# Supplementary materials

## Supplementary material 1 Literature search

Databases: Ovid MEDLINE(R), Embase (Ovid). Cochrane Library: Cochrane Database of Systematic Reviews, Other Reviews (DARE), Cochrane Central Register of Controlled Trials (Central), Health Technology Assessments (HTA), Centre for Reviews and Dissemination: DARE, HTA, NHS EED. Web of Science, PubMed, SweMed+, SBU, Google scholar, PROSPERO.

Date: 2015.02.26.

Update: 2015.11.09 updated search for RCT

Study designs: Systematic Review using Ovids search filter "reviews (maximizes specificity)" and text words: ((systematic\* or literature) adj2 (review\* or overview\*)) in title or abstract. Search fliter Ovids "therapy (maximizes specificity)" and search filters for RCT’s from Cochrane Handbook, chapter 6.4.11.1/2.

Limits: 2013-2015 - Randomized controlled trials

Results: 1006 records (277 SR + 729 RCT )

Searched by: Ingrid Harboe, research librarian

**Search strategies:**

**Databases: Embase** 1974 to 2015 February 25,  Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to resent

Embase: oemezd

MEDLINE: pmoz

**#Searches Results**

1 Multiple sclerosis/ or Multiple sclerosis, chronic progressive/ or Multiple sclerosis, relapsing-remitting/ or Neuromyelitis Optica/ use pmoz [Medline] 130140

2 Multiple sclerosis/ use oemezd [Embase] 84701

3 ((multiple or disseminated) adj sclerosis).tw. 124063

4 (sclerosis multiplex or Neuromyelitis Optica).tw. 5340

5 ((progressive or relapsing or remitting or aggressive or inflammatory or active) adj MS).tw. 9306

6 (SPMS or PPMS or RRMS).tw. 7859

7 MS.ti. 48528

8 or/1-7 195757

9 Fumaric acid dimethyl ester/ use oemezd 1068

10 (dimethyl fumarate\* or dimethylfumarate\*).tw. 1054

11 Teriflunomide/ use oemezd 1128

12 teriflunomide.tw. 502

13 Interferon-beta/ use pmoz 7464

14 Beta interferon/ use oemezd 17923

15 (interferon adj1 beta\*).tw. 16726

16 Glatiramer/ use oemezd 5518

17 (glatirameracetat\* or glatiramer acetat\*).tw. 3213

18 Natalizumab/ use oemezd 5744

19 natalizumab.tw. 3941

20 Fingolimod/ use oemezd 4436

21 fingolimod.tw. 2150

22 Alemtuzumab/ use oemezd 10765

23 alemtuzumab.tw. 5127

24 or/9-23 57825

25 8 and 24 19920

26 limit 25 to "reviews (maximizes specificity)" 229

27 ((systematic\* or literature) adj2 (review\* or overview\*)).ti,ab. 347467

28 25 and 27 236

29 or/26,28 352

30 limit 29 to yr="1995 -Current" 350

31 exp animals/ 37620453

32 humans/ 29132069

33 31 not (31 and 32) 8488384

34 25 not 33 19194

35 limit 34 to "therapy (maximizes specificity)"1986

36 randomized controlled trial.pt. use pmoz 385465

37 controlled clinical trial.pt. use pmoz 88645

38 randomized.ti,ab. use pmoz 331972

39 placebo.ab. use pmoz 158299

40 clinical trials as topic.sh. use pmoz 170938

41 randomly.ab. use pmoz 224453

42 trial.ti. use pmoz 133387

43 or/36-42 940316

44 34 and 43 1211

45 randomized controlled trial/ use oemezd 363421

46 crossover-procedure/ use oemezd 41657

47 double-blind procedure/ use oemezd 120547

48 single-blind procedure/ use oemezd 19566

49 randomized.ab. use oemezd 417485

50 placebo.ab. use oemezd 206226

51 randomly.ab. use oemezd 282429

52 trial.ti. use oemezd 176165

53 or/45-52 974635

54 34 and 53 2056

55 35 or 44 or 543363

56 limit 55 to yr="2013 -Current" 816

**Database: Cochrane Library**

ID Search

#1 MeSH descriptor: [Multiple Sclerosis] this term only 1378

#2 MeSH descriptor: [Neuromyelitis Optica] this term only 5

#3 MeSH descriptor: [Multiple Sclerosis, Chronic Progressive] this term only 152

#4 MeSH descriptor: [Multiple Sclerosis, Relapsing-Remitting] this term only 426

#5 ((multiple or disseminated) next sclerosis) or (sclerosis next multiplex) or

"neuromyelitis optica" or "MS" or SPMS or PPMS or RRMS:ti,ab,kw 21763

#6 #1 or #2 or #3 or #4 or #5 21761

#7 (dimethyl fumarate\* or dimethylfumarate\*):ti,ab,kw 63

#8 teriflunomide\*:ti,ab,kw 45

#9 MeSH descriptor: [Interferon-beta] this term only 524

#10 (interferon next beta\*):ti,ab,kw 1005

#11 (glatiramer aceta\* or glatirameraceta\*):ti,ab,kw 205

#12 natalizumab:ti,ab,kw 135

#13 fingolimod:ti,ab,kw 128

#14 alemtuzumab:ti,ab,kw 251

#15 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 1589

#16 #6 and #15 1150

#17 #16 in Cochrane Reviews (Reviews and Protocols), Other Reviews,

Technology Assessments and Economic Evaluations 122

#18 #16 Publication Year from 2013 to 2015, in Trials 181

#19 #16 Publication Year from 2015 to 2015, in Trials 29

**Database: Centre for Reviews and Dissemination (CRD)**

Line Search Hits

1 MeSH DESCRIPTOR Multiple Sclerosis 201

2 MeSH DESCRIPTOR Multiple Sclerosis, Chronic Progressive 12

3 MeSH DESCRIPTOR Multiple Sclerosis, Relapsing-Remitting 60

4 MeSH DESCRIPTOR Neuromyelitis Optica 1

5 ((multiple sclerosis OR disseminated sclerosis OR sclerosis multiplex OR "neuromyelitis optica")) 408

6 ((MS OR SPMS OR PPMS OR RRMS)) 808

7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 1052

8 ((dimethyl fumarate\* or dimethylfumarate\*)) 12

9 (teriflunomide\*) 8

10 MeSH DESCRIPTOR Interferon-beta 68

11 ((interferon next beta\*)) 94

12 ((glatiramer aceta\* or glatirameraceta\*)) 32

13 (natalizumab) 34

14 (fingolimod) 22

15 (alemtuzumab) 34

16 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 178

17 #7 AND #16 129

18 (#17) IN DARE, HTA 83

19 (#17) IN NHSEED 46

**Database: PubMed**

SR:

((((multiple sclerosis[MeSH Terms]) OR (("multiple sclerosis" OR "disseminated sclerosis" OR "sclerosis multiplex" OR "neuromyelitis optica")) OR "MS" OR SPMS OR PPMS OR RRMS))))

AND ((((((((("dimethyl fumarate"[Title/Abstract] OR dimethylfumarate[Title/Abstract]))) OR teriflunomide[Title/Abstract]) OR (("interferon beta"[Title/Abstract] OR interferon-beta[Title/Abstract]))) OR (("glatiramer aceta"[Title/Abstract] OR glatirameraceta[Title/Abstract]))) OR natalizumab[Title/Abstract]) OR fingolimod[Title/Abstract]) OR alemtuzumab[Title/Abstract])) AND review AND Pubstatusaheadofprint

RCT:(((randomized[Title/Abstract] OR randomly[Title/Abstract]))) AND (((((multiple sclerosis[MeSH Terms]) OR (("multiple sclerosis" OR "disseminated sclerosis" OR "sclerosis multiplex" OR "neuromyelitis optica")) OR "MS" OR SPMS OR PPMS OR RRMS)))) AND ((((((((("dimethyl fumarate"[Title/Abstract] OR dimethylfumarate[Title/Abstract]))) OR teriflunomide[Title/Abstract]) OR (("interferon beta"[Title/Abstract] OR interferon-beta[Title/Abstract]))) OR (("glatiramer aceta"[Title/Abstract] OR glatirameraceta[Title/Abstract]))) OR natalizumab[Title/Abstract]) OR fingolimod[Title/Abstract]) OR alemtuzumab[Title/Abstract])) AND pubstatusaheadofprint)

Jiklhklhkhkjk

**Web of Science**

# 16 66 #15 AND #14

Timespan=2013-2015

Search language=Auto

# 15 Approximately

6,298,345 YEAR PUBLISHED: (2013-2015)

Timespan=2013-2015

Search language=Auto

# 14 730 #2 AND #1 Refined by: Databases: ( WOS ) AND Databases: ( WOS ) AND DOCUMENT TYPES: ( CLINICAL TRIAL )

Timespan=1995-2015

Search language=Auto

# 13 Approximately

14,598 #2 AND #1

Refined by: Databases: ( WOS ) AND Databases: ( WOS )

Timespan=1995-2015

Search language=Auto

# 12 11 #9 AND #4

Refined by: Databases: ( WOS ) AND DOCUMENT TYPES: ( CLINICAL TRIAL )

Timespan=2013-2015

Search language=Auto

# 11 50 #9 AND #4

Refined by: Databases: ( WOS )

Timespan=2013-2015

Search language=Auto

# 10 50 #9 AND #4

Timespan=2013-2015

Search language=Auto

# 9 Approximately

113,246 TOPIC: (("randomized controlled trial" or randomized\* or randomly or "controlled clinical trial")) OR TITLE: (("randomized controlled trial" or randomized\* or randomly or "controlled clinical trial"))

Timespan=2013-2015

Search language=Auto

# 8 53 #5 AND #4

Refined by: Databases: ( WOS ) AND DOCUMENT TYPES: ( REVIEW )

Timespan=1995-2015

Search language=Auto

# 7 68 #5 AND #4

Refined by: Databases: ( WOS )

Timespan=1995-2015

Search language=Auto

# 6 68 #5 AND #4

Timespan=1995-2015

Search language=Auto

# 5 Approximately

181,139 TOPIC: (systematic\* review\*) OR TITLE: (systematic\* review\*)

