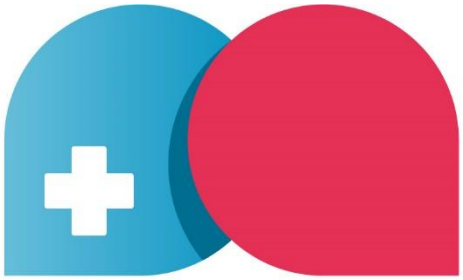
Evidence report

Treatment of relapsing-remitting multiple sclerosis, which is not highly active

Version 3



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LIST OF ABBREVIATIONS

AE: *adverse events*
AMSTAR: *A MeaSurement Tool to Assess systematic Reviews*
CDSR: *Cochrane Library of Systematic Reviews*
CENTRAL: *Cochrane Controlled Register of Trials*
CI: *confidence interval*
CIS: *clinically isolated syndrome*
EAN: *European Academy of Neurology*
ECTRIMS: *European Committee of Treatment and Research in Multiple Sclerosis*
EMA: *European Medicines Agency*
FAQ: *Frequently asked question*
GIN: *Guidelines International*
GRADE: *Grading of Recommendations, Assessment, Development and Evaluation*
INAHTA: *International Network of Agencies for Health Technology Assessment*
KSR: *Kleijnen Systematic Reviews*
MS: *multiple sclerosis*
n.a.: *not applicable*
NICE: *National Institute for Health and Care Excellence*
NMA: *Network Meta-Analysis*
PEG: *pegylated*
PICOS: *participants, intervention, comparators, outcomes, and study design*
PML: *progressive multifokale Leukenzephalopathie*
RCT: *randomized controlled trial*
RIS: *radiologically isolated syndrome*
RoB: *risk of bias*
RRMS: *relapsing-remitting multiple sclerosis*
SUCRA: *surface under the cumulative ranking curve*

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PROJECT OBJECTIVES

A key aim of the present project is to update the existing decision aid "Immunotherapy of relapsing-remitting multiple sclerosis (RRMS) which is not highly active". The decision aids focusses on drugs which correspond to category 1 drugs according to the German guideline for multiple sclerosis [1].

For version 1.0 of the decision aid (the current version online), the evidence report has been prepared by Kleijnen Systematic Reviews (KSR) in June 2018. An evidence update has been provided by KSR in December 2021. The evidence team of Share to care concluded on 12.04.2022 that the new evidence does not warrant an update of the decision aid.

This report aims to retrieve and appraise more recent evidence to update the existing decision aid, if necessary.

METHODS

FREQUENTLY ASKED QUESTIONS

This report relies on the frequently asked questions (FAQs) which have been developed for previous versions of the evidence report.

- FAQ 1: What is it and how does the treatment work?
- FAQ 2: What is the effect on the relapse rate?
- FAQ 3: What is the effect on disability progression?
- FAQ 4: What adverse events are linked to the treatment?

The update aims to answer the questions:

- Are there new treatment options available than the ones mentioned in the current version of the decision aid? (FAQ 1)
- Are there newer data for benefit and harm which warrant a modification of the current decision aid? (FAQ 2-4)

INCLUSION CRITERIA

This report relies on the characteristics of participants, intervention, comparators, outcomes, and study design (PICOS) which have been developed for previous versions of the evidence report (Table 1). For this update, PICOS has been slightly modified:

- Population: In the previous evidence reports, population has been defined as patients with RRMS. For clarification, children and adolescents have been added to the exclusion criteria. Other forms of multiple sclerosis or clinically isolated syndrome (CIS) or radiologically isolated syndrome (RIS) are excluded for efficacy but may be included for safety outcomes.
- Intervention: In the previous evidence reports, interventions have been defined as interferon beta (interferon beta-1a, interferon beta-1b, PEG interferon beta-1a); glatiramer acetate; terifluonomide; dimethyl fumarate. If other treatment options of the same category have become available, they are added to inclusion criteria.
- Outcomes: The previous versions of the decision aid reported the outcomes for benefit as relapse rate at 24 months and disability progression at 24 months. Outcomes for harm were a) qualitatively reported: common adverse events (AE); rare, but severe AE; and harm on pregnancy/breastfeeding b) quantitatively reported: discontinuation due to AE.
- Included study designs followed a stepwise approach according to FAQ as described below.

Table 1: Inclusion and exclusion criteria

	Included	Excluded
Population	Patients with RRMS	Update: children and adolescents (efficacy and safety); other forms of multiple sclerosis OR CIS OR RIS (efficacy)
Intervention	Interferon beta: interferon beta-1a (Avonex®, Rebif®), interferon beta-1b (Betaferon®, Betaseron®, Extavia®[a]), PEG interferon beta-1a (Plegridy®); glatiramer acetate (Copaxone®); terifluonomide (Aubagio®); dimethyl fumarate (Tecfidera®). Update: Any other available drug of the same category.	n.a.
Comparator	Other listed intervention, placebo, no therapy.	n.a.
Outcomes	Disability progression, relapse rate, adverse events	Update: Other time frames than 24 months for efficacy.
Study design	Systematic reviews and guidelines. Update: stepwise approach	n.a.
PEG = pegylated; AE = adverse events; n.a.= not applicable. [a]In the EU, the marketing authorization for Extavia® has been withdrawn in November 2024 for commercial reasons.		

LITERATURE SEARCHES

In the previous evidence report, searches have been conducted on 15.11.2021. We restricted our searches to evidence published thereafter. The full search strategies are reported in Appendix 1:

FAQ 1

We searched the International Guidelines library of the Guidelines International Network (GIN) to identify recent MS guidelines in German or English which are relevant for the target population of the decision aid and are of high quality.

FAQ 2-4

We followed a stepwise and focussed approach:

1) We first checked if the guidelines identified for FAQ 1 are suitable for an update of the evidence on benefit and harm.

Criteria:

- The guideline relies on a systematic search and appraisal of the evidence.
- The evidence search is newer than December 2021.
- The guideline answers the questions in sufficient depth.

2) If we did not find a suitable guideline in step 1, we proceeded to a focused search for high-quality systematic reviews and HTA reports in the Cochrane Library of Systematic Reviews (CDSR) and in the International HTA Database of the International Network of Agencies for Health Technology Assessment (INAHTA) (for data on benefit and harm).

3) If the results from step 2 were not sufficient, we conducted a stepwise systematic literature search, according to the previous versions of the evidence reports.

FAQ 1-4

Additionally, we hand-searched the website of the European Medicines Agency (EMA) for new marketing authorizations and updated safety information on authorized medicines.

Handling of citations

Identified references from the bibliographic database searches were downloaded and transferred into Rayyan App for screening. Excluded references were tagged with the reasons for exclusion. The results of the abstract screening were downloaded including the tags. Results of the full text screening were documented in the appendices.

Quality assurance within the search process

One reviewer (IH) developed the search strategy, a second reviewer (JP) checked the strategy according to the PRESS Peer Review of Electronic Search Strategies Checklist [2].

METHODS OF STUDY SELECTION

One reviewer (IH) inspected the title and abstract of each reference identified by the search and documented reasons for exclusion. For potentially relevant articles, the full article was obtained, inspected, and inclusion criteria applied. Reasons for exclusion were documented. All decisions were checked by a second reviewer (JP). Any disagreements were resolved through discussion.

Methods of data extraction

For each study, data were extracted by one reviewer (IH) and checked by another (JP). Any disagreements were resolved through discussion.

Methods for appraising the quality of the evidence

For the risk of bias (RoB) assessment, we used A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2) for systematic reviews [3], the Risk of Bias in Network Meta-Analysis tool (RoB NMA) for network meta-analyses [4].

One reviewer (IH) checked the risk of bias and rated the certainty of the evidence. The results were checked by a second reviewer (JP). Any disagreements were resolved through discussion.

Certainty of the evidence is presented using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach which assesses risk of bias, publication bias, imprecision, inconsistency, indirectness, magnitude of effect, dose-response gradient and the effects of any confounding according to the quality assessment criteria published by the GRADE working group [5].

The evidence certainty is rated as follows:

- High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate certainty: 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. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low uncertainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. I. e. we are very uncertain about the estimate.

Where systematic reviews presented GRADE assessments, we adopted the ratings for the evidence report.

RESULTS

Literature search and inclusion assessment

Details of the literature search and inclusion assessment can be found in Appendix 1: .

FAQ 1

We searched for guidelines in the GIN library and included two [1,6].

FAQ 2–4

Step 1

For FAQ 1, we identified two relevant guidelines. The German S2k-guideline on multiple sclerosis [1] did not rely on a systematic review of the evidence and was therefore excluded. The British National Institute for Health and Care Excellence (NICE) guideline on multiple sclerosis [6] relied on a systematic technology assessment [7]. However, the quantitative data on benefit and harm are blacked out and therefore not usable (see Appendix 2:). Therefore, we proceeded to Step 2.

Step 2

In the INAHTA Database and in the CDSR, we retrieved 35 references, 7 of which were eligible for full-text screening. We finally included two references [8,9]. As the searches of these systematic reviews were as of 2022, we conducted an additional search for trials published thereafter (Step 3).

Step 3

We searched PubMed and the Cochrane Controlled Register of Trials (CENTRAL) for randomized controlled trials (RCTs). We restricted the search to publication dates 2022 to 2025 to supplement the searches of the systematic reviews identified in step 2. Of the 280 references retrieved after deduplication, none fulfilled the inclusion criteria. As the systematic reviews identified in Step 2 include RCTs, we did not search for non-randomized trials or observational studies.

Hand-searching

We hand-searched the website of the European Medicines Agency (EMA) on 16 July 2025 for relevant safety updates. In total, we included 7 product informations [10–16]. Details can be found in Appendix 2: . As medicines with glatiramer acetate are only nationally approved, the product information [17] was retrieved via the official German drug information website PharmNet.Bund.

Risk of bias assessment

A risk of bias assessment has been conducted for both included sources [8,9]. Both are considered to have low risk of bias. Details can be found in Appendix 3: .

Overview of the evidence

FAQ 1

The updated search identified an additional category 1 drug which is mentioned in guidelines: diroximel fumarate. Both guidelines present qualitative data which can be used for FAQ 1:

- The German guideline [1] rates the relative efficacy of diroximel fumarate and advises for use in pregnancy, also for the other drugs.
- The NICE technology assessment [7] provides background information on the new drug diroximel fumarate as mode of action, dosing and marketing authorization.

FAQ 2–4

For data on benefit and harm of the treatment options, the previous versions of the evidence report relied on the guideline of the European Committee of Treatment and Research in Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) for the treatment of multiple sclerosis, Montalban 2018 [18], which has been informed by a systematic review. Our updated search identified two Cochrane Reviews which both included RCTs and used a NMA approach. We searched for more recent trials but did not find any that matched our inclusion criteria. Therefore, we consider both reviews to reflect the recent evidence.

Gonzalez-Lorenzo 2024 [8] included trials up to 8 August 2022. Inclusion was restricted to RCTs where the study population comprised at least 80 % patients with RRMS and the follow-up was at least 12 months. The systematic review reports on benefit and harm.

Tramacere 2023 [9] included RCTs up to 4 March 2022. Inclusion criteria for population were broad and comprised any type of multiple sclerosis (MS) or CIS. There were no limitations for follow-up. The systematic review reports on harm only.

Evidence for benefit (FAQ 2 and FAQ 3): Gonzalez-Lorenzo 2024 has a more recent literature search than Montalban 2018. Additionally, Gonzalez-Lorenzo 2024 uses a NMA approach which overcomes some of the limitations of the pairwise comparisons of Montalban 2018. Therefore, we decided to use the data from Gonzalez-Lorenzo 2024 for the decision aid and to delete the data from Montalban 2018.

For the new drug diroximel fumarate, there is no data on benefit in Gonzalez-Lorenzo 2024. This is due to the inclusion criteria of the systematic review (RCTs with minimum 12 months follow-up) and the circumstances of the marketing authorization for diroximel fumarate. For the application, no long-term RCT data was presented. As reported in the NICE technology assessment, regulatory approval relied on data showing bioequivalence with dimethyl fumarate, which has the same active metabolite. The regulators accepted the reasoning that the clinical efficacy of dimethyl fumarate reflects the clinical efficacy of diroximel fumarate. We will include this information as qualitative data in the decision aid.

Evidence for harm (FAQ 4, quantitative data): Both Gonzalez-Lorenzo 2024 and Tramacere 2023 report data on harm. The estimates in Tramacere 2023, however, rely on more trials than Gonzalez-Lorenzo 2024. Therefore, we decided to use the data from Tramacere 2023 in the decision aid and to delete the data from Montalban 2018.

There is only one short-term (1 month) RCT comparing AE of diroximel fumarate and dimethyl fumarate. Data from this trial has been included in the NMA in Tramacere 2023.

Evidence for harm (FAQ 4, qualitative data): Product informations [10–17] contain qualitative data on AE and their frequencies; rare, but serious AE as well as information on safety in pregnancy and while breastfeeding.

Table 2 summarises the sources of evidence used to answer the FAQs.

Table 2: Overview of evidence sources

Reference	**FAQ1 What is it and how does the treatment work?**	**FAQ2 What is the effect on the relapse rate?**	**FAQ3 What is the effect on disability progression?**	**FAQ4 What adverse events are linked to the treatment?**			
		Relapse rate at 24 months	***Clinical progression, confirmed at 3 or 6 months***	***Discontinuation due to AE***	***Very common AE***	***Rare, but severe AE***	***Safety in pregnancy and whilst breastfeeding***
German guideline [1] [a]							✓[b]
NICE Technology Assessment [7] [a]	✓[a,b]	✓[a,b]	✓[a,b]				
Gonzalez-Lorenzo 2024 [8]		✓[c]	✓[c]				
Tramacere 2023 [9]				✓			
Product information of the medicines [10–17]					✓[b]	✓[b]	✓[b]

[a] For diroximel fumarate only
[b] Qualitative data
[c] Not for diroximel fumarate

FAQ 1: What is it and how does the treatment work?

Diroximel fumarate is an oral drug for the treatment of RRMS. It is a different molecule than dimethyl fumarate but is converted in the body to the same active metabolite, monomethyl fumarate. Diroximel fumarate is given as a capsule twice a day, with or without a meal [7].

The German guideline categorizes diroximel fumarate as the same efficacy category as interferon beta, dimethyl fumarate, glatiramer acetate and teriflunomide [1].

Conclusion for the decision aid:

- Diroximel fumarate should be included in the decision aid.
- For FAQ 1, the decision aid should describe shortly the mode of action and the similarity to dimethyl fumarate as well as give the details to the mode of administration.

FAQ 2: What is the effect on the relapse rate?

Data for the effect on the relapse rate (Table 3) have been extracted from the source Gonzalez-Lorenzo 2024 [8], Summary of findings Table 2. Results have been converted to per 100 persons.

