement restrictions, absence of active inflammation and/or relapse, lack of treatment effectiveness, patient eligibility and an unfavorable risk-benefit analysis.
- In the first calendar year of treatment, absenteeism, short-term disability productivity loss and costs are similar for DMTs oral and injectable users. Patients initiating oral DMTs had less than half the number of days on long-term disability than patients initiating injectable DMTs. Other measures of productivity were similar between route of administration

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Feasibility

Which intervention is more feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
No: **Probably no:** Mitoxantrone **Probably yes:** Interferon beta 1a, Dimethylfumarate, Ocrelizumab, Cladribine, Interferon beta 1b, Glatiramer acetate **Yes:** **Varies:** Natalizumab, Alemtuzumab, Fingolimod **Don't know:**	Long-term resource requirements are influenced by the DMTs patent status around the world. Patent landscape of DMTs available here: http://www.msif.org/wp-content/uploads/2022/03/DMTs-patent-overview-March-22.pdf We found one systematic reviews, 11 observational studies (cross-sectional, surveys) and two additional studies (comment, editorial/letter) reported results on the feasibility of treatment with DMTs . No studies on feasibility from health systems were found. **CONSIDERATIONS for PEOPLE AFFECTED BY MS** **Cost** **Atlas of MS clinical management 2021**. A global survey on the availability of resources and services for people with MS in different regions of the world found that it is common for people with MS to have to pay some or all of the cost of their DMTs, sometimes referred to as 'out of pocket costs'. This was reported to occur in 60 countries (57%) worldwide, ranging from 39% of countries in Europe to 76% of countries in the Americas. The reasons people have to pay for DMTs are varied. Of the 60 country coordinators reporting that people have to pay at least some of their DMT costs: • 48% report the government, healthcare or insurance provider requires a co-payment or will only pay part of the cost • 40% report that people with MS do not have health insurance • 35% report that DMTs are not covered by health insurance • 35% report that even if people with MS have health insurance, the DMT recommended is not approved or they don't meet the eligibility criteria. **National Multiple Sclerosis Society 2019** conducted a survey on the impact of increasing costs of DMTs on people living with MS recruited from the National Multiple Sclerosis Society database. Cost related insurance company exclusions and limitations often create significant access barriers for patients. Further, nearly half of respondents noted that they have altered how they take their DMT (e.g., skipped doses, delayed treatment) and changed other lifestyle choices (e.g., spend less on entertainment) because of high DMT costs. 45% of people living with MS do not pay anything out-of-pocket (OOP) for their DMT. However, the average annual OOP cost among those who do pay is nearly $2300. Moreover, 31% of people living with MS feel at least some financial burden because of their OOP cost. This goes up to 54% among those who have an OOP cost. **Simacek 2018**, a web-based online survey. Participants were selected for interviews based on their survey response, reporting either a current or past issue with DMT access, at least one MS relapse during the period of their DMT access difficulty, and consent to a follow-up interview in the first survey. The study found the most frequently reported reasons for DMT-related access difficulties were "insurance required authorizing documentation" (9/42, 21.4%, current issue and 78/182, 42.9%, past issue) and "high out-of-pocket costs" (13/42, 31.0%, current issue and 54/182, 29.7%, past issue). Other reasons included administrative coordination problems among insurance companies, pharmacies, and clinician's offices. Furthermore, participants reported that the effort to overcome barriers could be exceptionally time consuming, complex, and stressful for people with RRMS.	Feasibility of implementation is affected by resource requirements. MSIF has provided several pathways for affordability in criteria 7 'resource requirements'. On-label/off-label status may be relevant to feasibility as linked to (a) current availability and (b) other organisations doing access initiatives, e.g. pre-qualification and push for rituximab for cancer by WHO and CHAI. There is a lack of evidence on feasibility and Atlas insight on DMTs used may be relevant. Consideration of feasibility for all key stakeholders is important. Please refer to feasibility assessment by expert input spreadsheet for information on mode of administration, frequency of administration, storage, required and optional pre-tests and monitoring and feasibility assesment from Malaysia and Zambia: http://www.msif.org/wp-content/uploads/2022/08/Clinical-Feasibility_expert-input_300522_RMS.xlsx [https://www.msif.org/supporting-documents-memp-etd/] Cold-chain, healthcare infrastructure (e.g. infusion suites), access to pre-tests and monitoring all affect feasibility. ECG and OCT sometimes only available at national referral hospitals. Panel judgements: Natalizumab and alemtuzumab 'varies' due to pre-tests and specialist care required. For alemtuzumab, even in HICs not all clinics can administer it. For both, the amount of required monitoring is significant over a sustained period of time. Mitoxantrone 'not feasible' due to the safety concerns, the required monitoring and the long-term monitoring. Concern for rebound effect in settings where medicine supply or access may be disrutpted for fingolimod and natalizumab, making them less feasible. None of the other DMTs are known to have this issue. Panel agreed to keep fingolimod as 'probably yes' for PMS but judge it as 'varies' in RMS as rebound is a much higher risk for RMS. All other DMTs were judged as 'probably yes'.