Timespan=1995-2015

Search language=Auto

# 4 Approximately

14,598 #2 AND #1

Refined by: Databases: ( WOS )

Timespan=1995-2015

Search language=Auto

# 3 Approximately

15,657 #2 AND #1

Timespan=1995-2015

Search language=Auto

# 2 Approximately

266,458 TOPIC: (("dimethyl fumarate" OR dimethylfumarate OR teriflunomide OR interferon OR glatirameraceta\* OR "glatiramer aceta" OR natalizumab OR alemtuzumab)) OR TITLE: (("dimethyl fumarate" OR dimethylfumarate OR teriflunomide OR interferon OR glatirameraceta\* OR "glatiramer aceta" OR natalizumab OR alemtuzumab))

Timespan=1995-2015

Search language=Auto

# 1 Approximately

113,294 TOPIC: (("multiple sclerosis" OR "disseminated sclerosis" OR "sclerosis multiplex" OR "neuromyelitis optica")) OR TITLE: (("multiple sclerosis" OR "disseminated sclerosis" OR "sclerosis multiplex" OR "neuromyelitis optica"))

Timespan=1995-2015

Search language=Auto

**Database: PROSPERO**

Results: 1

Search: multiple sclerosis

**Database: SweMed+**

Results: 8

Search: Multiple sclerosis AND

("dimethyl fumarate" OR dimethylfumarate OR teriflunomide OR interferon OR glatirameraceta\* OR "glatiramer aceta\*" OR natalizumab OR alemtuzumab)

**Webpage: SBU**

Results: 0

Search: Multipel sckleros

**Webpage: Google scholar**

Results: 2

Search:

"Multiple sclerosis" AND name of the intervention drugs AND "technology assessment" AND allintitle

"Multiple sclerosis" AND name of the intervention drugs AND “systematic review" AND allintitle

## Supplementary material 2 Protocol for the systematic review and the economic evaluation

**Project plan for**

**Health Technology Assessment of medicines used for multiple sclerosis**

|  |  |
| --- | --- |
| **Prosjektnummer:** | 1030 |
| **Plan utarbeidet** (dd.mm.yyyy): | February 2015 |

**Kort beskrivelse/sammendrag (norsk)**

Multippel sklerose er en sykdom som er forårsaket av skade på isolasjonslaget rundt nervecellene (myelin) i hjernen og ryggmargen. Når myelinet blir skadet hemmes nervesignalene. Forekomsten av multippel sklerose i Norge er blant de høyest rapporterte i verden. Sykdommen, som vanligvis starter rundt 30 års alder (fra 20-40 år), utvikler seg oftest gjennom ulike faser (f.eks. en relapserende-remitterende fase og en sekundær progressiv fase). De fleste pasienter med MS får etter hvert økende problemer med funksjoner som involverer motoriske, sensoriske, visuelle og autonome systemer. Legemidlene som brukes i dag kan ikke helbrede MS, men de er sykdomsmodifiserende. Det er imidlertid uklart hvilke av disse legemidlene som er mest effektive og kostnadseffektive. Denne fullstendige metodevurderingen tar sikte på å undersøke effekt og kostnadseffektivitet av legemidler som brukes for multippel sklerose i Norge.

**Short description and summary (English)**

Multiple sclerosis is a disease caused by damage to the protective coating around nerve cells (the myelin sheath). Such lesions slows down or stop nerve signals. Prevalence rate for multiple sclerosis in Norway is among the highest reported worldwide. This disease, which usually starts around the age of 30 (range 20-40), most commonly evolves through different phases (e.g. a relapsing-remitting phase and a secondary progressive phase). Most patients experience increasing dysfunctions involving motor, sensory, visual, and autonomic systems. The medicines used today are disease-modifying drugs. It is, however, unclear which of these drugs are most effective and cost-effective. This health technology assessment aims at examining the relative effect and cost-effectiveness of the medicines used for multiple sclerosis in Norway.

|  |  |
| --- | --- |
| **Project category and commissioner** | |
| **Product (program area):** | Health Technology Assessment |
| **Thematic areas:** | Pharmaceuticals,  Health economic evaluation |
| **Commissioner** | RHF-Bestillerforum |
| **Project management and participants** | |
| **Project manager:** | Elisabeth Couto |
| **Responsible for the project**: | Marianne Klemp |
| **Internal project participants:** | Vida HamidiIngrid Harboe Tove Ringerike  Einar Bjørner Torkilseng  Jan Odgaard-Jensen |
| **External project participants:** | Elisabeth Gulowsen Celius (Oslo Universitetssykehus) |
| **Plan for replacement by project participants' absence :** | Replacements will be decided by the person  responsible for the project |
| **Internal reviewers:** | Enrique Jiménez  Signe Agnes Flottorp |
| **External reviewers:** | Torbjørn Wisløff (Universitet i Oslo, Oslo Universitetssykehus)  Rune Midgard (Helse Møre og Romsdal, Molde sjukehus) |

**Mandate**

The National system for managed introduction of new methods in specialist health services (*Nasjonalt system for innføring av nye metoder i spesialisthelsetjenesten*) ordered a comprehensive health technology assessment (HTA) to compare efficacy and cost-effectiveness of different disease modifying medicines in use for multiple sclerosis (MS).

**Goal**

*Overall objective*

* To compare the effect and cost-effectiveness of the disease modifying medicines used for MS in Norway.

*Specific objectives*

* To conduct a systematic review to assess the efficacy and safety of the different disease modifying medicines used for MS and outcomes related to this disease.
* To carry out a health economic evaluation ascertaining cost-effectiveness of the disease modifying medicines used for MS.

**Background**

MS is caused by damage to the protective coating around nerve cells (the myelin sheath). This damage, primarily due to an inflammation disorder of the brain and spinal cord, slows down or stop nerve signals ([1](#_ENREF_1), [2](#_ENREF_2)). This can occur along any area of the brain, optic nerve, and spinal cord ([2](#_ENREF_2)). There are many symptoms and signs of the disease ([1](#_ENREF_1)). Some indicate the involvement of motor, sensory, visual, and autonomic systems ([1](#_ENREF_1)).

MS is more common among women than men ([3](#_ENREF_3)). Norwegian MS prevalence rate is among the highest reported worldwide ([1](#_ENREF_1), [4](#_ENREF_4)). A study, using the Oslo MS Registry and the Norwegian MS Registry and Biobank, estimated prevalence rates of 195/100, 000 (95% confidence interval: 191-199) overall, 272 (266-279) for women, and 119 (115-124) for men ([4](#_ENREF_4)).

The disease usually starts around the age of 30 (range 20-40). In 20% of patients, the illness is progressive from onset ([1](#_ENREF_1)). In most patients the disease follows, first, a relapsing-remitting course that can last several years ([5](#_ENREF_5)). With time, recovery from each episode is incomplete and persistent symptoms accumulate ([1](#_ENREF_1)). Around 65% of relapsing-remitting patients evolve to a phase of increasing dysfunction (secondary progressive phase) ([1](#_ENREF_1)). Medicines in use are disease modifying drugs that inhibit the inflammatory process, avoid progression, and reduce disabilities due to the disease. While several of these medicines are used in Norway, it is unclear which of these drugs are most effective and cost-effective.

**Methods used to carry out the systematic review**

We will perform the systematic review using the methodology described in the handbook of The Norwegian Knowledge Centre for the Health Services (Kunnskapssenteret)  ([6](#_ENREF_6))

**Criteria of selecting studies for this HTA**

***Type of studies***

We will first search for published HTA reports or systematic reviews (SR) including randomised controlled trials (RCT). These should be of high quality and fit our inclusion criteria. If identified HTA or SR are based on literature searches that are older than one year from the date of our literature search, we will supplement the HTA or SR with recently published RCTs. If possible, we will update existing meta-analyses with newly published data. If we do not identify SRs or HTA reports of high quality meeting our inclusion criteria, we will search for RCTs.

We will use the following inclusion criteria to include SRs and/or RCTs:

***Type of participants (Population of interest)***

Men and women aged 18 and above diagnosed with MS. We will consider Clinical Isolated Syndrome (CIS), Relapse-remitting MS (RRMS), and Secondary progressive MS (SPMS).

Exclusion: We will exclude patients with Primary progressive MS and Radiologically isolated syndrome.

Studies that include patients from our exclusion group, further to patients who fit our inclusion criteria, will be included if results are presented separately for each type of patients (so that we can extract results for patients who fit our inclusion criteria).

***Types of interventions***

* dimethyl fumarate
* teriflunomide
* interferon beta
* peg-interferon
* glatiramer acetate
* natalizumab
* fingolimod
* alemtuzumab

***Comparisons***

* Placebo
* One of the medicines listed above as interventions

***Types of outcome measures***

Primary outcomes

* Number of clinical relapses
* Disability progression measured using the expanded disability status scale (EDSS)
* Mortality
* Serious adverse events

Secondary outcomes:

* Withdrawal from study due to adverse events
* Stay at hospitals (We will not consider hospital visits)
* Health related quality of life EQ-5D

**The literature search and publications selection**

***The literature search***

We will systematically search the literature using the following databases:

* Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
* Embase
* Cochrane Library; Cochrane Database of Systematic Reviews, Other Reviews, Technology Assessments, Cochrane Central Register of Controlled Trials (Central)
* Centre for Reviews and Dissemination; DARE, HTA
* ISI web of Science
* PubMed (epub ahead of print)
* Epistemonikos

We will also hand search the following websites:

* Canadian Agency for Drugs and Technologies in Health (CADTH)
* Agency for Healthcare Research and Quality (AHRQ),
* [**FinOHTA**- Finnish Office for Health Technology Assessment](http://www.inahta.org/our-members/members/finohta/)
* Statens beredning för medicinsk utvärdering (SBU)
* EUnetHTA POP database (POP = Planned and Ongoing Projects)
* PROSPERO – Centre for Reviews and Dissemination

The research librarian/information specialist (in collaboration with the project team) will conduct the literature search using index terms (Medical Subject Headings and EMTREE terms), and free text terms relating to the population and the interventions of interest. All retrieved articles published in the period covered by these databases until the date of search will be considered. The search will be supplemented with relevant papers found in bibliographies of selected articles. WHO ICTRP and ClinicalTrials will be searched to identify relevant ongoing or unpublished trials.