Data on interferons

Whereas Montalban 2018 pooled data for all interferon beta trials, Gonzalez-Lorenzo 2024 reports results according to the type of interferon beta. Interferon beta 1a-1b is not available in Germany, therefore we only extracted data on interferon beta-1a and interferon beta-1b. For the outcome relapse rate at 24 months, no data on PEG interferon beta 1a is available. However, comparing data for interferon beta-1a, interferon beta 1-b and PEG interferon beta 1a show similar results (overlapping confidence intervals) for the outcome relapse rate at 12 months (Gonzalez-Lorenzo 2024, Summary of findings Table 1).

Data on diroximel fumarate

Gonzalez-Lorenzo 2024 does not present data for diroximel fumarate. The clinical efficacy of diroximel fumarate is considered the same as that of dimethyl fumarate (see FAQ 1).

Table 3: Effect on relapse rate (24 months)

Intervention	**Effect estimate**			**Ranking metrics**		**Certainty of evidence**
	Intervention risk	***Placebo risk***	***Difference***	***SUCRA (%)***	***Mean Rank***	***For comparison to placebo***
Dimethyl fumarate/ Diroximel fumarate[a]	32 per 100	51 per 100	19 fewer per 100 (23 fewer to 15 fewer per 100)	64.1	6.4	Moderate[c], 2 RCTs, 2307 participants
Glatiramer acetate	43 per 100	51 per 100	8 fewer per 100 (12 fewer to 4 fewer per 100)	28.9	11.7	Moderate[b], 3 RCTS, 1014 participants
Interferon beta-1a	43 per 100	51 per 100	8 fewer per 100 (11 fewer to 5 fewer per 100)	27.2	11.9	Moderate[b], 3 RCTs, 1629 participants
Interferon beta-1b	43 per 100	51 per 100	8 fewer per 100 (12 fewer to 3 fewer per 100)	26.5	12.0	Low[b], 1 RCT, 372 participants
Teriflunomide	42 per 100	51 per 100	9 fewer per 100 (15 fewer to 3 fewer per 100)	32.5	11.1	Very low[b,c], 1 RCT, 1088 participants

Data for the effect estimates and the certainty of the evidence have been extracted from Gonzalez-Lorenzo 2024 [8], Summary of findings Table 2. Numbers have been converted from as per 1,000 to as per 100. Data on rankings have been extracted from Gonzalez-Lorenzo 2024, Appendix 14. SUCRA: Surface under the cumulative ranking curve.

[a] There is no data for diroximel fumarate in Gonzalez-Lorenzo 2024. But diroximel fumarate and dimethyl fumarate are considered to have the same clinical efficacy.

[b] due to imprecision. Downgraded by two levels for teriflunomide and interferon beta-1b as the 95% Cis include a trivial positive effect.

[c] due to risk of bias

Data on head-to-head comparisons

Indirect evidence: Gonzalez-Lorenzo 2024 reports head-to-head comparisons from the NMA (indirect evidence) in Table 3, but only relative risks:

- No statistically significant difference comparisons of teriflunomide, glatiramer acetate, interferon beta-1a and interferon beta-1b.

A statistically significant difference is noted for the head-to-head comparisons of dimethyl fumarate vs. teriflunomide, glatiramer acetate, interferon beta-1a or interferon beta-1b, respectively: Dimethyl fumarate is more effective in preventing relapses than the other immunomodulators. This is reflected in the confidence intervals in Table 3 of this evidence report. According to the 95% CIs, the difference between dimethyl fumarate and the other treatments might be as small as 3 per 100 or as big as 20 per 100.

Gonzalez-Lorenzo also describes the rankings of the treatments. The surface under the cumulative ranking curve (SUCRA) and the Mean Rank values suggest that teriflunomide, glatiramer acetate, interferon beta-1b and interferon beta-1a are very similar in clinical efficacy. Dimethyl fumarate ranks higher in SUCRA and Mean Rank. However, no credible intervals are given for Mean Rank, so it is difficult to ascertain if the values really differ between the treatments. Gonzalez-Lorenzo 2024 points out that due to the small number of studies for comparison and the large number of treatments, the results should be interpreted with caution.

Direct evidence: Gonzalez-Lorenzo 2024 reports head-to-head comparisons from the pairwise meta-analysis (direct evidence) in Analysis 1.2, but only relative risks:

- No statistically significant difference for: glatiramer acetate vs. dimethyl fumarate (Analysis 1.2.6), although the 95% confidence interval (0.99; 1,47) is trending towards more relapses with glatiramer acetate. The same applies to the comparison interferon beta-1a vs interferon beta-1b (95% confidence interval 1.00; 1,52).
- No statistically significant difference for interferon beta-1b or interferon beta-1a vs. glatiramer acetate

There is no direct evidence for all other head-to-head comparisons. Notably, there is no clear direct evidence to back the benefit of dimethyl fumarate compared to the other treatment options as seen in the indirect evidence (see above).

Certainty of the evidence: Gonzalez-Lorenzo 2024 did not report GRADE assessments for the head-to-head comparisons (neither for the direct nor the indirect evidence). As the certainty of the evidence is moderate to very low for many comparisons with placebo and as there are fewer trials which compare two active substances, it might be safe to assume that the certainty of evidence for the head-to-head comparisons is also low or very low.

Conclusion for the decision aid:

- For placebo comparisons, the decision aid should report point estimates per 100 persons according to Table 3 and add information about the certainty of the evidence.
- Data for different types of interferon beta can be summarized. A note should explain that there is no data for PEG interferon beta-1a for relapse at 24 months, but that results for relapse at 12 months were similar to that of other interferons.
- As there is no separate data for diroximel fumarate, the drug can be subsumed under dimethyl fumarate. A note should explain that the clinical efficacy is considered to be same as that of dimethyl fumarate.
- The effect sizes for the comparisons of the medicines vs placebo are clinically relevant.
- As for head-to-head comparisons, the decision aid should mention that dimethyl fumarate (and diroximel fumarate) might prevent relapses at 24 months a little bit better than the other drugs, but that the certainty of the evidence is very low and the comparative benefit cannot be quantified reliably.

FAQ 3: What is the effect on disability progression?

In the previous evidence reports, disability progression has been described as clinical progression confirmed at 3 months. Gonzalez-Lorenzo 2024 reports clinical progression confirmed at 3 or 6 months over 24 months follow-up.

Data for the effect on disability progression (Table 4) have been extracted from Gonzalez-Lorenzo 2024, Summary of findings Table 4. Results have been converted to per 100 persons.

Data on interferons

Whereas Montalban 2018 pooled data for all interferon beta trials, Gonzalez-Lorenzo 2024 reports results according to interferon beta type. Interferon beta 1a-1b is not available in Germany, therefore we only extracted data on interferon beta-1a and interferon beta-1b. For the outcome disability progression at 24 months, no data on PEG interferon beta 1a is available. This outcome has only been studied at 12 months in the main trial. Gonzalez-Lorenzo 2024 did not include an analysis of disability progression at 12 months.

Data on diroximel fumarate

Gonzalez-Lorenzo 2024 does not present data for diroximel fumarate. The clinical efficacy of diroximel fumarate is considered the same as that of dimethyl fumarate (see FAQ 1).

Table 4: Effect on disability progression (24 months)

Intervention	**Effect estimate**			**Ranking metrics**		**Certainty of evidence**
	Intervention risk	***Placebo risk***	***Difference***	***SUCRA (%)***	***Mean Rank***	***For comparison to placebo***
Dimethyl fumarate/ Diroximel fumarate[a]	12 per 100	19 per 100	7 fewer per 100 (8 fewer to 4 fewer)	65.1	7.3	Low[b,c], 2 RCT, 2307 participants
Glatiramer acetate	14 per 100	19 per 100	5 fewer per 100 (7 fewer to 2 fewer)	46.2	10.7	Very low[b,c], 3 RCT, 1014 participants
Interferon beta-1a	17 per 100	19 per 100	2 fewer per 100 (5 fewer to 3 fewer)	19.7	15.5	Low[b], 2 RCTs, 1069 participants
Interferon beta-1b	15 per 100	19 per 100	4 fewer per 100 (7 fewer to 1 fewer)	40.9	11.6	Low[b], 1 RCT, 372 participants
Teriflunomide	14 per 100	19 per 100	5 fewer per 100 (7 fewer to 1 fewer)	40.9	11.6	Very low[b,c], 1 RCT, 1088 participants

Data on the effect estimates and the certainty of the evidence have been extracted from Gonzalez-Lorenzo 2024 [8], Summary of findings Table 4. Numbers have been converted from as per 1,000 to as per 100. Data on rankings have been extracted from Gonzalez-Lorenzo 2024, Appendix 14. SUCRA: Surface under the cumulative ranking curve.

[a] Diroximel fumarate and dimethyl fumarate are considered to have the same clinical efficacy.
[b] due to imprecision. Downgraded by two levels for glatiramer acetate, interferon beta-1b, interferon beta 1a and teriflunomide as the 95% Cis include a trivial positive effect.
[c] due to risk of bias

Data on head-to-head comparisons

Indirect evidence: According to Gonzalez-Lorenzo 2024, Table 5, there is no statistically significant difference for most head-to-head comparisons. The only exception is the comparison between dimethyl fumarate and interferon beta-1a: Dimethyl fumarate (and diroximel fumarate) prevents disease progression better than interferon beta-1a. This is reflected in the confidence intervals in Table 4 of this evidence report. According to the 95% CIs, the difference between dimethyl fumarate and interferon beta-1a might be as small as 1 per 100 or as big as 3 per 100.

Gonzalez-Lorenzo also describes the rankings of the treatments. SUCRA and Mean Rank values suggest that teriflunomide, glatiramer acetate and interferon beta-1b are very similar in clinical efficacy. Dimethyl fumarate ranks higher in SUCRA and Mean Rank, whereas interferon beta-1a ranks lower. However, no credible intervals are given for Mean Rank, so it is difficult to ascertain how if the values really differ between the treatments. Gonzalez-Lorenzo 2024 points out that due to the small number of studies for comparison and the large number of treatments, the results should be interpreted with caution.

Direct evidence: According to Gonzalez-Lorenzo, Analysis 1.4, there is no statistically significant difference for glatiramer acetate vs. dimethyl fumarate, interferon beta-1a vs. glatiramer acetate, interferon beta-1a vs interferon beta-1b. For other head-to-head comparisons, there is no direct evidence. Notably, there is no direct evidence to back the benefit of dimethyl fumarate compared to interferon beta-1a as seen in the indirect evidence (see above).

Certainty of the evidence: Gonzalez-Lorenzo 2024 did not report GRADE assessments for the head-to-head comparisons (neither for the direct nor the indirect evidence). As the certainty of the evidence is low or very low for many comparisons with placebo and as there are fewer trials which compare two active substances, it might be safe to assume that the certainty of evidence for the head-to-head comparisons is also low or very low.

Conclusion for the decision aid:

- For placebo comparisons, the decision aid should report numbers per 100 persons according to Table 3 and add information about the certainty of the evidence.
- Data for different types of interferon beta can be summarized. As the numbers for interferon beta-1a and interferon beta-1b are not identical, data should be given as a range. A note should explain that there is no data for PEG interferon beta-1a for this outcome at 24 months, only at 12 months.
- As there is no separate data for diroximel fumarate, the drug can be subsumed under dimethyl fumarate. A note should explain that the clinical efficacy is considered to be same as that of dimethyl fumarate.
- The effect sizes for the comparisons vs placebo are marginally clinically relevant.

- As for head-to-head comparisons, the decision aid should mention that dimethyl fumarate (and diroximel fumarate) might prevent disease progression a little bit better than interferon beta-1a, but not than the other drugs. A note should explain that the certainty of the evidence is very low and that the comparative benefit cannot be quantified reliably.

FAQ 4: What adverse events are linked to the treatment?

For FAQ 4, we report quantitative data for discontinuation due to AE and qualitative data for common AE, severe AE and use in pregnancy and while breastfeeding.

Discontinuation due to AE

Data for discontinuation due to AE (Table 5) have been extracted from Tramacere 2023, Summary of findings Table 2. The systematic review reported only the effect estimates for the comparison to placebo, but not the difference of effects. We therefore calculated the differences of the effect estimates, the confidence intervals of the differences (CIs) from the CIs of the effect estimates and converted all results as per 100 persons.

Other than the data on efficacy (FAQ 1 and FAQ 2), the follow-up for discontinuation due to AE is not 24 months, because trials with shorter follow-up were also included in the NMA. The data in Tramacere 2023, Summary of findings Table 2 is reported mostly at 1 or 2 years but also includes trials with a shorter follow-up.

Data on interferons

Tramacere 2023 reported results for interferons separately not only for the different drugs (interferon beta-1a, interferon beta-1b, PEG interferon beta 1a), but also for the different brands of interferon beta-1a (Avonex®, Rebif®).

Data on diroximel fumarate

Data on dimethyl fumarate and diroximel fumarate are reported separately.

Table 5: Discontinuation due to AE

Intervention	**Effect estimate**			**Ranking metrics**	**Certainty of evidence**[a]
	Intervention risk (CI)	***Placebo risk***	***Difference***	***P-Score***	
Dimethyl fumarate	9 per 100	7 per 100	2 more per 100 (0 to 6 more)	0.64	Very low[b,d,e], 4 RCTs, 2578 participants
Diroximel fumarate	3 per 100	7 per 100	4 less per 100 (6 fewer to 2 more)	0.95	Very low[b,d,e], no direct evidence
Glatiramer acetate	11 per 100	7 per 100	5 more per 100 (2 more to 8 more)	0.43	Low[b], 9 RCTs, 5032 participants
Interferon beta-1a/ Avonex	10 per 100	7 per 100	3 per 100 (1 to 7 more)	0.54	Very low[b,c], 6 RCT, 2169 participants
Interferon beta-1a/ Rebif	14 per 100	7 per 100	7 more per 100 (3 more to 12 more)	0.29	Low[b], 7 RCT, 2693 participants
Interferon beta-1b	18 per 100	7 per 100	11 more per 100 (6 more to 19 more)	0.20	Low[b], 6 RCT, 2601 participants
PEG interferon beta-1a	23 per 100	7 per 100	16 more per 100 (3 more to 48 more)	0.16	Very low[b,d], 1 RCT, 1512 participants
Teriflunomide	9 per 100	7 per 100	2 more per 100 (1 more to 6 more)[f]	0.63	Low[b,c], 4 RCT, 3044 participants

Data for the effect estimates, the certainty of the evidence and the P-Score have been extracted from Tramacere 2023, Summary of findings Table 2. RCT: randomized controlled trial

[a] Numbers for RCTs and participants refer to direct evidence only.

[b] due to risk of bias

[c] due to heterogeneity

[d] due to incoherence

[e] due to imprecision

[f]The lower limit of the confidence interval is 1 per 1,000 persons, corresponding nominally to 0.1 per 100 persons. To preserve the statistical significance, the lower limit has been set to 1 per 100 persons.