Access to therapy

Atlas of MS clinical management 2021 reported that even if people have access to DMTs, there are also barriers to the continuous provision of their treatment. Experts in almost half of countries worldwide report problems with the continuous provision of DMT treatment, meaning that once initiated on a DMT, people with MS are unable to receive future doses without interruption or delay. The main reasons cited are an irregular supply of DMT (27% of all countries) or the delays associated with people needing to get their reimbursement renewed (19%) or the need to take regular tests to prove continued eligibility (13%).

Rojas 2021 conducted a survey in Latin America with 80 physicians to understand availability of: 1) imaging tests for diagnosing MS and NMOSD and its barriers; 2) diagnostic laboratory tests for diagnosing MS and NMOSD and its barriers; and 3) treatments for MS and NMOSD in the acute and chronic phases of the disease. They found that diagnostic tests (AQP4-ab test) for MS were widely available in the almost half of the countries of the region. Available to almost all of the region's countries were lumbar puncture (LP) and CSF analysis, optic coherence tomography (OCT), magnetic resonance image (MRI) and visual evoked potentials (VEP) test, while the possibility to calculate brain volume loss (BVL) was available in half of the countries explored. Access to treatment for MS relapse was high. All countries had available to them high doses of intravenous methylprednisolone, oral steroids, plasmapheresis, and intravenous immunoglobulins.
For chronic DMD of MS, IFN beta and glatiramer acetate were available in almost all countries. oral treatments were mostly available for teriflunomide, fingolimod, dimethyl-fumarate and cladribine. Regarding monoclonal antibodies, natalizumab, ocrelizumab and alemtuzumab were also mostly available in surveyed countries, except for Venezuela. Siponimod was not available in any country of the region in this survey. In patients with MS the most common challenge and barrier identified was the cost of medications to the health sector, followed by the inability to consistently obtain medicine supplies for affected patients. With respect to health coverage, half of the countries partially cover treatments. Despite discussion among physicians concerning the lack of access to preferred medicine, this barrier was not the most relevant in clinical practice in MS. In MS patients, the treatment was fully covered by the health care system in most of the surveyed countries.

Off-label status

Atlas of MS clinical management 2021. A global survey on the availability of resources and services for people with MS in different regions of the world found that the use of off-label DMTs (therapies that have not been approved specifically for MS) is common. Experts in 87% of countries report the use of off-label drugs to treat MS.
It is common for people with MS to have to pay some or all of the cost of their DMTs, sometimes referred to as 'out of pocket costs'. This was reported to occur in 60 countries (57%) worldwide, ranging from 39% of countries in Europe to 76% of countries in the Americas.

Mode of administration, frequency and storage of DMTs

Ross 2021, a multicenter survey conducted with 80 MS patients and 50 MS nurses across the US, Germany, France and Italy. The survey included patients with RMS who received a disease-modifying treatment through a subcutaneous/intramuscular injection via an autoinjector for ≥2 months and MS nurses who had ≥3 years of practice with experience in training patients on ≥2-6 MS autoinjector devices. Nurses and patients were asked a set of qualitative open-ended and quantitative closed-ended questions, rating the importance of predefined attributes for the Sensoready autoinjector pen for administration of ofatumumab versus other autoinjectors that are used for other DMTs. The answers were measured on a Likert scale from 1 (not at all important) to 10 (extremely important). The Sensoready® autoinjector pen scored highly across the majority of attributes (>8.0 out of a possible 10) versus other autoinjectors and was similarly rated by both nurses and patients.