***Publications selection process***

We will select articles that will be included in the systematic review through two steps. In both steps, two persons will work independently considering inclusion criteria. In the first step, these two persons will read all titles and abstracts retrieved by the literature search and select possible relevant full-articles. Any disagreement will be discussed between the two to reach a consensus on which full-text articles should be considered in the second step of the selection process. In the second step, the persons will read all the selected full text articles to decide which articles should be included in the systematic review. In case of disagreement, similarly as described above, the two persons will discuss to reach an agreement. In both steps, if necessary, a third person will help and/or the publication authors will be contacted to retrieve the necessary information to reach an agreement.

**Ascertaining quality of SR and risk of bias of individual included studies**

***Assessment of quality of SR(s)***

The quality of possible identified SR will be ascertained using the checklist for SR of the handbook of The Norwegian Knowledge Centre for the Health Services (Kunnskapssenteret)  ([6](#_ENREF_6)).

***Risk of bias***

Individual included RCTs will be assessed for possible risk of bias using the Cochrane Collaboration tool for assessing risk of bias ([7](#_ENREF_7)). Risk of bias will be rated as low risk of bias, unclear risk of bias, or high risk of bias.

**Data collection and analysis**

***Data extraction***

One of the two review authors will extract the data from the selected publications. The second will verify the data.

Data extraction of systematic review(s)

We will extract the following data: publication information (authors, year of publication), date of the literature search, characteristics of included studies (study design, origin, setting, comparisons and endpoints used), and information on quality assessment. We will extract data from primary RCTs included in SR as described below.

Data extraction of RCTs

The following data will be extracted: information on publication (authors names, year of publication), RCT description (design and setting, clinical trial identification, source of funding), participants characteristics (number of participants in the trial, age, and gender, MS diagnosis, length of disease), description of intervention and comparison (when provided, we will extract data considering medicine doses), and outcomes (number of events, methods used to ascertain outcome data, estimates of risk, length of follow-up).

Measures of treatment effect

We will express the comparative effectiveness of the treatments as the relative risk (RR) for dichotomous outcomes and the mean difference (MD) for continuous outcomes. If a continuous outcome has been measured/reported using different instruments/scales in the included RCTs we will calculate the standardised mean difference (SMD). For all outcomes 95% confidence intervals (CI, results from pairwise meta-analyses) or credibility intervals (CrI, results from Network meta-analyses) will be calculated for the RR, MD or SMD. The credibility interval is the Bayesian analogue to confidence intervals used in traditional frequentist statistical approaches. We will consider a result "significant" if the CrI does not include RR = 1 or MD/SMD=0.

Dealing with missing data

For the endpoints clinical relapse (measured as event yes or no) and disability progression (measured as progression yes or no), we will assume that participants who dropped out experienced the event (which seems to be a likely scenario). For all other outcomes, we will not perform imputations for missing data. We will base the statistical analyses on the intention to treat principle (all participants analysed in the group to which they were allocated, and all available data included in the analyses).

***Statistical analyses and presentation of results***

If no SR of high quality is identified, data from individual studies will be quantitatively combined as described below. Similar methods will be used if we need to update meta-analysis or network-meta-analysis.

We will first conduct pairwise meta-analyses for each available endpoint and, for each identified intervention vs. control group comparison. Random effect models will be assumed. Estimates of risk ratios and corresponding 95% CI will be provided. These analyses will be performed using the software RevMan 5.3.

We will perform a network-meta-analysis (NMA) for each primary endpoint. This will be performed combining direct and indirect effects of the interventions of interest for each endpoint. The analysis will primarily be based on Multiple Treatments Meta-analysis (MTM) as described by Salanti ([8](#_ENREF_8)). We will use the arm-based network meta-analysis method (a Bayesian method based on Markov Chain Monte Carlo simulation). All MTM will be performed using Winbugs version 1.4.3 (Imperial College and MRC, UK). The statistical analysis is based on binomial likelihoods (dichotomous outcomes) and normal likelihood (continuous outcomes), with vague priors for the trial baselines, basic parameters (normal distribution with mean 0 and standard deviation 0.0001) and the random effects standard deviation (uniformly distributed in the interval 0 to 2), and takes the correlation structure induced by multi-arm trials into account. We will use a random effects model. We will check for incoherence between direct and indirect evidence by "node-splitting" ([9](#_ENREF_9)). We will calculate the direct and indirect estimates of effect and the corresponding Bayesian "P-values" for incoherence.

We also intend to rank the different treatments in terms of their likelihood of leading to the best results for each primary endpoint. We will base the rankings on the surface under the cumulative ranking curve (SUCRA) ([10](#_ENREF_10)). We will interpret the rankings cautiously taking into account the quality of evidence.

When possible, we will perform subgroup analyses for each type of MS diagnosis (CIS, RRMS, SPMS).

We will perform sensitivity analyses where participants who dropped are excluded from the analyses of the outcomes clinical relapse and disability progression, that is base the analyses on the available data.

If a SR(s) of high quality is identified, we will present risk effect estimates extracted from the SR(s). If the SR is older than one year, and additional studies are identified, we will update the risk estimates. This will be performed using the statistical methods described above.

**Grading the quality of evidence**

Two review authors will assess independently the quality of the evidence for each selected outcome. The quality of the evidence for the pairwise comparisons will be evaluated using GRADE (Grading of recommendations Assessment, Development, and Evaluation) ([7](#_ENREF_7)). The quality of the direct evidence, indirect evidence, and the combined evidence from the NMAs will be evaluated using the GRADE approach adapted for NMA ([11](#_ENREF_11)). GRADE provides specific criteria to consider when rating the quality of evidence. This will be performed ascertaining the strength of the study design, possible risk of bias, imprecision and inconsistency of the estimates, and indirectness and magnitude of effect, dose response gradient and potential confounding factors. The overall quality of the evidence will be classified as high, moderate, low, or very low for each endpoint. The definition for each category is described in the following table.

**Table: Definition of each category for GRADE**

|  |  |
| --- | --- |
| Grade | Definition |
| **High** | We are very confident that the true effect lies close to that of the estimate of effect |
| **Moderate** | We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different |
| **Low** | Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect |
| **Very low** | We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect |

**Economic evaluation**

If the systematic review uncovers no effect estimates for the primary outcomes, we will not perform a cost-effectiveness analysis.

In order to assess the cost-effectiveness of the different medicines used for MS, we will develop a probabilistic Markov decision analytic model.

Efficacy estimates and adverse events will be taken from the results of the systematic literature review. These will inform the transition probabilities used in the model (see previous section). We will estimate costs with official Norwegian unit prices (e.g. DRG and GP-tariffs). We will, as well, conduct separate searches for health-related quality of life weights. Primarily we aim to utilize Norwegian epidemiological data. If Norwegian data are not available or are not compatible with the developed model, we will critically discuss the transferability of the data to the Norwegian context. We will use Norwegian treatment guidelines, and expert advice to inform the model assumptions and structure where appropriate.

The analysis will be carried out both from a health care provider and societal perspectives. The model will calculate quality-adjusted life years (QALYs) and costs related to the different treatment strategies. Both costs and effects will be discounted with the current discount rates recommended by the Ministry of Finance ([13](#_ENREF_13)).

All uncertain parameters will be included in the model as probability distributions representing the degree of uncertainty relating to these parameters. Sensitivity analyses will be performed to assess the robustness of the results.

The PICO for this economic evaluation is:

*Population:* Patients diagnosed with RRMS

*Intervention:* Dimetylfumarat, teriflunomid, interferon beta, peg-interferon, glatirameracetat, natalizumab, fingolimod, alemtuzumab

*Control:* Any of the above mentioned interventions*[[1]](#footnote-1)*

*Outcome:* Cost per QALY gained, net health benefit (NHB), probability of being cost-effective (CEAC), value of information analysis (VOI)

*Study design:* Probabilistic Markov model

*Perspective:* Health care provider and societal

**Activities and schedule**

* Carry out the literature search
* Search for inputs to health economic model (health-related quality of life weights, incidence, morbidity, mortality and costs)
* Select studies to include according to inclusion criteria
* Ascertain possible risk of bias
* Build economic model
* Extract data from selected studies
* Extract data for model and enter as probability distributions
* Conduct statistical analyses
* GRADE the quality of the selected evidence for each endpoint
* Run the model
* Produce the report (write report, send report for peer-review, modify report according to peer-reviewers comments/suggestions, publish report after approval)

**End date**

Expected publishing 1. half 2016

**Publication/dissemination**

The HTA report will be published as a report from the Norwegian Knowledge Centre for the Health Services, and possibly also as a scientific article. Abstracts may be submitted to relevant conferences.

**References**

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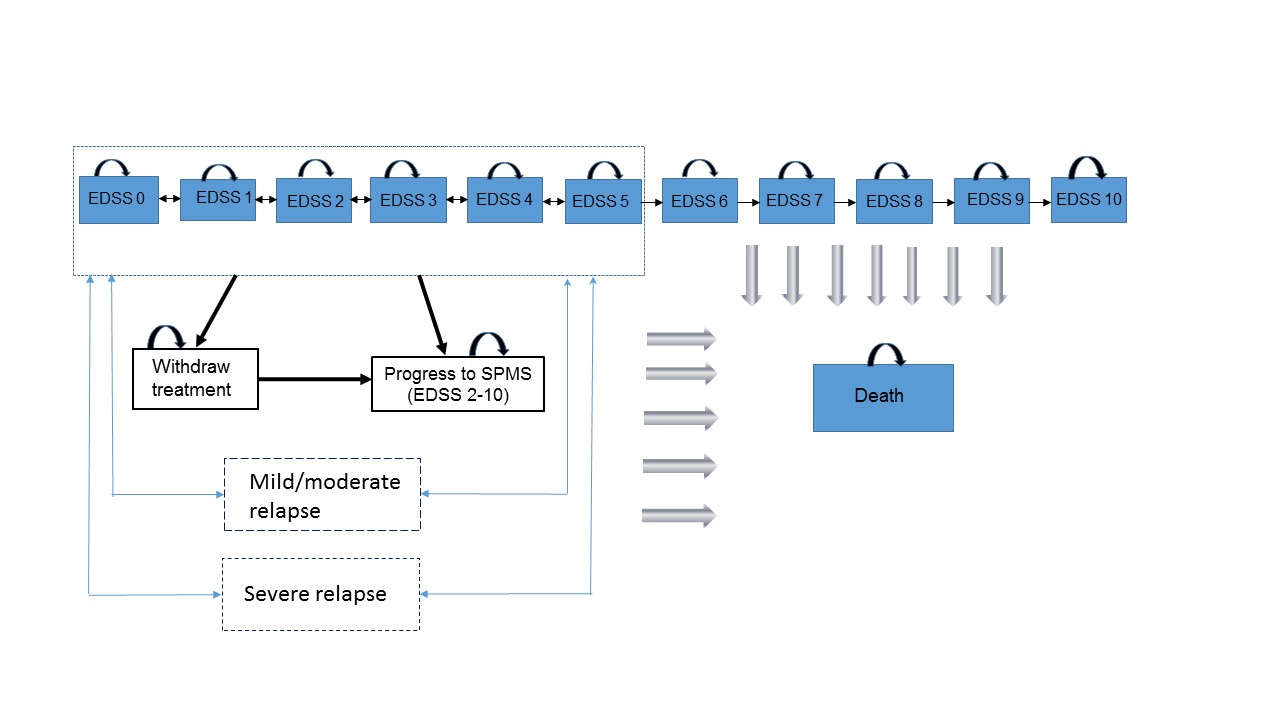
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## Supplementary material 3 Model structure