Data on head-to-head comparisons

Indirect evidence: According to Tramacere 2023, Table 3, some of the head-to-head comparisons show statistically significant differences for the risk ratios for the outcome discontinuation due to AE:

- Diroximel fumarate has a lower discontinuation rate than any of the other medicines.
- With dimethyl fumarate, the discontinuation rate is lower than with interferon beta-1a (Rebif), interferon beta-1b and PEG-interferon beta-1a, but not than with interferon beta-1a (Avonex).
- With teriflunomide, the discontinuation rate is lower than with interferon beta-1a (Rebif) and interferon beta-1b.
- With interferon beta 1a (Avonex), the discontinuation rate is lower than with Interferon beta 1b.

These significant differences are not, however, reflected in the confidence intervals of the risk differences (Table 5) which overlap for most comparisons. For all other head-to-head comparisons, the risk ratios are not significantly different.

Tramacere 2023 also describes the rankings of the treatments. P-Scores suggest that diroximel fumarate ranks best in tolerability, followed by dimethyl fumarate and teriflunomide. Glatiramer acetate and interferon beta-1a (Avonex®) rank in the middle, whereas interferon beta-1a (Rebif®), interferon beta-1b and PEG interferon-1a rank lowest.

Direct evidence: According to Tramacere 2023, Analysis 1.2, there is no statistically significant difference for most of the pairwise comparisons:

- interferon beta-1a (Avonex) vs. interferon beta-1b
- interferon beta-1a (Rebif) vs. interferon beta-1a (Avonex)
- interferon beta-1b (Rebif) vs. interferon beta-1b
- glatiramer acetate vs. interferon beta-1b
- glatiramer acetate vs. interferon beta-1a (Avonex)
- glatiramer acetate vs. interferon beta-1a (Rebif)
- dimethyl fumarate vs. glatiramer acetate

There is, however, a statistically significant difference for the comparisons:

- teriflunomide vs. interferon beta-1a (Rebif) (benefit for teriflunomide)
- diroximel fumarate vs. dimethyl fumarate (benefit for diroximel fumarate)

This partly supports the indirect evidence (see above). For all other comparisons, there is no direct evidence.

Certainty of the evidence: Tramacere 2023, however, did not report GRADE assessments for the head-to-head comparisons (neither for the indirect nor for the direct comparisons). As the certainty of the evidence is low or very low for many comparisons with placebo and as there are fewer trials which compare two active substances, it might be safe to assume that the certainty of evidence for the head-to-head comparisons is also low or very low.

Conclusion for the decision aid:

- For placebo comparisons, the decision aid should report numbers per 100 persons according to Table 5 and add information about the certainty of the evidence.
- Data for different types of interferon beta can be summarized. As the numbers are not identical, data should be given as a range of the point estimates. A note should explain that the tolerability of interferon beta-1a (Avonex®) might be a little bit better than that of the other interferon options but that the magnitude of the effect and the evidence overall is not certain.
- Data for diroximel fumarate can be reported separately from dimethyl fumarate. However, a note should explain that there is less data for diroximel fumarate than for dimethyl fumarate and only from a short-term trial. Therefore, it might be reasonable to assume that the tolerability might be quite similar to that of dimethyl fumarate.
- The effect sizes for the comparisons vs placebo are marginally clinically relevant.
- As for head-to-head comparisons, the decision aid should mention that dimethyl fumarate (and diroximel fumarate) as well as teriflunomide might be more tolerable than the other options. A note should explain that the data is not very reliable and the difference between the options cannot be quantified reliably.
- The decision aid should mention that the timeframes for the outcome in the different trials is not identical and might add to the uncertainty.

Adverse events

As the previous version of the evidence report used different sources for AE, we decided to replace all information for better consistency. We extracted information about AE from the product information of the treatments [10–17]. To focus on the most relevant data, we only included information on very common and common AE as well as serious AE (separately pointed out in the package leaflet), even if the latter might be rare.

The information was extracted in German to allow direct use in the decision aid and because the product information for glatiramer acetate is only available in German.

Table 6: Data on AE

Treatment	(Very) Common AE	Serious, but rare AE
Dimethyl fumarate	Rötung im Gesicht oder am Körper mit Wärmegefühl (Flush), Magen-Darm-Beschwerden, Beschwerden an der Haut wie Juckreiz oder Hautausschlag, Haarausfall, verringerte Anzahl der weißen Blutkörperchen mit erhöhtem Risiko für Infektionen, Veränderungen der Nieren- und Leberwerte	Ernsthafte allergische Reaktion, eine seltene Gehirninfektion (progressive multifokale Leukenzephalopathie, PML)
Diroximel fumarate[a]	Rötung im Gesicht oder am Körper mit Wärmegefühl (Flush), Magen-Darm-Beschwerden, Beschwerden an der Haut wie Juckreiz oder Hautausschlag, Haarausfall, verringerte Anzahl der weißen Blutkörperchen mit erhöhtem Risiko für Infektionen, Veränderung der Nierenwerte	Ernsthafte allergische Reaktion, eine seltene Gehirninfektion (progressive multifokale Leukenzephalopathie, PML)
Glatiramer acetate	Grippeähnliche Symptome wie Kopfschmerzen, Schüttelfrost oder Fieber, Gefühl von Schwäche und Müdigkeit Magen-Darm-Beschwerden, Gewichtszunahme, psychische Beschwerden wie Angst, Nervosität oder Depression, neurologische Beschwerden wie Migräne, Störungen von Sprechen, Hören oder Sehen, Schmerzen, etwa an Muskeln oder Gelenken, Beschwerden an der Haut wie Juckreiz oder Hautausschlag, Probleme beim Wasserlassen, etwa Harndrang Reaktionen an der Haut und am ganzen Körper nach der Injektion, Gewebeveränderungen an der Injektionsstelle Veränderung der Leberwerte erhöhtes Risiko für Infektionen	Ernsthafte allergische Reaktion, Leberprobleme, anhaltende Reaktionen am ganzen Körper nach der Injektion

Interferon beta-1a (Avonex)	Grippeähnliche Symptome wie Kopfschmerzen, Schüttelfrost oder Fieber, Hitzewallungen, vermehrtes Schwitzen, Gefühl von Schwäche und Müdigkeit Magen-Darm-Beschwerden, psychische Beschwerden wie Depression oder Schlafstörungen, Schmerzen, etwa an Muskeln oder Gelenken, Beschwerden an der Haut wie Taubheitsgefühl, Kribbeln, Ausschlag oder blaue Flecken, Hautreaktionen an der Injektionsstelle; Verringerte Anzahl der roten Blutkörperchen Verringerte Anzahl der weißen Blutkörperchen mit erhöhtem Risiko für Infektionen	Ernsthafte allergische Reaktion, Depression, Leberprobleme
Interferon beta-1a (Rebif)	Grippeähnliche Symptome wie Kopfschmerzen, Muskelschmerzen, Schüttelfrost oder Fieber, Gefühl von Schwäche und Müdigkeit, Magen-Darm-Beschwerden, psychische Beschwerden wie Schlafstörungen, Schmerzen, etwa an Muskeln oder Gelenken, Beschwerden an der Haut wie Juckreiz oder Hautausschlag, Haarausfall, Hautreaktionen an der Injektionsstelle, Verringerte Anzahl der roten Blutkörperchen Verringerte Anzahl der weißen Blutkörperchen mit erhöhtem Risiko für Infektionen	Ernsthafte allergische Reaktion, Depression, Leberprobleme

Interferon beta-1b	Grippeähnliche Symptome wie Kopfschmerzen, Muskelschmerzen, Schüttelfrost oder Fieber, Unwohlsein, Gefühl von Schwäche und Müdigkeit, psychische Beschwerden wie Schlafstörungen Neurologische Probleme wie Verwirrtheit Schmerzen, etwa an Muskeln oder Gelenken Beschwerden an der Haut wie Juckreiz oder Hautausschlag, Haarausfall, Hautreaktionen und Gewebeschäden an der Injektionsstelle Probleme beim Wasserlassen, etwa Harndrang Verringerte Anzahl der roten Blutkörperchen Verringerte Anzahl der weißen Blutkörperchen mit erhöhtem Risiko für Infektionen Veränderung der Leberwerte, Gewichtsveränderung Überempfindlichkeitsreaktionen Einlagerung von Flüssigkeit (Ödem) vergrößerte Lymphknoten Funktionsstörung der Schilddrüse Herz-Kreislauf-Beschwerden wie beschleunigter Herzschlag oder erhöhter Blutdruck Vermehrte Blutungen Impotenz	Ernsthafte allergische Reaktion, Depression, Leberprobleme, Nierenprobleme, vermehrte Infektionen, vermehrte Blutungen

PEG interferon beta-1a	Grippeähnliche Symptome wie Kopfschmerzen, Muskelschmerzen, Schüttelfrost oder Fieber, Gefühl von Schwäche und Müdigkeit, Magen-Darm-Beschwerden, Schmerzen, etwa an Muskeln oder Gelenken, Beschwerden an der Haut wie Juckreiz oder Hautausschlag, Haarausfall, Hautreaktionen und Gewebeschäden an der Injektionsstelle Veränderung der Leberwerte, Verringerte Anzahl der roten Blutkörperchen Verringerte Anzahl der weißen Blutkörperchen mit erhöhtem Risiko für Infektionen,	Ernsthafte allergische Reaktion, Depression, Leberprobleme, Nierenprobleme, Krampfanfälle, Schädigung an der Injektionsstelle, Nierenprobleme, hämolytisch-urämisches Syndrom (Blutgerinnsel in den kleinen Blutgefäßen, die die Nieren beeinträchtigen können)
Teriflunomide	Kopfschmerzen Gefühl von Schwäche und Müdigkeit Magen-Darm-Beschwerden, Gewichtsverlust Psychische Beschwerden wie Ängstlichkeit Schmerzen, etwa in Muskeln, Gelenken oder Nerven, Beschwerden an der Haut wie Juckreiz oder Hautausschlag, Haarausfall, Veränderungen der Leberwerte Verringerte Anzahl der roten Blutkörperchen Verringerte Anzahl der weißen Blutkörperchen mit erhöhtem Risiko für Infektionen, Allergische Reaktionen, Herz-Kreislauf-Beschwerden wie beschleunigter Herzschlag oder erhöhter Blutdruck, Probleme beim Wasserlassen, etwa Harndrang Vermehrte Blutungen	Ernsthafte allergische Reaktion, Leberprobleme, Entzündung der Bauchspeicheldrüse, schwere Hautreaktionen, schwere Infektionen
The data has been extracted from the product informations [10–17]. [a]The product information of diroximel fumarate points out that due to a similar metabolism, the same AE are to be expected as with dimethyl fumarate, even if not reported so far.		

Conclusion for the decision aid: Information for the treatments should be reported in the decision aid according to Table 6. Some aspects should be considered:

- For similar AE, the same verbal description should be used.
- The decision aid should explain that all immunotherapies can lower the number of immunocompetent cells in the blood and raise the risk of infection. It should also note that for all treatments which are used as an injection, reactions at the site of injection can occur. These two AE do not have to be repeated in the list of AEs for the individual treatments.
- The product information of diroximel fumarate points out due to similar metabolism, the same AE are to be expected as with dimethyl fumarate even if not reported so far. Therefore, the decision aid should summarize the information for the two medicines and report the same AE for diroximel fumarate as for dimethyl fumarate.
- The AE descriptions of interferons are slightly different in the product information. However, it is not clear if there is really a difference between the treatments or if the monitoring and reporting of AE in the clinical trials varied. In the decision aid, the AE can be summarized for all interferons as they are similar.

Pregnancy and breastfeeding

We used the most recent version of the product informations [10–17] and the German S2k guideline [1] to extract information on use in pregnancy and whilst breastfeeding (Table 7). The guideline also contains information on the interaction of MS and pregnancy.

Table 7: Data on use of treatments in pregnancy and whilst breastfeeding

Treatment	Use in pregnancy	Use whilst breastfeeding
None	Pregnancy has not per se a negative effect on the course of the disease. Also, MS does not per se negatively affect the course of the pregnancy.	Breastfeeding might reduce the relapse rate post-partum.
Dimethyl fumarate	Dimethyl fumarate should not be used during pregnancy.	Dimethyl fumarate is not recommended whilst breastfeeding.
Diroximel fumarate	Diroximel fumarate should not be used during pregnancy.	Diroximel fumarate is not recommended whilst breastfeeding.
Glatiramer acetate	If necessary, glatiramer acetate can be used during pregnancy after an assessment of benefits and risks, especially in women with high disease activity.	Glatiramer acetate can be used whilst breastfeeding.
Interferon beta-1a, Interferon beta-1b, PEG interferon beta-1b	If necessary, interferon beta can be used during pregnancy after an assessment of benefits and risks, especially in women with high disease activity.	Interferon beta can be used whilst breastfeeding.
Teriflunomide	Teriflunomide is contraindicated in pregnancy.	Teriflunomide is contraindicated whilst breastfeeding.
Information has been extracted from product informations [10–17] and the German S2k guideline on multiple sclerosis [1].		

Conclusion for the decision aid: Information on the use of the treatments during pregnancy and whilst breastfeeding should be explained according to the information in Table 7.

DISCUSSION

SUMMARY OF MAIN FINDINGS

The immunotherapy treatments described in the decision aid are very similar in terms of efficacy and general tolerability. There are small differences for some outcomes.

The treatments, however, differ in the mode of application, the individual AE and the possibility to use them in pregnancy or whilst breastfeeding. All the treatments have in common that they potentially lower the number of immunocompetent blood cells and therefore increase the risk for infections. All treatments that are applied by injection can cause adverse reactions at the injection site, including tissue damage.

STRENGTH, LIMITATIONS AND UNCERTAINTIES

One strength of our evidence report is that it relies on two up-to-date high quality systematic reviews, including 50 [8] and 123 trials [9], respectively. However, these numbers refer to all treatments included in the network, and there are fewer trials included for the treatments relevant for this evidence report.

As both reviews summarize the evidence in NMAs, we cannot only report the direct comparisons in the trials, but also the indirect evidence for head-to-head comparisons which have not been studied yet. This allows for a common baseline risk for all treatments to be reported in the decision aid.

Although the analyses include some older trials for which the inclusion criteria were somehow different from more recent trials, the review authors did not find systematic differences comparing age, disease duration, and baseline disability status across the trials and concluded that there is no evidence against the transitivity assumption in the NMAs.

Another strength is the abundant pool of trials in Tramacere 2023 which we used to extract data for the outcome discontinuation due to AE. The review included not only trials in patients with RRMS, but also CIS and other types of MS. A sensitivity analysis including only studies on RRMS did not change the findings, so the results are quite robust.

There are, however, some limitations in the evidence:

- The proportion of trials with active comparators in the network was only 50 % [8]and 30 % [9], respectively. Head-to-head comparisons therefore rely mainly on indirect evidence.
- There are no separate long-term data on the clinical efficacy of diroximel fumarate. The reporting therefore relies on the assessment of the agencies responsible for marketing authorization that the clinical efficacy is considered to be the same as that of dimethyl fumarate.