Rath 2021, a cross-sectional study of patients attending an academic tertiary referral hospital infusion service in Australia. Patients were asked to complete a questionnaire exploring eight domains, including preferences for time of infusions and location of infusion centers. Sixty-four patients (77%) reported their preference for hospital-based infusions to be completed in a stand-alone ambulatory center in contrast to an in-patient ward environment. Fifty patients (60%) reported that they would prefer a home infusion to hospital-based infusion. Age was a strong predictor of preference for infusion timing: Patients 50 years and older were the most likely (23%) to request pre–8

am infusions whereas younger people than 30 years were the least likely request treatment before 8 am (8%). Patients who were unable to walk 100 m (n = 10) were more interested in treatment earlier in the day. Patients with working or studying commitments had a slight preference for afternoon/late afternoon infusion slots. Women and those with long travel distances had a strong preference for home infusions.

Rahimi 2018 did a conjoint analysis studies in people with MS to determine and measure their preferences for IFN-β in Isfahan province, Iran. On the base of the available published studies, opinion-polling experts (experts in pharmacoeconomics, neurology, and clinical pharmacy) and availability in Iran's market, six attributes were selected:
· Manufacturing Country: imported interferon or the one produced in Iran.
· Monthly costs of the interferon: range 0 to 231 dollars
· Administration and frequency (muscular injection (once a week), subcutaneous injection (three times a week), and subcutaneous injection (every other day).
· Effectiveness (reduced frequency of relapses, the disease progression and disability progression): moderate and high
· Side effects: Low and medium levels
· Ease of injection: easy level (preparation of the syringe and lack of the need for pre- injection preparations) and the difficult level (drug preparation prior to injection by the patient or PWID (persons who inject drugs).
The highest relative importance was obtained for efficacy variable (20.91%), the manufacturing country (17.87%), and ease of injection (17.07%).

Requirement to attend a healthcare facility for administration and/or follow-up monitoring
Ng 2021 examined laboratory testing adherence by persons initiating an oral DMT (fingolimod, dimethyl fumarate or teriflunomide) for MS. Using multiple administrative health databases covering the province of British Columbia, Canada, linked to laboratory data they identified a total of 1600 patients. Adherence to recommended laboratory testing was high before starting their first oral DMT. This ranged from 87.8% to 91.4% for the biochemical liver tests and from 91.3% to 93.7% for the lymphocyte count.
Adherence to biochemical liver testing while on treatment varied across the oral DMTs. For people filling a prescription for dimethyl fumarate, the proportion who were adherent was high. For fingolimod and teriflunomide, for which the testing requirements were more frequent, on-treatment adherence to biochemical liver tests decreased over time. Overall, post-analysis indicated that 91.4%– 96.3% of people who had been exposed to a non-oral DMT completed a biochemical liver test before initiating an oral DMT, while only 77.3%–88.8% of those who had not been exposed to a non-oral DMT in the baseline year received the recommended test. Adherence to urinalysis prior to initiating DMF did not differ by previous use of a non-oral DMT.
Sex and previous exposure to a nonoral DMT was associated with adherence; compared with women who filled a prescription for DMF, men who filled a prescription for DMF were less likely to have a pre-treatment urinalysis, or to adhere to liver testing or lymphocyte counts while on treatment.

CONSIDERATIONS FOR PAYERS

Cost
Kotsopoulos 2020: The aim of this study was to estimate the effect of DMTs on government public economics by quantifying lost tax revenue and additional spending on social benefit transfer programs, i.e. transfers attributed to disability progression and preventable by DMTs, throughout a disease simulation model. The model simulates the natural history of cohorts of Swedish patients receiving no treatment (placebo) or one of the following DMTs: Interferon beta-1a, Pegylated interferon beta-1a, Dimethyl fumarate, Natalizumab. Patient expenditure for informal care and community services were the predominant public costs, followed by disease management costs. For active treatment, DMT costs were approximately the second highest expenditure category.