EDSS: Expanded Disability Status Scale; RRMS: relapsing-remitting multiple sclerosis; SMPM: Secondary-progressive multiple sclerosis

Note: Patients with EDSS over 5 can also progress to SPMS. Mild or moderate and severe relapses can occur in EDSS below 6 as events.

## Supplementary material 4 EDSS distribution used in the model

| **EDSS score** | **Distributions (%)** | **Standard error** |
| --- | --- | --- |
| 0 | 5.10 | 0.003 |
| 1 | 24.60 | 0.013 |
| 2 | 29.30 | 0.015 |
| 3 | 24.70 | 0.013 |
| 4 | 12.70 | 0.006 |
| ≥ 5 | 3.60 | 0.002 |

EDSS: Expanded Disability Status Scale

Source: Nixon *et.a*l 2014

## Supplementary material 5 Annual relapse rate

| **Year since MS onset** | **Base estimate** | **Standard error** |
| --- | --- | --- |
| **For patients with a EDSS 0 to 2.5** | | |
| 5 | 0.712 | 0.343 |
| 10 | 0.623 | 0.335 |
| 15 | 0.571 | 0.331 |
| 20 | 0.534 | 0.327 |
| 25 | 0.506 | 0.325 |
| **For patients with a EDSS 3 to 5.5** | | |
| 5 | 1.255 | 0.386 |
| 10 | 1.101 | 0.374 |
| 15 | 1.011 | 0.367 |
| 20 | 0.947 | 0.362 |
| 25 | 0.897 | 0.358 |

EDSS: Expanded Disability Status Scale

Source: Tran K. et al.. Comparative clinical and cost effectiveness of drug therapies for relapsing-remitting multiple sclerosis. PROSPERO/ CADTH, 2013.

## Supplementary material 6 Calculation of costs

**Table 6.1.** Drug costs per patient inclusive VAT

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Drug** | **Dosage and recommended treatment regimen a** | **Dosage form a** | **LIS price (NOK) a** | **Pills/**  **syringes per**  **package a** | **Annual drug cost (NOK)** |
| Alemtuzumab (Lemtrada) | 12 mg/1.2 ml per day for 5 days, 12 mg/1.2 ml per day for 3 days after one year (IV) | Vial | 63,757.09 | 1 | 318,785 (5 days first year), 191,271 (3 days second year) b |
| Dimethyl fumarate (Tecifidera) | 120 mgx2 for 7 days,  240mg x2 /dag | Capsule | 3,256.12 (start package)  12,936.70 | 14  56 | 168,670 |
| Fingolimod (Gilenya) | 0.5 mg/day | Capsule | 15,125.39 | 28 | 197,170 |
| Glatiramer acetate (Copaxone) c | 20mg/mL  I syringe/day (SC) | Pre-filled  Syringe | 6,702.38 | 28 | 87,370 |
| Interferon beta-1a (Avonex) | 30 mcg/0.5 ml  Once per week (IM) | Pre-filled  Syringe | 8,021.97 | 4 | 104,286 |
| Interferon beta-1a (Rebif) | 22 mcg/0.5 ml  3 times per week (IM) | Pre-filled syringe or auto-injector | 7,027.32 | 12 | 91,355 |
| Interferon beta-1a (Rebif) | 44 mcg/0.5 ml  3 times per week (IM) | Pre-filled syringe or auto-injector | 8,904.26 d | 12 | 115,755 |
| Interferon beta-1b (Betaferon) | 250 mcg /mL every other day (SC) | Powder for injection | 4,937.05 (start package)  5,513.18 | 1  15 | 66,318 |
| Interferon beta-1b (Extavia) | 250 mcg /mL every other day (SC) | Powder for injection | 4,950.14 | 15 | 60,062 |
| Natalizumab (Tysabri) | 300 mg/15 mL  Every four weeks (IV) | Vial | 14,757.51 | 1 | 191,848 |
| Peg-interferon  beta-1a (Plegridy) | 63 mcg/0.5 ml (first dose), 94 mcg/0.5 ml (second dose),  125 mcg/0.5 ml every 14 days (SC) | Prefilled syringe | 8,820.69 (start package)  8,820.69 | 1 (63 mcg) and 1 (94 mcg)  2 | 114,669 |
| Teriflunomide (Aubagio) | 14 mg/day | Tablet | 24,249.21 | 84 | 105,369 |

IM: intramuscular; IV: intravenous; mcg: microgram; mg: milligram; SC: subcutaneous

a Source: Drug procurement cooperation (LIS) 2015. b The majority of patients receiving Alemtuzumab would not need new treatment after 5 year treatment. It was assumed that 20% of patients need extra treatment (12 mg/day for 3 days) (84). C  Glatiramer acetate 40 mg/ml 3 times per week: LIS price 2015: 6702,38 (12 syringes per package). Annual drug cost was estimated to be NOK 87,131. d We used the LIS price 2015 for the products that had 85% of Rebif 44- market in the recent years in Norway (2013-2015). Those products were pre-filled syringe and autoinjector pen.

**Table 6.2.** Monitoring costs associated with each of the treatments (1. year)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug** | **NAB-analyses** | **Infusion costs** | **Eye examinations** | **Startup costs** | **Medical consultations** | **MRI** | **Blood tests**  **(outpatient visits)** | **Travel costs** | **Total** |
| **Alemtuzumab (Lemtrada)** | 0 | 9777  (5/year) | 0 | 0 | 7350  (4/year) | 2600  (1/year) | 1008  (9/year) | 2000 **a** | 22,735 |
| **Dimethyl fumarate (Tecifidera)** | 0 | 0 | 0 | 0 | 7350 (4/year) | 2600  (1/year) | 0 | 1600 b | 11,550 |
| **Fingolimod (Gilenya)** | 0 | 0 | 2500  (1/year) | 3750 c | 7350  (4/year) | 2600  (1/year) | 112  (1/year) | 1600 b | 17,912 |
| **Glatiramer acetate**  **(Copaxone)** | 0 | 0 | 0 | 0 | 7350 (4/year) | 2600  (1/year) | 0 | 1600 b | 11,550 |
| **Interferon beta-1a (Avonex)** | 7716  (2/year) | 0 | 0 | 0 | 7350 (4/year) | 2600 (1/year) | 0 | 1600 b | 19,266 |
| **Interferon beta-1a 44 mcg (Rebif)** | 7716  (2/year) | 0 | 0 | 0 | 7350 (4/year) | 2600 (1/year) | 0 | 1600 b | 19,266 |
| **Interferon beta-1a 22 mcg (Rebif)** | 7716  (2/year) | 0 | 0 | 0 | 7350 (4/year) | 2600 (1/year) | 0 | 1600 b | 19,266 |
| **Interferon beta-1b (Betaferon)** | 7716  (2/year) | 0 | 0 | 0 | 7350 (4/year) | 2600 (1/year) | 0 | 1600 b | 19,266 |
| **Interferon beta-1b (Extavia)** | 7716  (2/year) | 0 | 0 | 0 | 7350 (4/year) | 2600 (1/year) | 0 | 1600 b | 19,266 |
| **Natalizumab (Tysabri)** | 1840  (2/year) | 16,250  (13/year) | 0 | 0 | 7350  (4/year) | 2600  (1/year) | 0 | 5200 a | 33,240 |
| **Peg-interferon**  **beta-1a (Plegridy)** | 7716  (2/year) | 0 | 0 | 0 | 7350 (4/year) | 2600 (1/year) | 0 | 1600 b | 19,266 |
| **Teriflunomide (Aubagio)** | 0 | 0 | 0 | 0 | 7350 (4/year) | 2600 (1/year) | 1344 d | 1600 b | 12,894 |

a Analyses, MR, medical consultations and infusions will be done at the same day. b Analyses, MR, and medical consultations will be done at the same day (4/year).c 6 hours observation d Every 14 days for 6 months, then every other month (numbers of medical consultations were deducted)