- The follow-up in many RCTs was at most 2 years. As MS is a chronic disease and treatments are probably used for a longer period, long-term treatment effects have not been studied in high quality trials.
- As the treatments have been studied in trials with selected patients and in highly controlled settings, there is some uncertainty if the results correspond to those in a wider population.
- We cannot exclude the possibility that AEs have been reported differently across the trials which might explain the variance of the verbal descriptions in the product information. However, we tried to reconcile the variation by summarizing AEs where appropriate.
- Tramacere 2023 [9] also included short-term trials. While this increased the pool of trials, it also added heterogeneity in the length of follow-up. However, inconsistency was mostly not a concern for the comparisons.
- The authors of both reviews assessed assumptions of transitivity and consistency in the network and found no concerns. They acknowledge, however, that due to the few studies per comparison and limitations in study reporting as well as the limited power of statistical tests for consistency, the possibility of intransitivity and inconsistency cannot be fully excluded which might invalidate the results of the NMAs.
- The certainty of the evidence is varying. The most frequent reasons for downgrading the certainty of the evidence were study limitations and imprecision. Especially for the outcome discontinuation due to AE, the certainty is mostly low or very low. We therefore account for the possibility that the results may change when further research will become available. This also limits the usability of the rankings of treatments provided in the reviews.

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APPENDIX 1: SEARCH STRATEGIES AND OVERVIEW OF RETRIEVALS

FAQ 1

GIN Library 18.06.2025

https://guidelines.ebmportal.com/

Search term: multiple sclerosis, filter: 2022 and newer

	#	Details
GIN Library	3	
Excluded #	1	Guideline in Finnish
Included	**2**	

FAQ 2-4

Step 1: guidelines

Search strategy: see above (FAQ 1)

	#	Details
GIN Library	2	
Excluded #	2	See Appendix 2
Total	**0**	

Step 2: HTA reports and Cochrane Reviews

Search: 19.06.2025

INAHTA Database https://database.inahta.org/

Search term: multiple sclerosis, Filter: 2022-2025

Cochrane Database of Systematic Reviews https://cochranelibrary.com/

Search term: multiple sclerosis [Title Abstract Keyword], Publication 15.11.2021 to 19.06.2025

	#	Details
INAHTA	18	
Cochrane Library	17	
Total	**35**	
Abstract screening (after deduplication)	35	
Excluded	28	See RIS file

Full-text screening	7	
Excluded		See Appendix 2
Included		

Step 3: RCTs

PubMed 26 June 2025

#	Search term	Retrieval
1	"multiple sclerosis"[MeSH Terms] OR "multiple sclerosis*"[Title/Abstract] OR "MS"[Title/Abstract] OR "RRMS"[Title/Abstract]	548.158
2	"dimethyl fumarate"[MeSH Terms] OR "interferon beta"[MeSH Terms] OR "glatiramer acetate"[MeSH Terms] OR "teriflunomide"[Supplementary Concept]	13.289
3	"avonex*"[Title/Abstract] OR "rebif*"[Title/Abstract]	498
4	"aubagio*"[Title/Abstract] OR "teriflunomide*"[Title/Abstract]	989
5	"beta interferon*"[Title/Abstract] OR "beta 1 interferon*"[Title/Abstract] OR "interferon beta*"[Title/Abstract] OR "fiblaferon*"[Title/Abstract] OR "fibroblast interferon*"[Title/Abstract] OR "ifnbeta*"[Title/Abstract] OR "ifn beta*"[Title/Abstract] OR "interferon*"[Title]	75.846
6	"betaferon*"[Title/Abstract] OR "betaseron*"[Title/Abstract] OR "beta seron*"[Title/Abstract] OR "extavia*"[Title/Abstract]	320
7	"copaxone*"[Title/Abstract] OR "Cop 1"[Title/Abstract] OR "copolymer 1"[Title/Abstract] OR "glatiramer*"[Title/Abstract] OR "glatopa*"[Title/Abstract] OR "TV 5010"[Title/Abstract] OR "TV5010"[Title/Abstract]	2.458
8	"dimethylfumarate"[Title/Abstract] OR "dimethyl fumarate*"[Title/Abstract] OR "BG 00012"[Title/Abstract] OR "BG00012"[Title/Abstract] OR "BG 12"[Title/Abstract] OR "diroximel fumarate*"[Title/Abstract] OR "tecfidera*"[Title/Abstract] OR "vumerity*"[Title/Abstract]	2.191
9	"peginterferon*"[Title/Abstract] OR "pegylated interferon*"[Title/Abstract] OR "plegridy*"[Title/Abstract] OR "peg ifn beta*"[Title/Abstract]	9.581
10	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	87.664
11	#1 AND #10	9.031
12	"randomized controlled trial"[Publication Type] OR "random*"[Title/Abstract]	1.778.157
13	#11 AND #12	1.264
14	2022/01/01:3000/12/31[Date - Publication]	5.605.133
15	#13 AND #14	146

CENTRAL 26 June 2025

#	Search term	Retrieval
1	MeSH descriptor: [Multiple Sclerosis] explode all trees	5.377
2	((multiple NEXT sclerosis*) OR "MS" OR "RRMS"):ti,ab	30.198
3	#1 OR #2	30.376
4	MeSH descriptor: [Dimethyl Fumarate] explode all trees	136
5	MeSH descriptor: [Interferon-beta] explode all trees	961
6	MeSH descriptor: [Glatiramer Acetate] explode all trees	233
7	(avonex* OR rebif*):ti,ab	394
8	(aubagio* OR teriflunomide*):ti,ab	448
9	((beta NEXT interferon*) OR ("beta 1" NEXT interferon*) OR (interferon NEXT beta*) OR fiblaferon* OR (fibroblast NEXT interferon*) OR ifnbeta* OR (ifn NEXT beta*) OR interferon*):ti,ab	15.652
10	(betaferon* OR betaseron* OR (beta NEXT seron*) OR extavia*):ti,ab	149
11	(copaxone* OR "Cop 1" OR "copolymer 1" OR glatiramer* OR glatopa* OR "TV 5010" OR "TV5010"):ti,ab	717
12	(dimethylfumarate OR (dimethyl NEXT fumarate*) OR "BG 00012" OR "BG00012" OR "BG 12" OR (diroximel NEXT fumarate*) OR tecfidera* OR vumerity*):ti,ab	545
13	(peginterferon* OR (pegylated NEXT interferon*) OR plegridy* OR (peg NEXT ifn NEXT beta*)):ti,ab	3.721
14	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR 12 #13	17.395
15	#3 AND #14	3.125
16	Filters: Trials; 2022-2025; EMBASE	180

Retrieval	**#**	**Details**
PubMed	146	
CENTRAL	180	
Total	***326***	
Screening		
Abstracts screened (after deduplication)	280	
Excluded abstracts	278	See RIS file
Full texts screened	2	See Appendix 2
Full texts included	0	

Hand-searching

EMA website 15.07.2025

Search term: “multiple sclerosis”, Filters: Category “Human”, Topics “Medicines”

	#	Details
Retrieval	51	
Excluded	44	Marketing authorization withdrawn/revoked/refused: n = 14 Generics/biosimilars: n = 9 Related to medicines not category 1: n = 18 Opinion only/not authorized yet: n = 1 No product/safety information: 1 Direct health care professional communication, information already in product information: n = 1
Included	7	Product informations

APPENDIX 2: RESULTS OF THE FULL TEXT SCREENING

1. Guidelines

German S2k guideline (2024) [1]

https://register.awmf.org/assets/guidelines/030-050l_S2k_Diagnose-Therapie-Multiple-Sklerose-Neuromyelitis-Optica-Spektrum-MOG-IgG-assoziierte-Erkrankungen_2025-02.pdf

The guideline document states that no systematic search for evidence has been conducted. The guideline therefore will not be used to extract data on benefit and harm.

Drugs with moderate efficacy mentioned:

- beta interferons
- glatiramer acetate
- Teriflunomide
- dimethyl fumarate
- diroximel fumarate

New in comparison to former versions of this evidence report: diroximel fumarate.

NICE-Guideline (2022) [6]

New in comparison to former versions of this evidence report: diroximel fumarate.

DMARD are appraised in separate technology appraisal reports which rely on a systematic search and appraisal of the literature: https://www.nice.org.uk/guidance/conditions-and-diseases/neurological-conditions/multiple-sclerosis/products?GuidanceProgramme=TA

#	Drug	Published	Notes
TA794 [7]	Diroximel fumarate	08 June 2022	The evidence report contains information that is relevant for FAQ 1. The quantitative data on benefit and harm, however, are blacked out and therefore not usable.
TA624	Peginterferon beta-1a	19 February 2020	Too old, excluded
TA527	Beta interferons and glatiramer acetate	27 June 2018	Too old, excluded
TA320	Dimethyl fumarate	27 August 2014	Too old, excluded

2. HTA-Reports and systematic reviews

Reference	Last search	Data on benefit	Data on harm	Notes
Gonzalez-Lorenzo 2024 [8]	8 August 2022	x	x	Cochrane Review, network meta-analysis Included
Tramacere 2023 [9]	04 March 2022	--	x	Cochrane Review, network meta-analysis. Has data for serious AE plus discontinuation due to AE (like Gonzalez-Lorenzo 2024) and additionally, data for individual safety outcomes. Included
ICER 2023 [19]	November 2022	n.a.	n.a.	All trials already in previous evidence report (included in [18]), excluded
ICER 2024 (same reference as [19])	November 2022	n.a.	n.a.	Additional evidence sought from clinical experts and manufacturers but not received; report unchanged. Excluded
ACE 2022 [20]	18 August 2021	n.a.	n.a.	Full evidence report not found. Evidence is older than the previous version of this evidence report. Excluded
IQWiG 2022 [21]	12.10.2021	--	--	No RCTs, only single-arm study. Excluded

3. RCTs

Singer 2023 https://journals.sagepub.com/doi/10.1177/13524585231205708

RCT comparing Dimethyl fumarate and Diroximel fumarate

Wrong comparison, excluded

Wray 2022 https://pmc.ncbi.nlm.nih.gov/articles/PMC8870078/

No RCT, but single-arm study. Excluded

APPENDIX 3: RISK OF BIAS ASSESSMENT

	Gonzalez-Lorenzo 2024	**Tramacere 2023**
AMSTAR-2	Rating: High confidence Flaws: No consultation of content experts (minor)	Rating: High confidence Flaws: No consultation of content experts (minor)
RoB NMA	Low risk of bias	Low risk of bias
Overall rating	Low risk of bias	Low risk of bias

Treatment of multiple sclerosis: update searches and screening for Universitätsklinikum Schleswig-Holstein/Campus Kiel

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December 2021

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1. PROJECT OBJECTIVES

A key aim of the research project "Making SDM a reality" is to inform patients as part of shared decision making (SDM).

Kleijnen Systematic Reviews (KSR) Ltd has prepared an evidence report with a synthesis of the evidence of the treatment options for multiple sclerosis.

2. METHODS

LITERATURE SEARCHES

Literature searches were conducted to identify systematic reviews and evidence-based guidelines about relapsing multiple sclerosis (RRMS) to update the 2018 evidence report.

The search strategies were developed specifically for each database and the keywords adapted according to the configuration of each database. Searches were limited by date range for systematic reviews and guidelines to 2018-2021. Searches were not limited by language or publication status.

Systematic reviews and guidelines

The following systematic review and health technology assessment specific databases were searched:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley): issue 11 of 12, November 2021
- KSR Evidence (Internet) (https://ksrevidence.com/): 2018-2021
- Epistemonikos (Internet) (https://www.epistemonikos.org/): 2018-2021
- International HTA Database (INAHTA) (https://database.inahta.org/): 2018-2021

The following guidelines resources were searched:

- Guidelines International Network (GIN) (Internet) (https://www.g-i-n.net/home): 2018-2021
- NICE Evidence (Internet) (www.evidence.nhs.uk/): 2018-2021
- NICE Guidance (Internet) (https://www.nice.org.uk/guidance): 2018-2021
- ECRI Guidelines Trust (Internet) (https://guidelines.ecri.org/): 2018-2021
- Trip Database (https://www.tripdatabase.com/): 2018-2021
- Canadian Agency for Drugs and Technologies in Health (CADTH) (www.cadth.ca): 2018-2021

Full details of all search strategies are presented in Appendix 1.

Handling of citations

References identified from the searches were downloaded into EndNote bibliographic management software for further assessment and handling.

Supplementary searches

The bibliographies of included studies and review articles were also checked for additional relevant articles.

Prioritisation

During formal screening of titles and abstracts, studies were subject to a prioritisation process whereby the recency e.g., to most up-to-date clinical practice guidelines (CPG), methodological quality e.g., Cochrane systematic review (CSR), quality of the analyses per outcome (e.g., ratio of RCTs to observational studies), the number of included RCTs, the breadth of the timepoints reported etc. were considered to further prioritise which studies would be used to inform analyses. Studies were categorised into the following three categories: '1' = German, American, European or similar CPG; '2' = CSR or similar quality SR; '3' = potentially lower/other quality SR.

3. RESULTS

The original KSR searches were conducted on March 13, 2018; and of the 1,035 references screened, 6 studies were deemed eligible. In the current update, a total of 1,428 records were retrieved from the electronic literature searches (see Appendix 1). After the removal of duplicate records 970 titles and abstracts were screened by two reviewers. Forty-five records were found to be potentially eligible and were longlisted after a consensus. Of those, five were short-listed and included in the analyses (Table 1).[1-5] See also Table 2 for an overview of primary studies included in the identified SRs/CPGs.

UPDATE – Concluding Assessment by SHARE-TO-CARE Evidence Team (12/04/22)

Based on the update searches conducted by KSR Ltd in November 2021, we want to highlight the following aspects: While the 2020 NICE guideline confirms the effectiveness of peginterferon beta-1a as a first-line treatment for RRMS, other records investigated the role of highly active disease-modifying treatments, such as Alemtuzumab, Ocrelizumab, Natalizumab, Fingolimod or Rituximab (Tjelle et al., 2019; Fuchs, 2019, Li et al., 2019). For the purpose of our decision aid however, we will focus on the basis therapy options, i.e., beta interferons, glatiramer acetate, teriflunomide and dimethyl fumarate. This range aligns with the drugs recommended by the German AWMF-S2k-guideline (2021) for the treatment of patients with assumed non highly active disease progression. An updated version of this guideline is anticipated by the end of 2022, and we will reconsider any changes of the decision aid aftwerwards.

Conclusion regarding the evidence report: No evidence update required. The present evidence report (June, 2018) remains valid until further notice.