Neuberger 2021: data from a survey have been used for evaluate work and activity impairment in patients with MS treated with ocrelizumab (OCR) versus other disease-modifying therapies (DMTs). The evidence suggests that patients with MS treated with OCR experience lower work and activity impairment than patients treated with other DMTs

Bonafede 2021: reported the results of a retrospective, administrative claims-based US study that examined productivity loss and associated costs among patients with MS initiating a DMT compared with matched non-MS controls and the indirect burden and cost by route of administration of DMT. When DMT oral and injectable users were compared, their absenteeism and short-term disability productivity loss and costs were generally similar in the first calendar year. Patients initiating oral DMTs had less than half the number of days on long-term disability than patients initiating injectable DMTs. Other measures of productivity were similar between route of administration.

Atlas of MS clinical management 2021. A global survey on the availability of resources and services for people with MS in different regions of the world found a widening gap between high- and low-income countries in the access to DMTs. They found that 72% of countries cite barriers to accessing DMTs. Globally the most common barrier is the cost to the government, healthcare system or insurance provider, which is cited by experts in around half of all reporting countries. In addition to cost, experts in low income countries often report both a lack of healthcare professionals and a lack of knowledge of DMTs amongst professionals as a barrier to accessing therapies.

Access to therapy

No evidence was found

Off label status

No evidence was found

Mode of administration, frequency and storage of DMTs

No evidence was found

Requirement to attend a healthcare facility for administration and/or follow-up monitoring

No evidence was found

CONSIDERATIONS FOR CLINICIANS

Cost

Duddy 2021: explored the real-world management of SPMS in the UK. Healthcare professionals involved in the management of patients with SPMS from geographically distributed MS neurology centres in the UK participated in face-to-face or telephone interviews. Regarding DMTs management, approximately two-thirds of the respondents reported they followed a specific guideline for DMT management, most of whom followed the NHSE algorithm. Reasons reported by respondents for not using DMTs on some patients with confirmed SPMS included: funding/reimbursement mediated restrictions, absence of active inflammation and/or relapse, lack of treatment effectiveness, patient eligibility and an unfavourable risk-benefit analysis.

Filippi 2022: reviewed the evidence and the professional experiences from clinical healthcare professionals and payer advisors, on the importance of providing early and unrestricted access to high efficacy DMTs (HE-DMTs), such as fingolimod and natalizumab, alemtuzumab, ocrelizumab, and ofatumumab.
From a patient perspective early access to novel HE-DMTs with a positive benefit–risk profile could improve their long-term outcomes. From a budget impact perspective, the availability of HE DMTs with a positive risk/benefit profile and a reasonable price proposition allows for their use early in the course of the disease, which would positively impact affordability, health care sustainability and cost savings. From a clinician perspective early and unrestricted access to HE DMTs would provide the freedom of choice of an appropriate treatment by expert physicians.
Even though there is a need for long-term, real-world safety data, this should not be the reason to restrict access to novel HE DMTs, as this would potentially translate to 5- to 10-year delayed access.

Access to therapy

Narayanan 201414: survey aimed to assess health care provider (HCP) perception of barriers to prescribing medications to patients with Multiple Sclerosis (MS) in EU and the US. METHODS: HCP perceptions of the following barriers to prescribing interferons (all types), glatiramer acetate, natalizumab and fingolimod were assessed: patients prefer other medications (barrier-1), availability/cost (barrier-2), guidelines/license restrictions (barrier-3) and drug-related issues (barrier-4). Drug-related issue was the most frequently cited barrier to prescribing MS medications both in EU and the US. Drug availability/cost and guidelines/license restrictions were more often cited by HCPs in the US and 5EU respectively. See table below:

Drug	barrier-1 EU-US	barrier-2 EU-US	barrier-3 EU-US	barrier-4 EU-US
interferons	12%-13%	11%1-21%	9%-8%	55%-56%
glatiramer acetate	14%-12%	9%-18%	8%-6%	62%-60%
natalizumab	16%-17%	28%-36%	47%-23%	81%-92%
fingolimod	5%-21%	35%-48%	49%-21%	65%-84%

Off-label status

No evidence was found

Mode of administration, frequency and storage of DMTs

No evidence was found

Requirement to attend a healthcare facility for administration and/or follow-up monitoring