**Table 6.3.** Monitoring costs associated with each of the treatments (2. year)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug** | **NAB-analyses** | **Infusion costs** | **Eye examinations** | **Startup costs** | **Medical consultations** | **MRI** | **Blood tests**  **(outpatient visits)** | **Travel costs** | **Total** |
| **Alemtuzumab (Lemtrada)** | 0 | 5866  (3/year) | 0 | 0 | 3675 (2/year) | 2600  (1/year) | 1232  (11/year) | 1200 **a** | 14,573 |
| **Dimethyl fumarate (Tecifidera)** | 0 | 0 | 0 | 0 | 3675 (2/year) | 2600  (1/year) | 0 | 800 b | 7075 |
| **Fingolimod (Gilenya)** | 0 | 0 | 0 | 0 | 3675 (2/year) | 2600  (1/year) | 0 | 800 b | 7075 |
| **Glatiramer**  **acetate**  **(Copaxone)** | 0 | 0 | 0 | 0 | 3675  (2/year) | 2600  (1/year) | 0 | 800 b | 7075 |
| **Interferon beta-1a (Avonex)** | 7716  (2/year) | 0 | 0 | 0 | 3675 (2/year) | 2600 (1/year) | 0 | 800 b | 14,791 |
| **Interferon beta-1a 44 mcg (Rebif)** | 7716  (2/year) | 0 | 0 | 0 | 3675  (2/year) | 2600 (1/year) | 0 | 800 b | 14,791 |
| **Interferon beta-1a 22 mcg (Rebif)** | 7716  (2/year) | 0 | 0 | 0 | 3675 (2/year) | 2600 (1/year) | 0 | 800 b | 14,791 |
| **Interferon beta-1b (Betaferon)** | 7716  (2/year) | 0 | 0 | 0 | 3675 (2/year) | 2600 (1/year) | 0 | 800 b | 14,791 |
| **Interferon beta-1b (Extavia)** | 7716  (2/year) | 0 | 0 | 0 | 3675 (2/year) | 2600 (1/year) | 0 | 800 b | 14,791 |
| **Natalizumab (Tysabri)** | 0 | 16,250  (13/year) | 0 | 0 | 3675 (2/year) | 2600  (1/year) | 0 | 5200 a | 27,725 |
| **Peg-interferon**  **beta-1a (Plegridy)** | 7716  (2/year) | 0 | 0 | 0 | 3675 (2/year) | 2600 (1/year) | 0 | 800 b | 14,791 |
| **Teriflunomide (Aubagio)** | 0 | 0 | 0 | 0 | 3675 (2/year) | 2600 (1/year) | 448 c | 800 b | 7523 |

a Analyses, MR, medical consultations and infusions will be done at the same day. b Analyses, MR, and medical consultations will be done at the same day (2/year).c Every other month (numbers of medical consultations were deducted)

**Table 6.4.** Monitoring costs associated with each of the treatments (beyond 2. year)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug** | **NAB-analyses** | **Infusion costs** | **Eye examinations** | **Startup costs** | **Medical consultations** | **MRI** | **Blood tests**  **(outpatient visits)** | **Travel costs** | **Total** |
| **Alemtuzumab a (Lemtrada)** | 0 | 0 | 0 | 0 | 3675 (2/year) | 2600  (1/year) | 1232  (11/year; only for 3.-5. year) | 800 b | 8307 (3.-5.year)  7075 (+5.year) |
| **Dimethyl fumarate (Tecifidera)** | 0 | 0 | 0 | 0 | 3675 (2/year) | 2600  (1/year) | 0 | 800 b | 7075 |
| **Fingolimod (Gilenya)** | 0 | 0 | 0 | 0 | 3675 (2/year) | 2600  (1/year) | 0 | 800 b | 7075 |
| **Glatiramer**  **acetate**  **(Copaxone)** | 0 | 0 | 0 | 0 | 3675  (2/year) | 2600  (1/year) | 0 | 800 b | 7075 |
| **Interferon beta-1a (Avonex)** | 0 | 0 | 0 | 0 | 3675 (2/year) | 2600 (1/year) | 0 | 800 b | 7075 |
| **Interferon beta-1a 44 mcg (Rebif)** | 0 | 0 | 0 | 0 | 3675  (2/year) | 2600 (1/year) | 0 | 800 b | 7075 |
| **Interferon beta-1a 22 mcg (Rebif)** | 0 | 0 | 0 | 0 | 3675 (2/year) | 2600 (1/year) | 0 | 800 b | 7075 |
| **Interferon beta-1b (Betaferon)** | 0 | 0 | 0 | 0 | 3675 (2/year) | 2600 (1/year) | 0 | 800 b | 7075 |
| **Interferon beta-1b (Extavia)** | 0 | 0 | 0 | 0 | 3675 (2/year) | 2600 (1/year) | 0 | 800 b | 7075 |
| **Natalizumab (Tysabri)** | 0 | 16,250  (13/year) | 0 | 0 | 3675 (2/year) | 2600  (1/year) | 0 | 5200 c | 27,725 |
| **Peg-interferon**  **beta-1a (Plegridy)** | 0 | 0 | 0 | 0 | 3675 (2/year) | 2600 (1/year) | 0 | 800 b | 7075 |
| **Teriflunomide (Aubagio)** | 0 | 0 | 0 | 0 | 3675 (2/year) | 2600 (1/year) | 448 d | 800 b | 7523 |

a The majority of patients receiving Alemtuzumab would not need new treatment after 5 –year treatment. It was assumed that 20% of patients need extra treatment (12 mg/day for 3 days) (expert opinion).b Analyses, MR, medical consultations and infusions will be done at the same day. c Analyses, MR, and medical consultations will be done at the same day (2/year).d Every other month (numbers of medical consultations were deducted)

## Supplementary material 7 Quality of life data used in the model (base-case)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | **Utility weight** | **95% CL** | | **Probability distribution** |
| EDSS 0 | 0.870 | 0.782 | 0.958 | Beta |
| EDSS 1 | 0.799 | 0.799 | 0.617 | Beta |
| EDSS 2 | 0.705 | 0.705 | .0523 | Beta |
| EDSS 3 | 0.574 | 0.574 | 0.384 | Beta |
| EDSS 4 | 0.610 | 0.610 | 0.428 | Beta |
| EDSS 5 | 0.518 | 0.518 | 0.338 | Beta |
| EDSS 6 | 0.460 | 0.277 | 0.641 | Beta |
| EDSS 7 | 0.297 | 0.112 | 0.481 | Beta |
| EDSS 8 | -0.049 | -0.235 | -0.138 | Log-normal |
| EDSS 9 | -0.195 | -0.428 | -0.039 | Log-normal |
| SPMS a | -0.045 | -0.076 | -0.0.014 | Beta or Log-normal |
| Disutility associated with mild or moderate relapse | -0.071 | -0.096 | -0.046 | Log-normal |
| Disutility associated with severe relapse b | -0.236 | -0.295 | -0.174 | Log-normal |
| Disability associated with PML c | -0.40 | -0.30 | -0.50 | Log-normal |

CI: confidence interval; EDSS: Expanded Disability Status Scale; SPMS: Secondary Progressive MS

a Assumed fixed utility decrement over the corresponding RRMS EDSS state utility values.

b It was estimated based on the data reported by Orme et al. 2007 and Prosser et al. 2004.

c Ref: Campbellet al. 2013

## Supplementary material 8 Overview of the included studies

***Table 7.1.*** *Characteristics of the included HTA report (Tran K, et al. Comparative clinical and cost effectiveness of drug therapies for relapsing-remitting multiple sclerosis: PROSPERO/ CADTH; 2013.)*

|  |  |
| --- | --- |
| **Study types included** | RCTs (Number of included monotherapy RCTs: 26) |
| **Participants** | - All studies included patients with RRMS. One study included patients with clinically isolated syndrome (CIS), one study included patients with progressive-relapsing MS (PRMS), one study included patients with secondary-progressive, and one study included patients with secondary-progressive MS and progressive-relapsing MS.  - Randomized sample size: 75 to 1430.  - Female participants: 64% to 84%  - Mean age: 29 to 41 years |
| **Intervention (number of unique RCTs)** | Alemtuzumab (three)  Dimethyl fumarate (two)  Fingolimod (three)  Glatiramer acetate (eight)  Interferon beta-1a subcutaneous (nine)  Interferon beta-1a intramuscular (nine)  Interferon beta-1b (five)  Natalizumab (one)  Teriflunomide (two) |
| **Comparison** | Placebo  One of the drugs listed above |
| **Outcome** | - Relapse  - Disability progression  - MRI lesions  - Adverse events  - Serious adverse events  - Withdrawal due to adverse events  - Quality of life |
| **Follow-up** | 16 weeks to 3.5 years. |
| **Quality assessment** | This publication was assessed to be of high quality |