Table 1 Evidence sources

Study/year	Evidence type	Primary studies	Number of studies	Intervention(s)	Comparator(s)	Outcome(s)	Date searched	Conclusions
National Institute for Health and Care Excellence 2020[1]	CPG	RCT	2	Peginterferon beta-1a	Placebo	Annualised relapse rate	November 30, 2018	"Peginterferon beta-1a is clinically effective when compared with placebo"
National Institute for Health and Care Excellence 2021[2]	CPG	CPG, SR, RCT	23*	Multiple	Multiple	Multiple	August 2020	See e.g., sections 9-10 of the CPG
Tjelle 2019[3]	HTA	RCT, non-RCT,OS	13*	Disease-modifying treatments	Multiple	Multiple	May 23, 2018	"[…] alemtuzumab is most likely to be the best treatment with respect to annual relapse rate; ocrelizumab and alemtuzumab are equally likely to be the best treatments with respect to risk of disability progression"
Fuchs 2019[4]	SR	RCT, non-RCT	3	Natalizumab	Fingolimod, placebo, delayed treatment	Annualized relapse rate, disability progression, quality of life, serious adverse events	August 16, 2018	"The current evidence indicates that there are no significant differences between natalizumab and fingolimod in terms of annualized relapse rate and disability progression over a prolonged treatment period (≥36 months)"
Li 2019[5]	SR	CPG	1	Alemtuzumab, fingolimod,	Not applicable	Multiple	August 26, 2019	"One evidence-based guideline was identified with one strong

Study/year	Evidence type	Primary studies	Number of studies	Intervention(s)	Comparator(s)	Outcome(s)	Date searched	Conclusions
				natalizumab				recommendation regarding switching from an interferon or glatiramer acetate to a second-line therapy in patients with relapsing-remitting multiple sclerosis and evidence of disease activity"

* = pertains to studies published after 2015
CPG = clinical practice guideline; HTA = health technology assessment; OS = observational study; RCT = randomised controlled trial; SR = systematic review.

Table 2 Overview of primary studies included in the identified SRs/CPGs

Study/year	Primary study(ies)	Reference (first author & journal)
National Institute for Health and Care Excellence 2020[1]	RCT	1. Newsome SD, Scott TF, Arnold DL, Nelles G, Hung S, Cui Y, et al. Long-term outcomes of peginterferon beta-1a in multiple sclerosis: results from the ADVANCE extension study, ATTAIN. Ther Adv Neurol Disord. 2018;11:1756286418791143 2. Calabresi PA, Kieseier BC, Arnold DL, Balcer LJ, Boyko A, Pelletier J, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. Lancet Neurol. 2014 Jul;13(7):657-65.
National Institute for Health and Care Excellence 2021[2]	CPG,SR,RCT*	1. ABPI (2019) SPC for Baclofen tablets 10mg. Electronic Medicines Compendium. Datapharm Communications Ltd. https://www.medicines.org.uk/emc 2. Aharony, S.M., Lam, O. Corcos, J. (2017) Treatment of lower urinary tract symptoms in multiple sclerosis patients: review of the literature and current guidelines. Canadian Urological Association Journal 11(3-4). 3. BMJ Best Practice (2020) Multiple sclerosis. BMJ. https://bestpractice.bmj.com/topics/en-gb/140 4. BNF (2020) British National Formulary. BMJ Group and Pharmaceutical Press. https://bnf.nice.org.uk 5. Dobson, R., Dassan, P., Roberts, M. et al. (2019a) UK consensus on pregnancy in multiple sclerosis: Association of British Neurologists' guidelines. Practical Neurology 19(2), 106-114. 6. Dobson, R. and Giovannoni, G. (2019b) Multiple sclerosis - a review. European Journal of Neurology 26(1), 27-40.

Study/year	Primary study(ies)	Reference (first author & journal)
		7. Eccles, A. (2019) Delayed diagnosis of multiple sclerosis in males: may account for and dispel common understandings of different MS 'types'. British Journal of General Practice 69(680), 148-149. 8. Farez, M.F., Correale, J. and Armstrong, M.J. (2019) Practice guideline update summary: vaccine-preventable infections and immunization in multiple sclerosis. Neurology 93(13), 584-594. 9. Halabchi, F., Alizadeh, Z., Sahraian, M.A. et al. (2017) Exercise prescription for patients with multiple sclerosis; potential benefits and practical recommendations. BMC Neurology 17(1), 185. 10. Kalb, R., Beier, M., Benedict, R.H.B. et al. (2018) Recommendations for cognitive screening and management in multiple sclerosis care. Multiple sclerosis 24(13), 1665-1680. 11. MHRA (2019) Pregabalin (Lyrica), gabapentin (Neurontin) and risk of abuse and dependence: new scheduling requirements from 1 April. Medicines and Healthcare products Regulatory Agency. https://www.gov.uk 12. Montalban, X., Gold, R., Thompson, A.J. et al. (2018) CTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. European Journal of Neurology 25(2), 215-237. 13. NICE (2016) Multiple sclerosis (Quality standard). National Institute for Health and Care Excellence. http://www.nice.org.uk 14. NICE (2019) Multiple sclerosis in adults: management. National Institute for Health and Care Excellence. http://www.nice.org.uk 15. PHE (2020) Multiple sclerosis: prevalence, incidence and smoking status - data briefing. Public Health England. http://www.gov.uk 16. Rae-Grant, A., Day, G.S., Marrie, R.A. et al. (2018) Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. Neurology 90(17), 777-788. 17. Reich, D.S. and Lucchinetti, C.F. Calabresi, P.A. (2018) Multiple sclerosis. New England Journal of Medicine 378(2), 169-180. 18. Solari, A., Giordano, A., Sastre-Garriga, J. et al. (2020) European Association of Neurology (EAN) guideline on palliative care of people with severe, progressive multiple sclerosis. European Journal of Neurology 27(8), 1510-1529. 19. Solomon, A.J., Bourdette, D.N. and Cross, A.H. (2016) The contemporary spectrum of multiple sclerosis misdiagnosis: a multicenter study. Neurology 87(13), 1393-1399. 20. Thompson, A.J., Baranzini, S.E., Geurts, J. et al. (2018) Multiple sclerosis. Lancet 391(10130), 1622-1636. 21. Veauthier, C., Hasselmann, H., Gold, S.M. et al. (2016) The Berlin Treatment Algorithm: recommendations for tailored innovative therapeutic strategies for multiple sclerosis-related fatigue. EPMA Journal 7(1), 25.

Study/year	Primary study(ies)	Reference (first author & journal)
		22. Wallin, M.T., Culpepper, W.J., Nichols, E. et al. (2019) Global, regional, and national burden of multiple sclerosis 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurology 18(3), 269-285. 23. Yamout, B,, Sahraian, M., Bohlega, S. et al. (2020) Consensus recommendations for the diagnosis and treatment of multiple sclerosis: 2019 revisions to the MENACTRIMS guidelines. Multiple Sclerosis and Related Disorders 37(101459).
Tjelle 2019[3]	RCT,non-RCT,OS	1. Ernst FR, Barr P, Elmor R, Wong SL. Relapse outcomes, safety, and treatment patterns in patients diagnosed with relapsing-remitting multiple sclerosis and initiated on subcutaneous interferon beta-1a or dimethyl fumarate: a real-world study. Current Medical Research and Opinion 2017;33(12):2099-106 2. Comi G, Stefano N, Freedman M, Barkhof F, Uitdehaag B, Vos M, et al. Subcutaneous interferon beta-1a in the treatment of clinically isolated syndromes: 3-year and 5-year results of the phase III dosing frequency-blind multicentre REFLEXION study. Journal of neurology, neurosurgery and psychiatry 2017;88(4):285-94. 3. Boiko A, Lashch N, Sharanova S, Zakharova M, Trifonova O, Simaniv T, et al. A Comparative Placebo-Controlled Clinical Trial of the Efficacy and Safety of Glatiramer Acetate 20 mg in Patients with Remitting Multiple Sclerosis: first-Year Study Results. NeurosciBehavPhysiol 2018;48(3):351-7. 4. Saida T, Kira JI, Kishida S, Yamamura T, Ohtsuka N, Ling Y, et al. Safety and Efficacy of Natalizumab in Japanese Patients with Relapsing-Remitting Multiple Sclerosis: Open-Label Extension Study of a Phase 2 Trial. Neurology and Therapy 2017;6(1):39-55. 5. Frisell T, Forsberg L, Nordin N, Kiesel C, Alfredsson L, Askling J, et al. Comparative analysis of first-year fingolimod and natalizumab drug discontinuation among Swedish patients with multiple sclerosis. Multiple Sclerosis Journal 2016;22(1):85-93. 6. Guger M, Enzinger C, Leutmezer F, Kraus J, Kalcher S, Kvas E, et al. Real-life clinical use of natalizumab and fingolimod in Austria. Acta neurologica Scandinavica 2018;137(2):181-7. 7. Koch-Henriksen N, Magyari M, Sellebjerg F, Soelberg Sorensen P. A comparison of multiple sclerosis clinical disease activity between patients treated with natalizumab and fingolimod. MultScler 2017;23(2):234-41 8. Lanzillo R, Carotenuto A, Moccia M, Sacca F, Russo CV, Massarelli M, et al. A longitudinal real-life comparison study of natalizumab and fingolimod. Acta neurologica Scandinavica 2017;136(3):217-22.

Study/year	Primary study(ies)	Reference (first author & journal)
		9. Prosperini L, Sacca F, Cordioli C, Cortese A, Buttari F, Pontecorvo S, et al. Realworld effectiveness of natalizumab and fingolimod compared with self-injectable drugs in non-responders and in treatment-naive patients with multiple sclerosis. JNeurol 2017;264(2):284-94. 10. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. New England Journal of Medicine 2017;376(3):221-34 11. Alping P, Frisell T, Novakova L, Islam-Jakobsson P, Salzer J, Bjorck A, et al. Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. AnnNeurol 2016;79(6):950-8 12. Spelman T, Frisell T, Piehl F, Hillert J. Comparative effectiveness of rituximab relative to IFN-beta or glatiramer acetate in relapsing-remitting MS from the Swedish MS registry. Multiple Sclerosis Journal 2018;24(8):1087-95. 13. Granqvist M, Boremalm M, Poorghobad A, Svenningsson A, Salzer J, Frisell T, et al. Comparative Effectiveness of Rituximab and Other Initial Treatment Choices for Multiple Sclerosis. JAMA Neurology 2018;75(3):320-7.
Fuchs 2019[4]	RCT,non-RCT	1. Saida T, Kira J-I, Kishida S, Yamamura T, Sudo Y, Ogiwara K, et al. Efficacy, safety, and pharmacokinetics of natalizumab in Japanese multiple sclerosis patients: A double-blind, randomized controlled trial and open-label pharmacokinetic study. Multiple Sclerosis and Related Disorders. 2017;1:25-31. 2. Clerico M, Schiavetti I, De Mercanti SF, Piazza F, Gned D, Brescia Morra V, et al. Treatment of relapsing-remitting multiple sclerosis after 24 doses of natalizumab: evidence from an Italian spontaneous, prospective, and observational study (the TY-STOP Study). JAMA Neurology. 2014;71(8):954-60. 3. Koch-Henriksen N, Magyari M, Sellebjerg F, Soelberg Sorensen P. A comparison of multiple sclerosis clinical disease activity between patients treated with natalizumab and fingolimod. Multiple Sclerosis. 2017;23(2):234-41.
Li 2019[5]	CPG	1. Montalban X, Gold R, Thompson AJ, et al. ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis. Mult Scler. 2018;24(2):96-120
* = only studies published after 2015 were extracted CPG = clinical practice guideline; OS = observational study; RCT = randomised controlled trial; SR = systematic review.		

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[1] National Institute for Health and Care Excellence. *Peginterferon beta-1a for treating relapsing–remitting multiple sclerosis. Technology appraisal guidance 624 [Internet]*. London: National Institute for Health and Care Excellence, 2020 [accessed 15.11.21] Available from: https://www.nice.org.uk/guidance/ta624

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[3] Tjelle TE, Rose C, Ohm IK, Pike E, Haheim LL, Bidonde J, et al. *Disease-modifying treatments for relapsing remitting multiple sclerosis, including rituximab. A health technology assessment [Internet]*. Oslo, Norway: Norwegian Institute of Public Health, 2019 [accessed 15.11.21] Available from: https://www.fhi.no/en/publ/2019/Disease-modifying-treatments-for-relapsing-remitting-multiple-sclerosis-including-rituximab.-A-health-technology-assessment./

[4] Fuchs E. *Natalizumab for the treatment of relapsing-remitting multiple sclerosis. Systematic review. LBI-HTA Projektbericht. Nr.: 112; Jahr 2019 [Internet]*. Vienna, Austria: Ludwig Boltzmann Institut für Health Technology Assessment, 2019 [accessed 15.11.21] Available from: https://eprints.aihta.at/1190/1/HTA-Projektbericht_Nr.112.pdf

[5] Li KX, Picheca L. *Second-line therapy for patients with relapsing-remitting multiple sclerosis: a review of guidelines. CADTH rapid response report: summary with critical appraisal [Internet]*. Ottawa, Canada: CADTH, 2019 [accessed 15.11.21] Available from: https://www.cadth.ca/second-line-therapy-patients-relapsing-remitting-multiple-sclerosis-review-guidelines

APPENDIX 1: SEARCH STRATEGIES

Table 3. Systematic reviews and guideline search results

Database	Dates	Results
CDSR	2018 - Issue 11, November 2021	46
KSR Evidence	2018-2021	572
Epistemonikos	2018-2021	681
INAHTA	2018-2021	24
NICE Evidence	01/01/2018 - 15/11/2021	49
NICE Guidance	2018-2021	10
GIN	2018-2021	4
ECRI	2018-2021	6
Trip	2018-2021	29
CADTH	2018-2021	7
Total		**1428**
Total after de-duplication		**970**
Total after de-duplication v original results		**918**

Search strategies

Cochrane Database of Systematic Reviews (CDSR) (Wiley): Issue 11 of 12, November 2021 Searched: 15.11.21

#1 MeSH descriptor: [Multiple Sclerosis] explode all trees 3741
#2 MeSH descriptor: [Demyelinating Diseases] explode all trees 4063
#3 MeSH descriptor: [Demyelinating Autoimmune Diseases, CNS] explode all trees 3791
#4 MeSH descriptor: [Encephalomyelitis, Acute Disseminated] explode all trees 3
#5 MeSH descriptor: [Neuromyelitis Optica] explode all trees 38
#6 MeSH descriptor: [Myelitis, Transverse] explode all trees 49
#7 MeSH descriptor: [Optic Neuritis] explode all trees 180
#8 (MS or CPMS or CP-MS or PPMS or PP-MS or SPMS or SP-MS or RRMS or RR-MS or PRMS or PR-MS or RESMS or RES-MS):ti,ab 20845
#9 (Optic* near/1 (Neuromyelitis or neuritis or neurities)):ti,ab,kw 669
#10 ("myelooptic neuropathy" or "myelo-optic neuropathy" or "myeloptico neuropathy" or myelopticoneuropathy or neuropticomyelitis):ti,ab,kw 178
#11 (Encephalomyelitis or "clinically isolated syndrome" or "transverse myelitis"):ti,ab 396
#12 (demyelinati* near/1 (disease* or disorder* or syndrome*)):ti,ab,kw 485
#13 ((multiple or exacerbat* or disseminated or insular or progressive or relapsing-remitting or CP or RR or PP or SP or PR or multiplex or multi-plex) near/2 sclerosis):ti,ab,kw 10984
#14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 with Cochrane Library publication date Between Jan 2018 and Dec 2021, in Cochrane Reviews, Cochrane Protocols 46