No evidence was found

CONSIDERATIONS FOR HEALTH SYSTEM

No evidence found

KEY FINDINGS

- People with MS in different regions of the world have to pay some or all of the cost of their DMTs, ranging from 39% of countries in Europe to 76% of countries in the Americas
- Significant access barriers for patients for: cost-related insurance company, insurance required authorizing documentation, high out-of-pocket costs
- Global problems with the continuous provision of DMT treatment due to an irregular supply of DMT or for reimbursement renewed or need to take regular tests to prove continued eligibility. With respect to health coverage, one study found that half of the countries of the Latin America partially cover treatments
- Drug-related problems (circumstance involving drug therapy that actually or potentially interferes with desired health outcomes) is the most frequently cited barrier to prescribing MS medications both in EU and the US
- Patients preferred DMT with an easy level of preparation for injection, a home infusion to hospital-based infusion, mostly women and those with long travel distances
- Adherence to biochemical liver testing while on treatment varied across the oral DMTs. For people filling a prescription for dimethyl fumarate, the proportion who were adherent was high. For fingolimod and teriflunomide, for which the testing requirements were more frequent, on-treatment adherence to biochemical liver tests decreased over time
- MS treated with ocrelizumab experience lower work and activity impairment than patients treated with other DMTs. Overall, patients initiating oral DMTs had less than half the number of days on long-term disability than patients initiating injectable DMTs
- From a clinician and payers perspective, the availability of high efficacy DMTs with a positive risk/benefit profile and a reasonable price positively impact affordability, health care sustainability and cost savings
- From a clinician point of view, drug-related problems is a barrier to prescribing MS medications
- Reasons reported by neurologists for not using DMTs on some patients with confirmed SPMS included: funding/reimbursement restrictions, absence of active inflammation and/or relapse, lack of treatment effectiveness, patient eligibility and an unfavorable risk-benefit analysis
- In the first calendar year of treatment, absenteeism, short-term disability productivity loss and costs are similar for DMTs oral and injectable users. Patients initiating oral DMTs had less than half the number of days on long-term disability than patients initiating injectable DMTs. Other measures of productivity were similar between route of administration

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Protocol: https://osf.io/5edjf

Availability

What is the regulatory status, market availability, and availability of pharmacopoeial standards for this medicine?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Not available in most settings ○ Probably not available in most settings ○ Probably available in most settings ○ Available in most settings ● Varies ○ Don't know	No systematic review was performed for availability. The clinical management module of Atlas of MS (2021) collected data through a systematic survey on which DMTs were used in each country around the world in 2019/2020. Usage is a proxy for availability. No country reported daclizumab (de-registered), laquinimod, ofatumumab (approved 2020), ozanimod (approved 2020) or ponesimod (approved 2021) use as a DMT.	The panel considered availability across global settings surveyed in the MSIF atlas. The panel used a threshold of 60 countries reporting use as "probably available". The panel reviewed consistency with PMS judgements. Available in most settings: Fingolimod, interferon beta-1a, interferon beta-1b. Probably available in most settings: mitoxantrone Probably not available in most settings: alemtuzumab, cladribine, dimethyl fumarate Varies: Glatiramer acetate, ocrelizumab, natalizumab Concern raised to conclude any of these DMT are 'available' as only 107 countries have provided data, and the ones not reporting are likely to be LMICs with poor availability. Moreover, even from the 107 countries, there are 30 to 40 countries where they are not available. Highest judgement should be 'probably available'. However, panel decided to align approach with PMS, where some medicines were judged available. Ocrelizumab, natalizumab and glatiramer acetete were judged as 'varies' as more available in higher income countries, but not in LMICs. It is very challenging to get medications on to the EML list, and there is not a

RMS DMT	Global*		World Bank - High Income Countries	World Bank - Upper Middle Income Countries	World Bank - Lower Middle Income Countries	World Bank - Low Income Countries		WHO Region - African	WHO Region - Americas	WHO Region - Eastern Mediterranean	WHO Region - European	WHO Region - South-East Asia	WHO Region - Western Pacific
Number of countries completing survey	107		44	30	23	10		15	17	18	42	6	9
Alemtuzumab	56		39	14	3	0		0	12	8	31	0	5
Azathioprine	68		28	20	16	4		7	13	12	23	5	8
Cladribine (IV)	10		7	2	1	0		0	2	3	5	0	0
Cladribine (oral)	52		35	11	6	0		1	9	8	29	1	4
Daclizumab													
Dimethyl fumarate	58		39	14	5	0		0	8	10	31	2	7
Fingolimod	78		42	24	10	2		3	14	14	36	4	7
Glatiramer acetate	65		39	17	8	1		5	12	7	35	1	5
Immunoglobulin	3		2	1	0	0		0	0	2	1	0	0
Interferon beta-1a	88		44	26	14	4		7	14	15	40	5	7
Interferon beta-1b	82		44	23	12	3		6	14	14	38	2	8
Laquinimod													
Mitoxantrone	62		31	19	11	1		2	12	8	31	3	6
Natalizumab	69		43	18	8	0		4	11	13	34	0	7
Ocrelizumab	66		39	19	8	0		2	15	12	35	0	2
Ofatumumab													
Ozanimod													
PEG IFN-beta-1a	37		33	3	1	0		2	4	4	25	0	2
Ponesimod													
Rituximab	70		33	20	16	1		6	13	12	28	6	5
Teriflunomide	70		42	19	7	2		3	12	11	34	3	7