***Table 7.2.*** *Characteristics of included randomised clinical trials*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Name (publication) (reference) Study design** | **Intervention versus comparison (n=number randomised)** | | | **Treatment**  **history** | **Follow-up** |
| ***CAMMS223 (2008)***  *Coles AJ, Compston DA, Selmaj KW, Lake SL, Moran S, Margolin DH, et al. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med 2008;359(17):1786-1801.*  Rater-blinded, in 49 centres in Europe and US | - Alemtuzumab 12 mg IV q.d., 5 consecutive days at 1st month, 3 consecutive days at months 12 and 24 (n = 113)  - Alemtuzumab 24 mg IV q.d. (n = 110)  - Interferon beta-1a 44 mcg SC t.i.w. (n = 111) | | | Treatment-naive | 3 years |
| ***CARE-MS I(2012)***  Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet 2012;380(9856):1819-1828.  A rater-blinded, in 101 centres in 16 countries including Europe, Canada, and US. | - Alemtuzumab 12 mg IV q.d., 5 consecutive days at month 0, 3 consecutive days at month 12 (n = 386)  - Interferon beta-1a 44 mcg SC t.i.w. (n = 195) | | | Treatment-naive | 2 years |
| ***CARE MS II (2008)***  Coles AJ, Compston DA, Selmaj KW, Lake SL, Moran S, Margolin DH, et al. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med 2008;359(17):1786-1801.  Rater-blinded, in 194 academic medical centres and clinical practices in 23 countries including Europe, Canada, and US. | - Alemtuzumab 12 mg IV q.d., 5 consecutive days at month 0, 3 consecutive days at month 12 (n=436)  Alemtuzumab 24 mg IV q.d., 5 consecutive days at month 0, 3 consecutive days at month 12 (n=173)  - Interferon beta-1a 44 mcg SC t.i.w. (n=231) | | | Treatment-experienced | 2 years |
| ***DEFINE (2012)***  Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012;367(12)  Double-blind, in 28 countries including Europe, Canada, and US | - Dimethyl fumarate 240 mg oral twice daily (n = 410) [total 480 mg/day]  - Dimethyl fumarate 240 mg oral three times daily (n = 416) [total 720 mg/day]  - Placebo (n = 408) | | | Mixed | 2 years |
| ***CONFIRM (2012)***  Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med 2012;367(12):1087-1097.  Rater-blinded, in 200 research sites in 28 countries including Europe and North America | - Dimethyl fumarate 240 mg b.i.d, (n=359)  - Dimethyl fumarate 240 mg three times daily (n=345), subcutaneous daily injections of 20 mg of glatiramer acetate for 96 weeks (n=350)  - Placebo (n=363) | | | Mixed | 2 years |
| ***FREEDOMS (2010)***  Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010;362(5):387-401.  Double-blind, multi-centre in Australia, Canada, Europe, and South Africa (138 centers in 22 countries) | - Fingolimod oral 0.5 mg q.d. (n = 425)  - Fingolimod oral 1,25 mg q.d. (n = 429)  - Placebo (n = 418) | | | Mixed | 2 years |
| ***TRANSFORMS (2010)***  Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med 2010;362(5):402-415.  Double-blind, in 172 centres in 18 countries including Canada, Australia, Europe, and US. | - Fingolimod oral 0.5 mg q.d. (n=431)  - Fingolimod oral 1.25 mg q.d. (n=426)  - Interferon beta-1a 30 mcg IM q.w. (n=435) | | | Mixed | 1 year |
| **Saida T, Kikuchi S, Itoyama Y, Hao Q, Kurosawa T, Nagato K, et al. A randomized, controlled trial of fingolimod (FTY720) in Japanese patients with multiple sclerosis. Mult Scler 2012;18(9):1269-1277.**  Double-blind, multicentre in Japan | - Fingolimod oral 0.5 mg q.d. (n=57)  - Fingolimod oral 1.25 mg q.d. (n=57  - Placebo (n=57) | | | Unclear | 6 months |
| ***FREEDOMS II (2014)***  Corrections to Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): A double-blind, randomised, placebo-controlled, phase 3 trial. [Lancet Neurol 13 (2014) 545-56]. The Lancet Neurology 2014;13(6):536.  Calabresi PA, Radue EW, Goodin D, Jeffery D, Rammohan KW, Reder AT, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): A double-blind, randomised, placebo-controlled, phase 3 trial. The Lancet Neurology 2014;13(6):545-556.  Double-blind, in 117 academic and tertiary referral centres in 8 countries, most patients included in the USA | - Fingolimod 0.5 mg oral q.d. (n=358)  - Fingolimod 1.25 mg oral q.d. (n=370)  - Placebo (n=355) | | | Unclear | 2 years |
| ***Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology 1995;45(7):1268-1276.***  Double-blind, in 11 centres in the US | - Glatiramer acetate 20 mg SC q.d (n =125)  - Placebo (n=126) | | | Treatment-naive | 2 years |
| ***Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging--measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. Ann Neurol 2001;49(3):290-297.***    Double-blind, in 7 countries | - Glatiramer acetate 20 mg SC q.d. (n=119)  - Placebo (n=120) | | | Unclear | 9 months |
| ***REGARD (2008)***  Mikol DD, Barkhof F, Chang P, Coyle PK, Jeffery DR, Schwid SR, et al. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. Lancet Neurol 2008;7(10):903-914.    Open-label, rater-masked. 81 centres in 14 countries including Canada, South America, and Europe | - Glatiramer acetate 20 mg SC q.d. (n=378)  - Interferon beta-1a 44 mcg SC t.i.w. (n=386) | | | Treatment-naive | 96 weeks |
| ***BECOME (2009)***  Cadavid D, Wolansky LJ, Skurnick J, Lincoln J, Cheriyan J, Szczepanowski K, et al. Efficacy of treatment of MS with IFNbeta-1b or glatiramer acetate by monthly brain MRI in the BECOME study. Neurology 2009;72(23):1976-1983.  Rater-blinded, in one centre in the US | - Glatiramer acetate 20 mg SC q.d. (n = 39)  - Interferon beta-1b 250 mcg SC every other day (n = 36) | | | Treatment-naive | 2 years |
| ***BEYOND (2009)***  O'Connor P, Filippi M, Arnason B, Comi G, Cook S, Goodin D, et al. 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. Lancet Neurol 2009;8(10):889-897.    A rater-blinded, in 198 centres in 26 countries worldwide. | - Glatiramer acetate 20 mg SC q.d. (n = 448)  - Interferon beta-1b 250 mcg SC every other day (n = 897)  - Interferon beta-1b 500 mcg SC every other day (n = 899) | | | Treatment-naive | 2 to 3,5 years |
| ***Calabrese M, Bernardi V, Atzori M, Mattisi I, Favaretto A, Rinaldi F, et al. Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing-remitting multiple sclerosis. Mult Scler 2012;18(4):418-424.***    Rater-blinded, single-centre in Italy | - Glatiramer acetate 20 mg SC q.d. (n = 55)  - Interferon beta-1a 44 mcg SC t.i.w. (n = 55)  - Interferon beta-1a 30 mcg IM q.w. (n = 55) | | | Unclear | 2 years |
| ***GALA (2013)***  Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. Ann Neurol 2013;73(6):705-713.    Double-blind study, in 142 sites in 17 countries | - Glatiramer acetate sc 40mg (1ml) tiw (n=943)  - Placebo (n=461) | | | Mixed | 1 year |
| ***CombiRx (2013)***  Lublin FD, Cofield SS, Cutter GR, Conwit R, Narayana PA, Nelson F, et al. Randomized study combining interferon and glatiramer acetate in multiple sclerosis. Ann Neurol 2013;73(3):327-340.  Double-blind, in 68 sites, both private practice and academic, in the USA and Canada | - Interferon beta-1a 30µg IM q.d and glatiramer acetate (GA) 20mg q.d (n=499) (not considered))  - Glatiramer acetate 20mg q.d (n=259)  - Interferon beta-1a 30µg IM q.w (n=250)  - These interventions were compared one with another | | | Treatment-naïve | 3 years |
| ***MSCRG (1996)***  Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Ann Neurol 1996;39(3):285-294.    Double-blind, in 4 centres in the US | - Interferon beta-l a 30 mcg IM q.w. (n=158)  - Placebo (n=143) | | | Treatment-naive | 2 years |
| ***EVIDENCE (2002)***  Panitch H, Goodin DS, Francis G, Chang P, Coyle PK, O'Connor P, et al. Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. Neurology 2002;59(10):1496-1506.    Rater-blinded, in 56 centres in Europe, Canada, and US. | - Interferon beta-1a 30 mcg IM q.w. (n = 338)  - Interferon beta-1a 44 mcg SC t.i.w. (n = 339) | | | Unclear | 24 weeks |
| ***INCOMIN (2002)***  Durelli L, Verdun E, Barbero P, Bergui M, Versino E, Ghezzi A, et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). Lancet 2002;359(9316):1453-1460.  Open label, rater-masked, in 15 centres in Italy | - Interferon beta-1a 30 mcg IM q.w. (n = 92)  - Interferon beta-1b 250 mcg SC every other day (n = 96) | | | Treatment-naive | 2 years |
| ***Clanet M, Radue EW, Kappos L, Hartung HP, Hohlfeld R, Sandberg-Wollheim M, et al. A randomized, double-blind, dose-comparison study of weekly interferon beta-1a in relapsing MS. Neurology 2002;59(10):1507-1517.***  Double-blind, dose-comparison study. In 38 centers in Europe | - Interferon beta-1a 30 mcg IM once weekly (n=402)  - Interferon beta-1a 60 mcg IM once weekly N=(400) | | | Unclear | At least 3 years |
| **Kappos L, Li D, Calabresi PA, O'Connor P, Bar-Or A, Barkhof F, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet 2011;378(9805):1779-1787.**  79 centres in 20 countries in North America, east-central Europe, Asia, western Europe, and Latin America. | | - Ocrelizumab 600 mg IV day 1 and 15 (n=55, not our scope)  - Ocrelizumab 600 mg IV day 1 and 15 (n=55, not our scope)  - Interferon beta-1a 30 mcg IM q.d. (n=55)  - Placebo (n=54) | Mixed | | 24 weeks |