KSR Evidence (Internet): Database last updated 2021 Nov 15

www.ksrevidence.com
Searched 15.11.21

1 multiple sclerosis in Title 720 results
2 multiple sclerosis in Bottom line 64 results
3 demyelinating disease in All text 88 results
4 demyelinating disorder in All text 26 results
5 disseminated sclerosis in All text 12 results
6 encephalomyelitis in All text 80 results
7 #1 or #2 or #3 or #4 or #5 or #6 in All text Date published: 2018 - 2021 572 results
Search run Mon Nov 15 2021

Epistemonikos (Internet): up to 2021 Nov 11
https://www.epistemonikos.org/en/
Searched: 15.11.21

(title:("multiple sclerosis" OR "demyelinating disease" OR "demyelinating disorder" OR "disseminated sclerosis" OR "encephalomyelitis") OR abstract:("multiple sclerosis" OR "demyelinating disease" OR "demyelinating disorder" OR "disseminated sclerosis" OR "encephalomyelitis")) Publication type: Systematic Review; Cochrane Review, No; Pubmed Central, No PMC; Publication year: Custom year range: From 2018 To 2021
681 records

International HTA Database (INAHTA): up to 15 November 2021
https://database.inahta.org/
Searched: 15.11.21

1 "Multiple Sclerosis"[mh] 139
2 "Demyelinating Diseases"[mh] 0
3 "Demyelinating Autoimmune Diseases, CNS"[mh] 0
4 "Encephalomyelitis, Acute Disseminated"[mh] 0
5 "Neuromyelitis Optica"[mh] 5
6 "Myelitis, Transverse"[mh] 2
7 "Optic Neuritis"[mh] 0
8 MS or CPMS or CP-MS or PPMS or PP-MS or SPMS or SP-MS or RRMS or RR-MS or PRMS or PR-MS or RESMS or RES-MS 24
9 devic or devics or ADEM 1
10 "optic neuromyelitis" or "optic neuritis" or "optic neurities" 2
11 "myelooptic neuropathy" or "myelo-optic neuropathy" or "myeloptico neuropathy" or myelopticoneuropathy or neuropticomyelitis 0
12 encephalomyelitis or "clinically isolated syndrome" or "transverse myelitis" 10
13 "demyelinating disease" or "demyelinating disorder" or "demyelinating syndrome" or "demyelinating diseases" or "demyelinating disorders" or "demyelinating syndromes" 2
14 "multiple sclerosis" or "relapsing-remitting sclerosis" 153
15 #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 YEAR 2018 TO 2021 24

NICE Evidence Search (Internet): 15.11.21
https://www.evidence.nhs.uk/
Searched 15.11.21

Search terms	Results (Guidance only): 01/01/2018-15/11/2021
"multiple sclerosis"	134
"demyelinating disease"	10
"demyelinating disorder"	1
"disseminated sclerosis"	0
Total retrieved	**145**
Total (without duplicates)	**137**
Sifted for relevance	**49**

National Institute for Health and Care Excellence (NICE): Guidelines
https://www.nice.org.uk/
Searched 15.11.21

NICE Guidance Conditions and diseases Neurological conditions Multiple sclerosis 2018-2021

Guidance 9
Quality Standards 0
NICE Pathways 1
NICE Advice 0

Total 10

International Guideline Library (GIN) (Internet): up to 15.11.2021
http://www.g-i-n.net
Searched 15.11.21

Search terms	Results: 2018-2021
multiple sclerosis	4
demyelinating disease	1
demyelinating disorder	0
disseminated sclerosis	0

encephalomyelitis	0
Total retrieved	**5**
Total (without duplicates)	**4**

ECRI Institute Guidelines Trust (Internet): up to 15 November 2021
https://guidelines.ecri.org/
Searched: 15.11.21

multiple sclerosis OR demyelinating disease OR demyelinating disorder OR disseminated sclerosis OR encephalomyelitis
2018-2021
6 records retrieved

Trip Database: up to 15 November 2021
https://www.tripdatabase.com/
Searched: 15.11.21

"multiple sclerosis" OR "demyelinating disease" OR "demyelinating disorder" OR "disseminated sclerosis" OR "encephalomyelitis", 2018, 2021, in the Title
Guidelines: 29 records retrieved

Canadian Agency for Drugs and Technologies in Health (CADTH): up to 15 November 2021
https://www.cadth.ca/
Searched: 15.11.21

multiple sclerosis
demyelinating disease
demyelinating disorder
disseminated sclerosis
encephalomyelitis
Contains all words; Health Technology Review; 2018-2021
7 records retrieved

A Report for
Universitätsklinikum Schleswig-Holstein / Campus Kiel
on Shared Decision Making
for Relapsing Remitting Multiple Sclerosis

Kleijnen Systematic Reviews Ltd

June 2018

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LIST OF ABBREVIATIONS

CADTH	Canadian Agency for Drugs and Technologies in Health
CI	Confidence interval
CDSR	Cochrane Database of Systematic Reviews
DARE	Database of Abstracts of Reviews of Effects
DMD	Disease-modifying drug
DMF	Dimethyl fumarate
DMT	Disease-modifying treatment
EAN	European Academy of Neurology
ECTRIMS	European Committee for Treatment and Research in Multiple Sclerosis
EMA	European Medicines Agency
FAQ	Frequently asked question
GA	Glatiramer acetate
GIN	Guidelines International Network
HTA	Health Technology Assessment
IFN	Interferon
KSR	Kleijnen Systematic Reviews Ltd
MS	Multiple sclerosis
NHS	National Health Service
OIS	Optimal information size
PEG	Pegylated
PICO	Participants, intervention, comparators and outcomes
PML	Progressive multifocal leuko¬encephalo¬pathy
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
RCT	Randomised controlled trial
RR	Relative risk
RRMS	Relapsing-remitting multiple sclerosis
SDM	Shared decision making

PROJECT OBJECTIVE

One aim of the research project “Making SDM a reality” is to create interactive websites to inform patients as part of shared decision making (SDM).

For a range of topics, Kleijnen Systematic Reviews Ltd. (KSR) will prepare an evidence table of treatment options and an evidence report with a synthesis of the literature underpinning the evidence table.

The topic of this evidence report is relapsing remitting multiple sclerosis (RRMS) focusing on treatment options to reduce relapse rate and delay progression of disability.

DECISION MAKING IN MS

A number of studies have been published examining patient preferences in relation to disease-modifying treatments (DMTs) in multiple sclerosis (MS).[1-3] This is a reflection of the range of treatments available to the patient with MS, all of which have varying benefits and disadvantages. MS patients are faced with a complex risk-benefit profile when deciding on the best treatment for them. It has been suggested that a shared decision making approach is suited to a chronic condition such as MS where there is such complexity and uncertainty on the most suitable treatment for an individual.[2] Engaging patients in decision making might lead to improved adherence to treatments as patients with a good understanding of the treatment risk-benefits are less likely to discontinue treatment due to unrealistic expectations of their treatment.[2]

A recent study conducted in 17 MS units in Spain, including 221 patients with RRMS, examined patient preferences for 10 hypothetical DMT profiles.[1] It is important to note that in this study patients had been receiving a DMT for at least three months prior to inclusion in the study. This study found that patients placed the most importance on the treatment's potential side effects (32.9%), followed by the route of administration (26.1%), prevention of disease progression (10.0%) and prevention of relapse (8.3%).[1]

However, individual studies may find differing results depending on the characteristics of the included patients and other factors. A recent systematic review brought together the results of 22 studies on patient preferences for DMTs in MS.[2] This review had a number of interesting findings[2]:

- Overall risks (adverse events) of DMT treatments tended to be underestimated by patients and benefits overestimated.
- Patients preferred treatments offering extremely low levels of risks but were willing to accept higher risks in exchange for substantial long-term improvements.

It should be borne in mind though that assessments were often made in the studies using hypothetical rather than actual risks and benefits of disease modifying drugs. The authors concluded that effective ways to communicate risks and benefits about DMTs need to be identified and that patient preferences of DMT risks and benefits should be taken into account.[2]

It is hoped that the evidence provided in this report and its associated option table will help patients to make the most appropriate decision for them with a fuller understanding of the risks and benefits of their choice.

METHODS

INCLUSION CRITERIA

The research question underpinning the literature searches for this topic was developed in conjunction with clinical departments at Universitätsklinikum Schleswig-Holstein/Campus Kiel. The question was framed in terms of participants, intervention, comparators and outcomes (PICO), see Table 1. The clinicians asked to focus on "first-line therapies of MS" in Germany.

As detailed below, literature searches were carried out using a stepwise approach to identify relevant studies according to study design. In the first step, searches aimed to identify relevant systematic reviews and guidelines. For this project, no further searches were conducted as relevant results were extracted from the identified literature.

Table 1: Inclusion criteria for searches

PICO	
Patients	Patients with relapsing-remitting multiple sclerosis
Interventions	Interferon beta (IFNβ): • IFNβ1a (Avonex®, Rebif®) • IFNβ1b (Betaferon®, Betaseron®, Extavia®) • PEG IFN (Plegridy®) Glatiramer acetate (Copaxone®) Terifluonomide (Aubagio®) Dimethyl fumarate (Tecfidera®)
Comparators	Other listed intervention, placebo, no therapy
Outcomes	Disability progression Relapse rate Adverse events
Study design	Systematic reviews and guidelines

IFN = interferon; PEG = pegylated; PICO = participants, intervention, comparators, outcomes and study design

In consultation with the commissioner, questions frequently asked by patients in conjunction with outcomes identified in the literature were developed into an evidence table outline.

FREQUENTLY ASKED QUESTIONS

The following research questions were identified as frequently asked questions (FAQs):

- FAQ 1: What is it and how does the treatment work?
- FAQ 2: What is the effect on the relapse rate?
- FAQ 3: What is the effect on disability progression?
- FAQ 4: What adverse events are linked to the treatment?

LITERATURE SEARCHES

Literature searches were carried out using a stepwise approach to identify relevant studies according to study design:

1. Systematic reviews and guidelines
2. Randomised controlled trials

3. Observational studies
4. Supplementary searches

Only in the event of no relevant systematic reviews or guidelines being identified were further searches to be conducted to identify randomised controlled trials (RCTs, step 3), and if no RCTs were identified, only then would searches be undertaken to identify observational studies (Step 3).

The search strategies were developed specifically for each database and the keywords adapted according to the configuration of each database. Searches were limited by date range for systematic reviews and guidelines to five years (2012-2018). Where appropriate, searches were limited to remove animal studies. Searches were not limited by language or publication status.

Handling of citations

Identified references from the bibliographic database searches were downloaded into EndNote bibliographic management software for further assessment and handling. Individual records within the EndNote libraries were tagged with searching information, such as searcher, date searched, database host, database searched, strategy name and iteration, theme or search question. This enabled the information specialist to track the origin of each individual database record, and its progress through the screening and review process.

Quality assurance within the search process

The main Embase strategy was independently peer reviewed by a second KSR Information Specialist. Strategy peer review was informed by items based on the Canadian Agency for Drugs and Technologies in Health (CADTH) checklist.

SEARCH SOURCES

1. Systematic reviews and guidelines

The following systematic review specific databases were searched from 2012 to present:

- KSR Evidence (Internet): up to 2018/03/13 (https://ksrevidence.com/)
- Cochrane Database of Systematic Reviews (CDSR) (Wiley): up to 2018/03/Iss3
- Database of Abstracts of Reviews of Effects (DARE) (Wiley): up to 2015/04/Iss2
- Health Technology Assessment (HTA) database (Wiley): up to 2016/10/Iss4

The following guidelines resources were searched from 2012 to present:

- Guidelines International Network (GIN) (Internet): up to 2018/03/13 (http://www.g-i-n.net/library/international-guidelines-library)
- NHS Evidence (Internet): up to 2018/03/13 (www.evidence.nhs.uk/)

Full details of all search strategies are presented in Appendix 1.

2. RCTs

As the search for secondary sources was sufficient no additional searches for primary studies were undertaken.

3. Observational studies

As the search for secondary sources was sufficient no additional searches for observational studies were undertaken.

4. Supplementary searches

In addition to the formal searches documented above, reviewers conducted supplementary hand searches to identify potentially relevant references, e.g. guidance specific to Germany and websites of patient organisations. The bibliographies of included studies and review articles were also checked for additional relevant articles.

METHODS OF STUDY SELECTION

Two reviewers independently inspected the title and abstract of each reference identified by the search and determined the potential relevance of each article. For potentially relevant articles, or in cases of disagreement, the full article was obtained, independently inspected, and inclusion criteria applied. Any disagreements were resolved through discussion.

METHODS OF DATA EXTRACTION

An evidence hierarchy was used to select the most appropriate study(ies) to populate the evidence table. Where more than one study could provide evidence for the table the most relevant studies were extracted using the following criteria: recency (most recent preferred), quality (highest quality preferred), representativeness (populations representative of the general target population preferred). Where there were gaps in the evidence table (no systematic review or guideline available) relevant RCTs were extracted and where no RCTs observational studies were extracted.

For each study, data were extracted by one reviewer and checked by another. Any disagreements were resolved by consensus.

GRADE

Quality of identified evidence is presented using the GRADE approach which assesses risk of bias, publication bias, imprecision, inconsistency, indirectness, magnitude of effect, dose-response gradient and the effects of any confounding according to the quality assessment criteria published by the GRADE working group.[4] Several of these criteria are used to rate down the quality of a body of evidence based on the collective limitations of the underlying studies.

- Risk of bias describes any limitations in the design and execution of a collection of studies, for example failure to properly randomise the participants, failure to blind participants and investigators or selective reporting of outcomes.
- Publication bias is a measure of the degree to which the available published data are skewed by selective publication of trials dependent on their results, e.g. positive trials are more likely to be published than those with negative results.

- Imprecision assesses the degree to which random error influences the interpretation of the results.
- Inconsistency captures the degree of heterogeneity between studies in terms of their PICO elements, i.e. how comparable are the studies to each other.
- The remaining GRADE criteria can be used to rate up the quality of evidence if there is a very large effect of intervention, if there is evidence of a dose response or if the effects of any confounding would reduce rather than increase any observed effects.

Each of the GRADE criteria is described in detail in a series of papers published by the GRADE working group.[4] The evidence quality is rated as follows:

- High quality: Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low quality: We are very uncertain about the estimate.