Availability of on-label and off-label DMTs were analysed on 137 national essential medicines lists (EML) from the WHO national EML database (Laurson et al. 2021, *MSJ*). Listing on a national EML is a proxy for availability, but in some countries medicines can be available and reimbursed, despite not being listed on the national EML (e.g. Egypt). In other instances, medicines may be listed and prioritised, but still not continuously available in the clinic due to budgetary and other challenges. The analysis did not include immunoglobulin, laquinimod, siponimod and steroids.

Table 1. Number of countries listing DMTs that have been known to be used for MS on their national essential medicine list. Please note that most national medicine lists do not give details of approved indications for use. On-label for MS in (A) and off-label DMTs in (B). The Anatomical Therapeutic Chemical (ATC) codes used for the analysis are included. WHO's ATC codes classify the active ingredients of drugs according to the organ or system on which they act.

A		
Medicine	ATC code	Number of countries listing medicine
Interferon beta	L03AB02	39
Peginterferon	L03AB08	Not listed
Glatiramer acetate	L03AX13	19
Fingolimod	L04AA27	6
Cladribine	L04AA40	16
Teriflunomide	L04AA31	Not listed
Dimethyl fumerate	N07XX09	Not listed
Ocrelizumab	L04AA36	Not listed
Alemtuzumab	L04AA34	11
Natalizumab	L04AA23	9
Total listing at least one medicine		**42**
Not listing any medicine		95
(B)		
Medicine	ATC code	Number of countries listing medicine
Azathioprine	L04AX01	107
Rituximab	L01XC02	41
Leflunomide	L04AA13	30
Cladribine	L04AA40	16
Cyclophosphamide	L01AA01	114
Fludarabine	L01BB05	38
Methotrexate	L01BA01, L04AX03	126
Mitoxantrone	L01DB07	37
Total listing at least one medicine		**130**
Not listing any medicine		7

medication on the EML with a multiple sclerosis indication. Azathioprine and rituximab area already on the EML and are available to patients now in low- and middle-income countries. This means that they can really help people right now, if we were able to have them approved for MS. They should be considered by the panel.

SUMMARY OF JUDGEMENTS

	INTERFERON BETA 1A	NATALIZUMAB	DIMETHYLFUMARATE	ALEMTUZUMAB	OCRELIZUMAB	CLADRIBINE	MITOXANTRONE	FINGOLIMOD	INTERFERON BETA 1B	GLATIRAMER ACETATE
PROBLEM										
DESIRABLE EFFECTS	Large	Large	Large	Large	Large	Large	Large	Large	Large	Large
UNDESIRABLE EFFECTS	Trivial	Trivial	Trivial	Trivial	Trivial	Trivial	Trivial	Trivial	Trivial	Trivial
CERTAINTY OF EVIDENCE	Low	Low	Low	Low	Very low	Low	Very low	Low	Very low	Very low
VALUES	Probably no important uncertainty or variability	Probably no important uncertainty or variability	Probably no important uncertainty or variability	Probably no important uncertainty or variability	Probably no important uncertainty or variability	Probably no important uncertainty or variability	Probably no important uncertainty or variability	Probably no important uncertainty or variability	Probably no important uncertainty or variability	Probably no important uncertainty or variability
BALANCE OF EFFECTS	Favors the intervention	Favors the intervention	Favors the intervention	Favors the intervention	Probably favors the intervention	Favors the intervention	Probably favors the intervention	Favors the intervention	Probably favors the intervention	Probably favors the intervention
RESOURCES REQUIRED	Large costs	Large costs	Large costs	Large costs	Large costs	Large costs	Large costs	Large costs	Large costs	Large costs
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES										
COST EFFECTIVENESS	Varies	Varies	Varies	Probably favors the intervention	Varies	Probably favors the intervention	No included studies	Varies	Varies	Varies
EQUITY	Probably no impact	Probably reduced	Probably increased	Reduced	Probably reduced	Probably reduced	Reduced	Probably reduced	Probably no impact	Probably no impact