| ***Mokhber N, Azarpazhooh A, Orouji E, Rao SM, Khorram B, Sahraian MA, et al. Cognitive dysfunction in patients with multiple sclerosis treated with different types of interferon beta: A randomized clinical trial. J Neurol Sci 2014;342(1-2):16-20.***  ***S***ingle center in Iran | | - Interferon beta-1a (Avonex ) 30 mcg once per week IM injection; (n=23)  - Interferon beta-1a (Rebif) 44 mcg t.i.w. SC injection; (n=23)  - Interferon beta-1a (Betaferon) 0.25 mg every other day SC injection (n=23) | Treatment-naive | | 1 year |
| ***BRAVO (2014)***  Vollmer TL, Sorensen PS, Selmaj K, Zipp F, Havrdova E, Cohen JA, et al. A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. J Neurol 2014;261(4):773-783.  In 18 countries | | - Laquinimod 0.6 mg capsule q.d. (n=434)[not our scope]  - Interferon beta-1a IM 30 mcg once-weekly injection (n = 447)  *-* Placebo (matching laquinimod) (n = 450) | Mixed | | 2 years |
| ***PRISMS (1998)***  Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Lancet 1998;352(9139):1498-1504.  Double-blind, in 22 centres in 9 countries including Australia, Canada, and Europe | | - Interferon beta-1a 22 mcg SC t.i.w.(n=189)  - Interferon beta-1a 44 mcg SC t.i.w. (n=184)  - Placebo (n=187) | Treatment-naive | | 2 years |
| ***IMPROVE (2010)***  De Stefano N, Curtin F, Stubinski B, Blevins G, Drulovic J, Issard D, et al. Rapid benefits of a new formulation of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis. Mult Scler 2010;16(7):888-892.  Double-blind, multi-centre, multi-country in European countries. | | - Interferon beta-1a 44 mcg SC t.i.w. (n = 120)  - Placebo (n = 60) | Unclear | | 16 weeks |
| ***IFNB-MS (1993)***  Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. Neurology 1993;43(4):655-661.  Multi-centre Canada and the US. | | - Interferon beta-1b 250 mcg SC every other day (n = 124)  - Interferon beta-1b 50 mcg SC every other day (n=125)  - Placebo (n = 123) | Treatment-naïve | | 3 years |
| ***Etemadifar M, Janghorbani M, Shaygannejad V. Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis. Acta Neurol Scand 2006;113(5):283-287.***    Rater-blinded, neurology outpatient clinics in Iran | | - Interferon beta-1b 250 mcg SC every other day (n = 30)  - Interferon beta-1a 30 mcg IM q.w. (n = 30)  - Interferon beta-1a 44 mcg SC t.i.w. (n = 30) | Unclear | | 2 years |
| ***Kappos L, Li D, Calabresi PA, O'Connor P, Bar-Or A, Barkhof F, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet 2011;378(9805):1779-1787. doi: 1710.1016/S0140-6736(1711)61649-61648. Epub 62011 Oct 61631.***  79 centres in 20 countries in North America, east-central Europe, Asia, western Europe, and Latin America. | | - Ocrelizumab 600 mg IV day 1 and 15 (n=55, not our scope)  - Ocrelizumab 600 mg IV day 1 and 15 (n=55, not our scope)  - Interferon beta-1a 30 mcg IM q.d. (n=55)  - Placebo (n=54) | Mixed | | 24 weeks |
| ***Mokhber N, Azarpazhooh A, Orouji E, Rao SM, Khorram B, Sahraian MA, et al. Cognitive dysfunction in patients with multiple sclerosis treated with different types of interferon beta: A randomized clinical trial. J Neurol Sci 2014;342(1-2):16-20.***  ***S***ingle center in Iran | | - Interferon beta-1a (Avonex ) 30 mcg once per week IM injection; (n=23)  - Interferon beta-1a (Rebif) 44 mcg t.i.w. SC injection; (n=23)  - Interferon beta-1a (Betaferon) 0.25 mg every other day SC injection (n=23) | Treatment-naive | | 1 year |
| ***BRAVO (2014)***  Vollmer TL, Sorensen PS, Selmaj K, Zipp F, Havrdova E, Cohen JA, et al. A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. J Neurol 2014;261(4):773-783.  In 18 countries | | - Laquinimod 0.6 mg capsule q.d. (n=434)[not our scope]  - Interferon beta-1a IM 30 mcg once-weekly injection (n = 447)  *-* Placebo (matching laquinimod) (n = 450) | Mixed | | 2 years |
| ***PRISMS (1998)***  Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Lancet 1998;352(9139):1498-1504.  Double-blind, in 22 centres in 9 countries including Australia, Canada, and Europe | | - Interferon beta-1a 22 mcg SC t.i.w.(n=189)  - Interferon beta-1a 44 mcg SC t.i.w. (n=184)  - Placebo (n=187) | Treatment-naive | | 2 years |
| ***IMPROVE (2010)***  De Stefano N, Stromillo ML, Giorgio A, Bartolozzi ML, Battaglini M, Baldini M, et al. Establishing pathological cut-offs of brain atrophy rates in multiple sclerosis. J Neurol Neurosurg Psychiatry 2015;22(309903):2014-  Double-blind, multi-centre, multi-country in European countries. | | - Interferon beta-1a 44 mcg SC t.i.w. (n = 120)  - Placebo (n = 60) | Unclear | | 16 weeks |
| ***IFNB-MS (1993)***  Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. Neurology 1993;43(4):655-661.  Multi-centre Canada and the US. | | - Interferon beta-1b 250 mcg SC every other day (n = 124)  - Interferon beta-1b 50 mcg SC every other day (n=125)  - Placebo (n = 123) | Treatment-naïve | | 3 years |
| ***Etemadifar et al. (2006)***  Etemadifar M, Janghorbani M, Shaygannejad V. Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis. Acta Neurol Scand 2006;113(5):283-287.    Rater-blinded, neurology outpatient clinics in Iran | | - Interferon beta-1b 250 mcg SC every other day (n = 30)  - Interferon beta-1a 30 mcg IM q.w. (n = 30)  - Interferon beta-1a 44 mcg SC t.i.w. (n = 30) | Unclear | | 2 years |
| ***ADVANCE study(2014)***  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. The Lancet Neurology 2014;13(7):657-665.  Double-blind, in 26 countries, in north/south America, Europe, India | | - Peg-interferon beta-1a 125 mcg SC once every 2 weeks (n=512)  - Peg-interferon beta-1a 125 mcg SC once every 4 weeks (n=500)  - Placebo (n=500) | Mixed | | 2 years |
| ***AFFIRM (2006)***  Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006;354(9):899-910.  Double-blind, in 99 centres in Europe, North America, Australia, and New Zealand. | | - Natalizumab 300 mg IV every 4 weeks (n = 627)  - Placebo (n = 315) | Unclear | | 2 years |
| ***Gobbi C, Meier DS, Cotton F, Sintzel M, Leppert D, Guttmann CRG, et al. Interferon beta 1b following natalizumab discontinuation: One year, randomized, prospective, pilot trial. BMC Neurol 2013;13(101).***  Rater blinded. One centre, Switzerland. | | - Continue on natalizumab 300 mg IV q.m. (n=10)  - Switch to interferon beta-1b 250 mcg every other day (n=9) | Treatment experienced | | 1 year |
| ***RESTORE (2014)***  Fox RJ, Cree BAC, De Seze J, Gold R, Hartung HP, Jeffery D, et al. MS disease activity in RESTORE: A randomized 24-week natalizumab treatment interruption study. Neurology 2014;82(17):1491-1498.  Randomized partially, in North America and Europe | | - Natalizumab 300 mg IV every 4 weeks (n=45)  - Alternate immunomodulatory therapy (n=88) (not our scope)  *-* Placebo IV every 4 weeks (n=42) | Treatment experienced | | 24 weeks |
| ***Zecca C, Riccitelli GC, Calabrese P, Pravata E, Candrian U, Guttmann CR, et al. Treatment satisfaction, adherence and behavioral assessment in patients de-escalating from natalizumab to interferon beta. BMC Neurol 2014;14:38.***  Rater-blinded, parallel-group study, single center, Switzerland | | - Continue Natalizumab monthly intravenous (i.v.) 300 mg (n=10)  - De-escalate to interferon beta-1b subcutaneous (s.c.) 250 mcg every other day (n=9) | Treatment experienced | | 1 year |
| ***O’Connor et al (2006)***  O'Connor PW, Li D, Freedman MS, Bar-Or A, Rice GP, Confavreux C, et al. A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. Neurology 2006;66(6):894-900.    Double-blind. Centres in Canada | | - Teriflunomide oral 7 mg q.d.(n=61)  - Teriflunomide oral 14 mg q.d.(n=57  - Placebo (n=61) | Treatment-naive | | 36 weeks |
| ***TEMSO (2011)***  O'Connor PW, Lublin FD, Wolinsky JS, Confavreux C, Comi G, Freedman MS, et al. Teriflunomide reduces relapse-related neurological sequelae, hospitalizations and steroid use. J Neurol 2013;260(10):2472-2480.  O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med 2011;365(14):1293-1303.  Double-blind, in 127 centres in 21 countries including Canada, Europe, and US. | | - Teriflunomide oral 7 mg q.d. (n=365)  - Teriflunomide oral 14 mg q.d. (n=358)  - Placebo (n=363) | Mixed | | 108 weeks |
| ***TOWER (2014)***  Confavreux C, O'Connor P, Comi G, Freedman MS, Miller AE, Olsson TP, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): A randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Neurology 2014;13(3):247-256.  Double-blind, in 189 centres mainly hospital-based sites in 26 countries | | - Teriflunomide 14 mg once daily (n=372)  - Teriflunomide 7 mg once daily (n=408)  - Placebo once daily (n=389) | Mixed | | Up to 48 weeks |
| ***TENERE (2014)***  Vermersch P, Czlonkowska A, Grimaldi LM, Confavreux C, Comi G, Kappos L, et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: A randomised, controlled phase 3 trial. Mult Scler 2014;20(6):705-716.  Rater-blinded study, multicentre study | | - Teriflunomide 14 mg oral once daily (n=111)  - Teriflunomide 7 mg oral once daily (n=109)  - Interferon beta-1a 44mcg s.c three times/week (n=104) | Mixed | | Up to 48 weeks |