RESULTS

LITERATURE SEARCHES AND INCLUSION ASSESSMENT

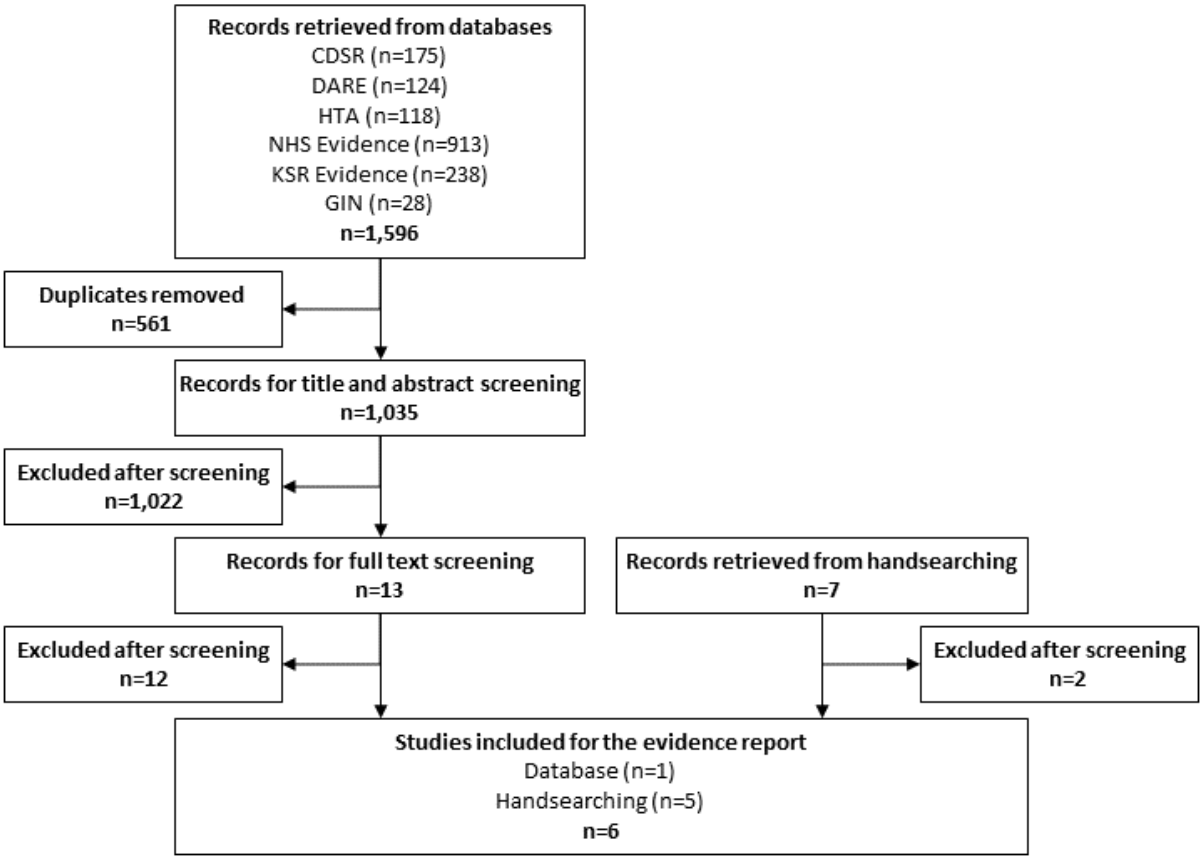
For this evidence report, systematic searches for systematic reviews and guideline were supplemented by hand searches.

Searches were conducted on 13 March 2018 to identify relevant questions (frequently asked questions; FAQs) and to answer the clinical questions focusing on systematic reviews, meta-analyses and evidence-based guidelines. A total of 1,596 titles and abstracts were retrieved from literature searches. After de-duplication, 1,035 titles and abstracts were screened by two reviewers. From these, full papers were obtained for 13 citations. Using the criteria described before (see Data extraction), the ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis, published in 2018, was selected as the main source of evidence in this report.[5]

These searches were supplemented by handsearching to identify additional guidelines (in particular German guidelines) and information by patient organisations which identified patient-driven arguments and prioritizations. A total of seven references were identified: evidence of five references[6-10] was extracted while two references[1, 3] contributed to the section on “Decision making in MS”.

A summary of the study selection process according to modified PRISMA reporting guidelines is reported in Figure 1.

Figure 1: Study selection process



OVERVIEW OF THE EVIDENCE

The information identified to answer the patient questions is given below in tables organised by question. Tables are provided showing the underpinning evidence for each question. Data to populate the tables of patient questions were taken from several sources (Table 2).

Risks in the placebo groups tend to be very different for the trials on interferons compared to the other interventions, where they seem to be fairly consistent. One possible explanation might be that definition of the disease changed between trials over time. This further limits the indirect comparison of risks for the different intervention groups between trials.

For the outcomes of relapse, disability progression and adverse events a recent European guideline prepared by ECTRIMS and EAN was deemed the most appropriate.[5] The "European Committee of Treatment and Research in Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) have joined forces to provide up-to- date, evidence-based recommendations for the treatment of patients with MS to assist physicians, patients, health-care providers and health-policy makers in Europe and worldwide in the decision-making process".[5] Relevant results on the second clinical question of the guideline ("In patients with relapsing–remitting multiple sclerosis (RRMS) and secondary-progressive MS, what is the benefit of treating with a DMD compared to no treatment/another DMD?") were used in this report. The guideline included a total of 33 randomised controlled trials (RCTs) for this question of which 28 RCTs included patients with relapsing–remitting forms of MS while five RCTs were restricted to patients with secondary-progressive MS.[5] In line with the inclusion criteria, only evidence from studies reporting on RRMS was used in this report.

The individual studies on which the guideline evidence is based are cited in our report where they contribute to an outcome. Where outcomes were assessed using the GRADE tool, the rating is reported. Supplementary information on adverse events and details on the treatments were obtained from the website of the MS Society.[6-9]

Table 2: Studies populating the evidence table

Study ID	What is it and how does the treatment work? Mode of administration	Relapse rate	Disability progression	Adverse events
EMA 2013[10]		x		
Montalban 2018[5]		x	x	x
MS Society 2016a[9]	x			x
MS Society 2016b[7]	x			x
MS Society 2016c[6]	x			x
MS Society 2016d[8]	x			x

Study ID	What is it and how does the treatment work? Mode of administration	Relapse rate	Disability progression	Adverse events
EMA = European Medicines Agency; MS = multiple sclerosis				

FAQ 1: What is it and how does the treatment work?

Table 3 provides an overview of the treatment as well as of the mode of administration. Table 4 provides further details on the mode of administration of the beta interferons.

Table 3: What is it and how does the treatment work?

Beta interferons: IFNβ1a (Avonex®, Rebif®), IFNβ1b (Betaferon®, Betaseron®, Extavia®), PEG IFN (Plegridy®)
Beta interferon is used as a disease modifying treatment (DMT) for 'active' relapsing MS. These are the oldest DMTs and have been used against relapsing MS since the 1990s. There are five versions of it known by the brand names: Avonex, Plegridy, Betaferon, Extavia and Rebif. It's thought that man-made beta interferons also reduce (and might prevent) inflammation.
All beta interferons are injected, see Table 4 for further details.
MS Society 2016a[9]
Glatiramer acetate (Copaxone®)
Glatiramer acetate is used as a disease modifying treatment (DMT) for 'active' relapsing MS. It's not clear exactly how glatiramer acetate works, but it seems to attach itself to and kill the immune cells that attack the protective myelin coating around the affected nerves. It also reduces inflammation.
This drug can be injected three times a week using a pre-filled syringe. It can be injected under the skin of arm, thigh, hip or stomach.
MS Society 2016b[7]
Teriflunomide (Aubagio®)
Teriflunomide is used as a disease modifying treatment (DMT) for 'active' relapsing MS. It is not known exactly how teriflunomide works, but it reduces inflammation. It seems to block certain cells made by the affected immune system (T cells) that fight infections.
Teriflunomide is taken orally. The recommended dose is 14 mg once a day.
MS Society 2016c[6]
Dimethyl fumarate (Tecfidera®)
Dimethyl fumarate is used as a disease modifying treatment (DMT) for 'active' relapsing MS. It is not known exactly how dimethyl fumarate works, but studies show it may help to prevent the inflammation that causes damage in the affected brain and spinal cord. It also seems to dampen down the reaction of the affected immune system and protect nerves from damage.
Dimethyl fumarate is taken orally at a dose of 240 mg a day.
MS Society 2016d[6]
DMT = disease modifying treatment; IFN = interferon; mg = milligram; MS = multiple sclerosis

Table 4: Modes of administration (beta interferons)

	Avonex®	Betaferon®	Extavia®	Plegridy®	Rebif®
Location	Injected into the muscle	Injected under the skin	Injected under the skin	Injected under the skin	Injected under the skin
Pharmaceutical form	Comes as a pre-filled syringe, automatic injecting pen or as powder that needs mixing before injecting	Comes as a powder that needs mixing before injecting	Comes as a powder that needs mixing before injecting with a syringe or automatic injecting pen	Comes as a pre-filled syringe or automatic injecting pen	Comes as a pre-filled syringe, automatic injecting pen or the RebiSmart electronic injection device
Frequency	Once a week	Every other day	Every other day	Every two weeks	Three times a week

Based on MS Society 2016a[9]

FAQ 2: What is the effect on the relapse rate?

Table 5 gives an overview of the data identified relating to relapse rate in RRMS. Supporting evidence is presented in Tables 6 to 9.

Using the GRADE tool, the evidence for interferons, glatiramer acetate and teriflunomide has been rated moderate. For dimethyl fumarate the evidence on which relapse rate is based is low.

Table 5: Relapse rate – Option data

	Beta interferon	Glatiramer acetate	Teriflunomide	Dimethyl fumarate
Relapse rate	Approx. 82 of 100 patients taking interferons are free from relapse at just under 12 months (Table 6)	Approx. 71 of 100 patients taking glatiramer acetate are free from relapse at between 12 and 24 months (Table 7)	Approx. 57 of 100 patients taking terifluonomide are free from relapse after 24 months (Table 8)	Approx. 72 of 100 patients taking dimethyl fumarate are free from relapse at up to 24 months (Table 9)
	Approx. 31 of 100 patients taking interferons are free from relapse at 24 months (Table 6)			

Based on Appendix 5 of Montalban 2018[5]

Table 6: Relapse rate – Evidence for interferons compared to placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**IFN**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Relapse free (no of participants) (follow-up 48 weeks)												
1[11]	RCT	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	422 / 512 (82.4%)	358 / 500 (71.6%)	RR 1.15 (1.08 to 1.23)	107 more per 1000 (from 57 more to 165 more)	MODERATE	CRITICAL
Relapse free (no of participants) (follow-up 104 weeks)												
3[12-14]	RCTs	Serious[b]	No serious inconsistency	No serious indirectness	Serious[c]	None	178 / 573 (31.1%)	71 /387 (18.3%)	RR 1.73 (1.35 to 2.21)	134 more per 1000 (from 64 more to 222 more)	LOW	CRITICAL

Based on Appendix 5 of Montalban 2018[5]

a. Unclear risk of detection bias; b. Unclear risk of randomisation sequence generation. Unclear allocation concealment (Jacobs 1996). Unclear risk of detection bias. Unclear risk of selective outcome reporting (all studies); c. Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

CI = confidence interval; IFN = interferon; MS = multiple sclerosis; OIS = optimal information size; RCT = randomised controlled trial; RR = relative risk

Table 7: Relapse rate – Evidence for glatiramer acetate compared to placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**GA**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Relapse free (no of participants) (follow-up 52-104 weeks)												
3[15-17]	RCTs	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	1006/ 1418 (70.9%)	550/ 950 (57.9%)	RR 1.17 (1.1 to 1.24)	98 more per 1000 (from 58 more to 139 more)	MODERATE	CRITICAL
Relapse free (no of participants) (follow-up 104 weeks)[b]												
2[15, 16]	RCTs	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	280/ 475 (58.9%)	248/ 489 (50.7%)	RR 1.16 (1.04 to 1.29)	81 more per 1000 (from 20 more to 147 more)	MODERATE	CRITICAL

Based on Appendix 5 of Montalban 2018[5]
a.High risk of performance bias and attrition bias (different reasons for drop-out across groups) (Fox 2012).[15] Unclear risk of selection bias and reporting bias (no protocol available) (Johnson 1995).[16] b. After removing Khan 2013[17] which is a 52 week study.
CI = confidence interval; GA = glatiramer acetate; RCT = randomised controlled trial; RR = relative risk

Table 8: Relapse rate – Evidence for teriflunomide compared to placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Teri-fluno-mide**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Relapse free (no of participants) (follow-up 108 weeks)												
2[18, 19]	RCTs	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	414 / 728 (56.8%)	347 /751 (46.2%)	RR 1.23 (1.11 to 1.36)	106 more per 1000 (from 51 more to 166	MODERATE	CRITICAL

										more)		

Based on summary of product characteristics for Aubagio, European Medicines Agency[10] and Appendix 5 of Montalban 2018[5]
a. High risk of attrition bias (30% lost to follow-up with different reasons for drop out) (Confavreux 2014).[18] Allocation concealment unclear (O'Conner 2011).[19]
CI = confidence interval; RCT = randomised controlled trial; RR = relative risk

Table 9: Relapse rate: Evidence for dimethyl fumarate compared to placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**DMF**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Relapse free (no of participants) (follow-up 104 weeks)												
2[15, 20]	RCTs	Serious[a]	Serious[b]	No serious indirectness	No serious imprecision	None	554 / 769 (72%)	434 /771 (56.3%)	RR 1.28 (1.14 to 1.43)	158 more per 1000 (from 79 more to 242 more)	Low	CRITICAL

Based on Appendix 5 of Montalban 2018[5]
a. High risk of attrition bias (different reasons for loss to follow-up between groups). Allocation concealment unclear (Fox 2012).[15]; b. Substantial heterogeneity (I^2=55%)
CI = confidence interval; DMF = dimethyl fumarate; RCT = randomised controlled trial; RR = relative risk

FAQ 3: What is the effect on disability progression?

Table 10 gives an overview of the data identified relating to disability progression in RRMS. Supporting evidence is presented in Tables 11 to 14.

Using the GRADE tool, the evidence on disability progression was generally rated low. Additionally, follow-up was limited to two years so long-term effectiveness of the treatments on disability progression are not clear from randomised trials.