ACCEPTABILITY	Probably yes	Probably yes	Probably yes	Probably yes	Yes	Yes	Probably no	Probably yes	Probably yes	Probably yes
FEASIBILITY	Probably yes	Varies	Probably yes	Varies	Probably yes	Probably yes	Probably no	Varies	Probably yes	Probably yes
AVAILABILITY	**Varies**									

CONCLUSIONS

Recommendation(s)

Conditional recommendation for the intervention

The MEMP suggests for in priority order (conditional recommendation): 1. cladribine (low certainty ⊕⊕OO), 2. dimethyl fumarate (low certainty ⊕⊕OO), 3. fingolimod (low certainty ⊕⊕OO), 4. ocrelizumab (very low certainty ⊕OOO), 5. interferon beta 1b (very low certainty ⊕OOO), 6. interferon beta 1a (low certainty ⊕⊕OO), 7. glatiramer acetate (very low certainty ⊕OOO), 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 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 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 person with MS.

Conditional recommendation for either the intervention or the comparison

The MEMP suggests either for or against in priority order (conditional and neutral recommendation, dependent on setting) the use of 1. natalizumab (low certainty ⊕⊕OO), 2. alemtuzumab (low certainty ⊕⊕OO), 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 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 and have an important role to play.

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 variable feasibility issues for low-resource settings in the access to and cost of pre-screening and 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.

Conditional recommendation against the intervention

The MEMP suggests against (conditional recommendation) the use of mitoxantrone (very low certainty ⊕OOO) 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 did not include these post-marketing surveillance and safety concerns.

Justification

Subgroup considerations

The MEMP panel assessed evidence for relapsing MS populations overall. The panel noted most evidence informing this assessment was from active and/or worsening RMS. The panel added subgroup considerations for the following populations:

Not active and not worsening or indeterminate forms of RMS**:** The panel suggested the benefit/harm ratio may be different in this population as evidence suggests DMTs are most effective in active populations. The panel suggests discussion with pwMS about the benefits/harms of different treatment options depending on their personal circumstances and individualised decisions about whether or not to take DMTs made in conjunction with their clinicians.

Active and/or worsening forms of RMS **when there is a lack of treatment response**: No randomised-controlled trial evidence was available to MEMP to inform specific recommendations for active and/or worsening RMS when there is a lack of treatment response. Consideration may be given to results of observational studies and individual circumstances including how rapidly MS is progressing, age, symptoms, disability, comorbid diseases, risk of infection and concomitant medication in the decision to try a different medicine based on the accessibility of medicines in the setting.

Multiple Chronic conditions and Polypharmacy

Consideration of concomitant medication and polypharmacy is important for pwMS, and MS DMTs should be frequently re-evaluated as pwMS age, develop new comorbidities, and begin new

medications.

Clinical considerations

For all DMTs the following infection screening is recommended: TB, HIV, Hep C, Hep B, VZV and syphilis.

In addition, the following tests and monitoring are needed:
http://www.msif.org/wp-content/uploads/2022/08/clinical-considerations-RMS_240622.png [https://www.msif.org/supporting-documents-memp-etd/]

Research priorities

MEMP suggests prioritizing research on:
1. Systematic review on non-randomised controlled studies for all DMTs to further inform comparative effectiveness.
2. Improving the evidence-base of medicines that are off-label and have follow-on products available, and therefore are more accessible, e.g. rituximab, azathioprine and methotrexate.
3. Comparative cost-effectiveness, including over the full duration of treatment and effects, including any additional courses of induction therapies, e.g cladribine and alemtuzumab.
4. Comparative cost-effectiveness in different resource settings.
5. Clinical effectiveness of off-label cladribine, which may be more available and affordable in low-resource settings.

REFERENCES SUMMARY