Table 10: Disability progression – Option data

Treatment → **↓ FAQ**	**Beta interferon**	**Glatiramer acetate**	**Teriflunomide**	**Dimethyl fumarate**
Disability progression confirmed at 3 months	Approx. 6 of 100 patients taking interferons have confirmed progression at 3 months (Table 11)	Approx. 17 of 100 patients taking glatiramer acetate have confirmed progression at 3 months (Table 12)	Approx. 18 of 100 patients taking teriflunomide have confirmed progression at 3 months (Table 13)	Approx. 15 of 100 patients taking dimethyl fumarate have confirmed progression at 3 months (Table 14)
Disability progression confirmed at 6 months	Approx. 10 of 100 patients taking interferons have confirmed progression at 6 months (Table 11)	Not reported	Not reported	Not reported
Based on Appendix 5 of Montalban 2018[5]				

Table 11: Disability progression – Evidence for interferons compared to placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**IFN**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Disability progression confirmed at 3 months (number of participants worsened) (follow-up 48 weeks)												
1[11]	RCT	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	31 / 512 (6.1%)	50 / 500 (10%)	RR 0.61 (0.39 to 0.93)	39 fewer per 1000 (from 7 fewer to 61 fewer	LOW	CRITICAL
Disability progression confirmed at 6 months (number of participants worsened) (follow-up 104 weeks)												
2[13, 21]	RCTs	Serious[c]	No serious inconsistency	No serious indirectness	Serious[c]	None	53 / 532 (10%)	75 / 537 (14%)	RR 0.71 (0.51 to 0.98)	41 fewer per 1000 (from 3 fewer to 68 fewer)	LOW	CRITICAL

Based on Appendix 5 of Montalban 2018[5]

a.Unclear risk of detection bias; b. Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met; c. Unclear risk of performance bias (Vollmer 2014).[21] Unclear risk of detection bias (Jacobs 1996)[13]

CI = confidence interval; IFN = interferon; MS = multiple sclerosis; OIS = optimal information size; RCT = randomised controlled trial; RR = relative risk

Table 12: Disability progression – Evidence for glatiramer acetate compared to placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**GA**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Disability progression confirmed at 3 months (number of participants worsened) (follow-up 96 to 104 weeks)												
2[15, 16]	RCTs	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	82 / 475 (17.3%)	98 / 489 (20%)	RR 0.86 (0.66 to 1.11)	28 fewer per 1000 (from 68 fewer to 22 more)	LOW	CRITICAL

Based on Appendix 5 of Montalban 2018[5]
a.High risk of performance bias and attrition bias (different reasons for drop-out across groups).[15] Unclear risk of selection bias and reporting bias (no protocol available) (Johnson 1995).[16] 2 Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
CI = confidence interval; GA = glatiramer acetate; MS = multiple sclerosis; OIS = optimal information size; RCT = randomised controlled trial; RR = relative risk

Table 13: Disability progression – Evidence for terifluonomide compared to placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Teri-fluno-mide**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Disability progression confirmed at 3 months (number of participants worsened) (follow-up 104-108 weeks)												
2[18, 19]	RCTs	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	130 / 728 (17.9%)	175 / 751 (23.3%)	RR 0.76 (0.62 to 0.93)	56 fewer per 1000 (from 16 fewer to 89 fewer)	MODERATE	CRITICAL

Based on Appendix 5 of Montalban 2018[5]
a.High risk of attrition bias (30% lost to follow-up with different reasons for drop out)[18] Allocation concealment unclear (O'Conner 2011).[19]
CI = confidence interval; MS = multiple sclerosis; OIS = optimal information size; RCT = randomised controlled trial; RR = relative risk

Table 14: Disability progression – Evidence for dimethyl fumarate compared to placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**DMF**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Disability progression confirmed at 3 months (number of participants worsened) (follow-up 104 weeks)												
2[15, 20]	RCTs	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	112 / 768 (14.6%)	172 / 771 (22.3%)	RR 0.66 (0.51 to 0.85)	76 fewer per 1000 (from 33 fewer to 109 fewer)	LOW	CRITICAL

Based on Appendix 5 of Montalban 2018[5]

a.High risk of attrition bias (different reasons for loss to follow-up between groups). Allocation concealment unclear (Fox 2012).[15] b. Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

CI = confidence interval; DMF = dimethyl fumarate; MS = multiple sclerosis; OIS = optimal information size; RCT = randomised controlled trial; RR = relative risk

FAQ 4: What adverse events are linked to the treatment?

Adverse events are listed in Table 15. Supporting evidence is presented in Tables 16 to 19.

Numbers of adverse events expected to lead to treatment discontinuation are given in the table and are based on generally low quality evidence. Common adverse events are listed without numbers but it is noted that 'common' usually indicates one or more patients in 10 may experience the adverse event.

Table 15: Adverse events

Treatment → ↓ Outcome	Beta interferon	Glatiramer acetate	Teriflunomide	Dimethyl fumarate
Discontinuation due to adverse events	Approx. 5 of 100 patients taking interferons discontinue treatment at up to 2 years due to adverse events (Table 16)	Approx. 3 of 100 patients taking glatiramer acetate discontinue treatment at up to 2 years due to adverse events (Table 17)	Approx. 13 of 100 patients taking teriflunomide discontinue treatment at up to 2 years due to adverse events (Table 18)	Approx 14 of 100 patients taking dimethyl fumarate discontinue treatment at up to 2 years due to adverse events (Table 19)
Common adverse events	Local injection site reactions; lipoatrophy (loss of fat in small areas under the skin at the injection site); flu-like symptoms; depression (your doctor might not give you a beta interferon if you've had depression in the past)	Local injection site reactions; lipoatrophy; infections; flu or flu-like symptoms; anxiety or depression; headache; feeling sick or weak; skin rash; pain in the joints or back	Feeling sick; diarrhoea; hair thinning (hair grows back after six months); increase in some liver enzymes (this doesn't cause symptoms)	Flushing and feeling hot; diarrhoea or upset stomach; feeling sick; headache; a drop in white blood cells (a part of the immune system); itchy skin or a rash
Rarer but serious adverse events	Some possible but very rare serious side effects include kidney problems, blood clots in small blood vessels that could affect your kidneys, heart or thyroid problems, seizures and	Not reported	Not reported	Up to one in 100 people can have a serious allergic reaction to dimethyl fumarate. The drug can increase your chances of getting a rare brain infection (progressive

Treatment → ↓ Outcome	Beta interferon	Glatiramer acetate	Teriflunomide	Dimethyl fumarate
	autoimmune diseases.			multifocal leukoencephalo-pathy (PML). The risk is extremely small. As of May 2016, there have been only four cases of PML in over 100,000 people taking dimethyl fumarate.
Women who are pregnant or may wish to become pregnant	Discuss with your MS specialist the possible risk these drugs might pose to your baby if you become pregnant.	No evidence, glatiramer acetate is harmful. Ask your MS specialist for advice	Women wanting to become pregnant or not using contraception should not use this medication.	Discuss with your MS specialist the possible risk these drugs might pose to your baby if you become pregnant.
Based on Appendix 5 of Montalban 2018[5], MS Society 2016[6-9] MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy				

Table 16: Discontinuation due to adverse events – Evidence for interferons compared to placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**INF**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Discontinuation due to side effects (follow-up 48 weeks)												
1[11]	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	24 / 512 (4.7%)	5 / 500 (1%)	RR 4.69 (1.8 to 12.19)	37 more per 1000 (from 8 more to 112 more)	MODERATE	CRITICAL
Discontinuation due to side effects (follow-up 104 weeks)												
3[13, 14, 21]	RCTs	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	48 / 905 (5.3%)	23 / 725 (3.2%)	RR 1.72 (1.04 to 2.86)	23 more per 1000 (from 1 more to 59 more)	LOW	CRITICAL

Based on Appendix 5 of Montalban 2018[5]

a. Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met. Unclear risk of detection bias;

b. Unclear risk of randomisation sequence generation. Unclear allocation concealment (Jacobs 1996).[13] Unclear risk of detection bias. Unclear risk of selective outcome reporting (all studies).

CI = confidence interval; INF = interferons; MS = multiple sclerosis; OIS = optimal information size; RCT = randomised controlled trial; RR = relative risk

Table 17: Discontinuation due to adverse events – Evidence for glatiramer acetate compared to placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	GA	Placebo	Relative (95% CI)	Absolute		
Discontinuation due to side effects (follow-up 52 weeks)												
1[15]	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	10 / 360 (2.8%)	11 / 363 (3%)	RR 0.92 (0.39 to 2.13)	2 fewer per 1000 (from 71 fewer to 23 more)	MODERATE	CRITICAL
Discontinuation due to side effects (follow-up 96-104 weeks)												
2	RCTs	Serious[b]	No serious inconsistency	No serious indirectness	Serious[c]	None	34/ 1068 (3.2%)	7/ 587 (1.2%)	RR 2.63 (1.17 to 5.9)	19 more per 1000 (from 2 to 58 more)	LOW	CRITICAL

Based on Appendix 5 of Montalban 2018[5]

a. Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

b. High risk of performance bias and attrition bias (different reasons for drop-out across groups) (Fox 2012).[14] Unclear risk of selection bias and reporting bias (no protocol available) (Johnson 1995).[15]

c. Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

CI = confidence interval; GA = glatiramer acetate; MS = multiple sclerosis; OIS = optimal information size; RCT = randomised controlled trial; RR = relative risk

Table 18: Discontinuation due to adverse events – Evidence for terifluonomide compared to placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Teri-fluno-mide	Placebo	Relative (95% CI)	Absolute		
Discontinuation due to side effects (follow-up up to 108 weeks)												
2[18, 19]	RCTs	Serious[a]	Serious[b]	No serious indirectness	Serious[c]	None	96 / 730 (13.2%)	55 / 752 (7.3%)	RR 1.77 (1.02 to 3.07)	56 more per 1000 (from 1 more to	VERY LOW	CRITICAL

										151 more)		

Based on Appendix 5 of Montalban 2018[5]
a.High risk of attrition bias (30% lost to follow-up with different reasons for drop out) (Confavreux 2014). [17] Allocation concealment unclear (O'Conner 2011).[19];
b. Substantial heterogeneity (I^2=63%); c. Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
CI = confidence interval; MS = multiple sclerosis; OIS = optimal information size; RCT = randomised controlled trial; RR = relative risk

Table 19: Discontinuation due to adverse events: Evidence for dimethyl fumarate compared to placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**DMF**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Discontinuation due to side effects (follow-up 96 weeks)												
2[15, 20]	RCTs	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	109 / 769 (14.2%)	93 / 771 (12.1%)	RR 1.17 (0.91 to 1.52)	21 more per 1000 (from 11 fewer to 63 more)	LOW	CRITICAL

Based on Appendix 5 of Montalban 2018[5], however, the numbers are re-calculated as there was inconsistency between the numbers reported in Montalban 2018[5] and the numbers reported in the primary studies Fox 2012[14] and Gold 2012.[19]
a. High risk of attrition bias (different reasons for loss to follow-up between groups). Allocation concealment unclear (Fox 2012).[15] b. Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
CI = confidence interval; DMF = dimethyl fumarate; MS = multiple sclerosis; OIS = optimal information size; RCT = randomised controlled trial; RR = relative risk

DISCUSSION

STRENGTHS, LIMITATIONS AND UNCERTAINTIES

The evidence presented in this report are based on a methodologically robust, recent European guideline citing randomised controlled trials (RCTs), the gold standard for medical research. Handsearching for relevant German guidelines found one relevant guideline on MS.[22] As it was undergoing updating at the time of writing this report (June 2018), it was not used as a source of evidence.

There are important limitations for patients and clinicians to bear in mind when making decisions about treatments. The majority of studies are short-term, therefore, the effects of treatments beyond two years remain uncertain. Secondly, several studies consider disability worsening confirmed after only three months of follow-up which 'is considered a surrogate marker for unremitting disability'.[23] The paucity of adverse event reporting should also be noted as a limitation.

Most studies in RRMS compare drugs to placebo while direct comparisons between drugs are rarer. There are a number of reviews including indirect comparisons of the various drugs using the technique of network meta-analysis whereby drugs are compared using an intermediary, usually placebo.[23-26] However, this report concentrated on the direct evidence.

Outcomes in this report are often based on two or even one trial. Often the evidence is rated low or very low due to limitations in the studies such as unclear assignment to groups and attrition bias (different reasons for drop-out across groups). According to the GRADE approach, implications for practice should be ideally based on moderate to high quality evidence since any estimate of effect based on low to very low quality evidence is very uncertain and further research is likely to change the estimate.[23]

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APPENDIX 1: SEARCH STRATEGIES

Database	Dates	Results
CDSR	up to Iss 3, Mar 2018	175
DARE	up to Iss 2, Apr 2015	124
HTA	up to Iss 4, Oct 2016	118
NHS Evidence	up to 13/03/2018	913
KSR Evidence	up to 2018/03/13	238
GIN	up to 2018/03/13	28
Total		**1596**
Total after de-duplication		**1035**
Duplicates removed		**561***

*This also includes pre 2012 records which were excluded in Endnote

Cochrane Database of Systematic Reviews (CDSR) (Wiley): Issue 3 of 12, March 2018
Database of Abstracts of Reviews of Effects (DARE) (Wiley): Issue 2 of 4, April 2015
Health Technology Assessment Database (HTA) (Wiley): Issue 4 of 4, October 2016
Searched: 13.3.18

ID Search Hits
#1 MeSH descriptor: [Multiple Sclerosis] explode all trees 2442
#2 MeSH descriptor: [Demyelinating Diseases] this term only 75
#3 MeSH descriptor: [Demyelinating Autoimmune Diseases, CNS] this term only 2
#4 MeSH descriptor: [Encephalomyelitis, Acute Disseminated] this term only 3
#5 MeSH descriptor: [Neuromyelitis Optica] this term only 9
#6 MeSH descriptor: [Myelitis, Transverse] this term only 7
#7 MeSH descriptor: [Optic Neuritis] explode all trees 105
#8 (MS or CPMS or CP-MS or PPMS or PP-MS or SPMS or SP-MS or RRMS or RR-MS or PRMS or PR-MS or RESMS or RES-MS):ti,ab 12060
#9 (devic or devics or ADEM):ti,ab 12
#10 (Optic* near/1 (Neuromyelitis or neuritis or neurities)):ti,ab,kw 358
#11 ("myelooptic neuropathy" or "myelo-optic neuropathy" or "myeloptico neuropathy" or myelopticoneuropathy or neuropticomyelitis):ti,ab,kw 76
#12 (Encephalomyelitis or "clinically isolated syndrome" or "transverse myelitis"):ti,ab 258
#13 (demyelinati* near/1 (disease* or disorder* or syndrome*)):ti,ab,kw 310
#14 ((multiple or exacerbat* or disseminated or insular or progressive or relapsing-remitting or CP or RR or PP or SP or PR or multiplex or multi-plex) near/2 sclerosis):ti,ab,kw 6702
#15 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 15055

CDSR search retrieved 175
DARE search retrieved 124
HTA search retrieved 118

NHS Evidence Search: limited to guidance and SRs only (Internet): 2012-2018/03/13
Searched 13.3.18
https://www.evidence.nhs.uk/

Search terms	Results (Guidance and SRs only)
"multiple sclerosis"	838
"demyelinating disease"	61
"demyelinating disorder "	12
"disseminated sclerosis"	2
Total retrieved	**913**
Total (without duplicates)	**845**

KSR Evidence: 2015-2018/03/13
Searched 13.3.18

Searched across any field

multiple sclerosis
OR
demyelinating disease
OR
demyelinating disorder
OR
disseminated sclerosis
OR
encephalomyelitis

2015-2018 = **238 results**

International Guideline Library (GIN) (Internet): up to 2018/03/13
Searched 13.3.18
http://www.g-i-n.net

Search terms	Results (Published guidelines only)
multiple sclerosis OR demyelinating disease OR demyelinating disorder OR disseminated sclerosis OR encephalomyelitis	28
Total retrieved	**28**