*mg=milligrams, mcg=micrograms, SC= subcutaneous; q.d.= once daily, q.w.=. once weekly, t.i.w.= three times weekly, IM= intra muscular*

## Supplementary material 9 Excluded trials and the reasons for the exclusions

* Information on the following tables:
* CIS= Clinical Isolated Syndrome
* P= population
* I=Intervention
* C=Comparator
* S=Study design
* Y=Yes (the study fits that criteria)
* N=No (the study does not fit that criteria)

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **CIS** | **Publication date** | **P** | **I** | **C** | **O** | **S** | **Exclusion/comments** |
| Corrections to Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): A double-blind, randomised, placebo-controlled, phase 3 trial. [Lancet Neurol 13 (2014) 545-56]. The Lancet Neurology 2014;13(6):536. |  |  |  |  |  |  | N | Exclude  Correction updated in online version |
| Agius M, Meng X, Chin P, Grinspan A, Hashmonay R. Fingolimod therapy in early multiple sclerosis: An efficacy analysis of the transforms and freedoms studies by time since first symptom. CNS Neuroscience and Therapeutics 2014;20(5):446-451. |  |  | N | Y | Y | Y | Y | Exclude  subgroups of patients <3 yrs since their first MS symptom |
| Arnold DL, Calabresi PA, Kieseier BC, Sheikh SI, Deykin A, Liu S, et al. Effect of peg-interferon beta-1a on MRI measures and freedom from measured disease activity: 2-year results from the phase 3 ADVANCE study. Mult Scler 2014;1):97. |  |  |  |  |  |  | N | Exclude  Abstract |
| Arnold DL, Calabresi PA, Kieseier BC, Sheikh SI, Deykin A, Zhu Y, Liu S, You X, Sperling B, Hung S. Effect of peg-interferon beta-1a on MRI measures and achieving no evidence of disease activity: results from a randomized controlled trial in relapsing-remitting multiple sclerosis. BMC Neurol. 2014 Dec  31;14(1):1058. |  |  | Y | Y | Y | N |  | Exclude  ADVANCE  Combined outcome of relapse and disability progression |
| Brinar V, Arnold DL, Cohen J, Coles AJ, Fox EJ, Hartung HP, et al. Alemtuzumab improves expanded disability status scale (EDSS) via effects on functional systems: CARE-MS II. Mult Scler 2013;1):283-284. |  |  |  |  |  |  | N | Exclude  Abstract |
| Calabresi PA, Kieseier BC, Arnold DL, Balcer L, Boyko A, Pelletier J, et al. Clinical efficacy of peg-interferon beta-1a in relapsingremitting multiple sclerosis: 2-year data from the phase 3 ADVANCE study. Mult Scler 2014;1):42-43. |  |  |  |  |  |  | N | Exclude  Abstract |
| Cascione M, Gaines C, Fang J, Dangond F, Miller A. Early and consistent reduction in relapses among patients with relapsing-remitting multiple sclerosis receiving subcutaneous interferon beta-1a: A post-hoc analysis of prisms data. Neurology 2014;1). |  |  |  |  |  |  | N | Exclude  Abstract |
| Cascione M, Wynn D, Barbato LM, Pestreich L, Schofield L, McCague K. Randomized, open-label study to evaluate patient-reported outcomes with fingolimod after changing from prior disease-modifying therapy for relapsing multiple sclerosis: EPOC study rationale and design. J Med Econ 2013;16(7):859-865. |  |  |  |  |  | N |  | Exclude  The comparator is disease-modifying therapies. |
| Chan A, Phillips JT, Fox RJ, Zhang A, Okwuokenye M, Kurukulasuriya NC. Differential recovery from relapse between treatment groups in the CONFIRM study of delayed-release dimethyl fumarate. Mult Scler 2014;1):110. |  |  |  |  |  |  | N | Exclude  Abstract |
| Cofield SS, Gustafson T, Cutter GR, Wolinsky JS, Lublin FD. Physician and participant treatment guesses in the double-blind CombiRx study. Mult Scler 2014;1):111-112. |  |  |  |  |  |  | N | Exclude  Abstract |
| Cohen JA, Belova A, Selmaj K, Wolf C, Oberye JJL, Van Den Tweel ERW, et al. Generic glatiramer acetate is equivalent to copaxone on efficacy and safety: Results of the randomized doubleblind GATE trial in multiple sclerosis. Mult Scler 2014;1):38-39. |  |  |  |  |  |  | N | Exclude  Abstract |
| Comi G, Freedman MS, Kappos L, Miller AE, Olsson TP, Wolinsky JS, et al. Effect of teriflunomide on lymphocyte and neutrophil counts: Pooled analyses from four placebo-controlled studies. Mult Scler 2014;1):93-94. |  |  |  |  |  |  | N | Exclude  Abstract |
| Comi G, Martinelli V, Rodegher M, Moiola L, Leocani L, Bajenaru O, et al. Effects of early treatment with glatiramer acetate in patients with clinically isolated syndrome. Mult Scler 2013;19(8):1074-1083. | Y |  |  |  |  |  |  | Exclude  Not RRMS patients |
| Comi G, Miller AE, Wolinsky JS, Benamor M, Bauer D, Truffinet P, et al. The effect of teriflunomide on lymphocyte and neutrophil count in patients with a first clinical episode consistent with multiple sclerosis: Results from the TOPIC study. J Neurol 2014;261:S91. |  |  |  |  |  |  | N | Exclude  Abstract |
| Confavreux C, Olsson TP, Comi G, Freedman MS, Miller A, Wolinsky JS, et al. Teriflunomide hepatic safety results: Pooled data from three placebo-controlled studies. J Neurol 2013;260:S122. |  |  |  |  |  |  | N | Exclude  Abstract |
| Cutter G, Wolinsky JS, Comi G, Ladkani D, Knappertz V, Vainstein A, et al. Comparable clinical and MRI efficacy of glatiramer acetate 40mg/mL TIW and 20mg/mL QD: Results of a systematic review and meta-analysis. Mult Scler 2014;1):90-91. |  |  |  |  |  |  | N | Exclude  Abstract |
| De Stefano N, Kappos L, Radue EW, Sprenger T, Piani Meier D, Haring D, et al. Fingolimod effect on diffuse tissue damage is partly independent of its effect on focal damage in relapsingremitting multiple sclerosis patients. Mult Scler 2014;1):379. |  |  |  |  |  |  | N | Exclude  Abstract |
| De Stefano N, Sprenger T, Freedman MS, Cree B, Sormani MP, Haring DA, et al. Including threshold rates of brain volume loss in the definition of disease-activity-free in multiple sclerosis using fingolimod phase 3 data. Mult Scler 2014;1):196-197. |  |  |  |  |  |  | N | Exclude  Abstract |
| Deykin A, Arnold D, Hung S, Sheikh S, Seddighzadeh A, Zhu Y, et al. Interim analysis of 2-year clinical efficacy and safety of peg-interferon beta-1a in patients with relapsing-remitting multiple sclerosis: Data from the pivotal phase 3 advance study. Neurology 2014;1). |  |  |  |  |  |  | N | Exclude  Abstract |
| Dhib-Jalbut S, Sumandeep S, Valenzuela R, Ito K, Patel P, Rametta M. Immune response during interferon beta-1b treatment in patients with multiple sclerosis who experienced relapses and those who were relapse-free in the START study. J Neuroimmunol 2013;254(1-2):131-140. |  |  |  |  | N |  | N | Exclude  Re-analysis of START study, which is observational with only interfreron (Betaseron) |
| Edan G, Kappos L, Montalban X, Polman C, Freedman M, Hartung H. Long term impact of early initiation of interferon beta-1B after a first clinical event suggestive of multiple sclerosis: Additional relapse rate, edss, and msss analyses after 8 years. 2013;80. |  |  |  |  |  |  | N | Exclude  Abstract |
| Fox E, Edwards K, Burch JG, Kim E, Pestreich L, McCague K, et al. Treatment satisfaction and clinical improvement after switch to fingolimod. J Neurol 2013;260:S126. |  |  |  |  |  |  | N | Exclude  Abstract |
| Freedman M, Wolinsky J, Comi G, Kappos L, Olsson T, Miller A, et al. Long-term safety and efficacy of teriflunomide in patients with relapsing forms of multiple sclerosis in the TEMSO extension trial. Mult Scler 2013;1):225. |  |  |  |  |  |  | N | Exclude  Abstract |
| Freedman M, Wolinsky J, Comi G, Kappos L, Olsson T, Miller A, et al. Safety and efficacy of teriflunomide for up to 9 years in relapsing forms of multiple sclerosis: Update of the temso extension trial. Neurology 2014;1). |  |  |  |  |  |  | N | Exclude  Abstract |
| Freedman MS. Evidence for the efficacy of interferon beta-1b in delaying the onset of clinically definite multiple sclerosis in individuals with clinically isolated syndrome. Ther Adv Neurol Disord 2014;7(6):279-288. | Y |  | N |  |  |  | N | Exclude  Review not SR |
| Freedman MS, Ben-Amor AF, Issard D, Casset-Semanaz F. Assessing a tool to predict disease activity in patients with multiple sclerosis: A post-hoc analysis of clinical trial data on patients treated with subcutaneous interferon beta-1a. Mult Scler 2013;1):262. |  |  |  |  |  |  | N | Exclude  Abstract |
| Freedman MS, Stefano N, Barkhof F, Polman CH, Comi G, Uitdehaag BMJ, et al. Patient subgroup analyses of the treatment effect of subcutaneous interferon beta-1a on development of multiple sclerosis in the randomized controlled REFLEX study. J Neurol 2014;261(3):490-499. | Y |  |  |  |  |  |  | Exclude  Not RRMS patients |
| Havrdova E, Gold R, Fox R, Kappos L, Phillips JT, Zhang A. BG-12 (dimethyl fumarate) treatment for relapsing-remitting multiple sclerosis (RRMS) increases the proportion of patients free of measured clinical and neuroradiologic disease activity in the phase 3 studies. 2013;80. |  |  |  |  |  |  | N | Exclude  Abstract |
| Hung S, Kieseier BC, Arnold DL, Balcer L, Boyko A, Pelletier J, et al. Peg-interferon beta-1a provides improvements in clinical and radiological disease activity in relapsing-remitting multiple sclerosis: Year 1 findings from the phase 3 advance study. Mult Scler 2014;20 (7):926. |  |  |  |  |  |  | N | Exclude  Abstract |
| Hunter SF, Hunter HM, Kantor D. Phase 1 trial monitoring response to alemtuzumab (ALE) in naive and ALE-experienced subjects with refractory multiple sclerosis (MS). Mult Scler 2013;1):265-266. |  |  |  |  |  |  | N | Exclude  Abstract |
| Hutchinson M, Bar-Or A, Fox RJ, Gold R, Giovannoni G, Kita M, et al. Effect of BG-12 (dimethyl fumarate) in subgroups of patients with relapsing-remitting multiple sclerosis: Findings from Two Phase 3 Studies (DEFINE and CONFIRM). Mult Scler 2013;19 (5):682-683. |  |  |  |  |  |  | N | Exclude  Abstract |
| Hutchinson M, Fox RJ, Havrdova E, Kurukulasuriya NC, Sarda SP, Agarwal S, et al. Efficacy and safety of BG-12 (dimethyl fumarate) and other disease-modifying therapies for the treatment of relapsing-remitting multiple sclerosis: A systematic review and mixed treatment comparison. Curr Med Res Opin 2014;30(4):613-627. |  |  |  |  |  |  | N | Exclude  Systematic review. Date of search 15/11/2012 |
| Hutchinson M, Fox RJ, Phillips JT, Miller DH, Havrdova E, Kita M, et al. Efficacy and safety of BG-12 (dimethyl fumarate) in relapsing-remitting multiple sclerosis in the phase 3 CONFIRM study. Mult Scler 2013;19 (5):683. |  |  |  |  |  |  | N | Exclude  Abstract |
| Kappos L, Cohen J, Collins W, De Vera A, Zhang-Auberson L, Ritter S, et al. Fingolimod in relapsing multiple sclerosis: An integrated analysis of safety findings. Multiple sclerosis and Related Disorders 2014;3(4):494-504. |  |  |  |  |  |  | N | Not RCT |
| Kappos L, O'Connor PW, Polman CH, Vermersch P, Wiendl H, Pace A, et al. Clinical effects of natalizumab on multiple sclerosis appear early in treatment course. J Neurol 2013;260(5):1388-1395. |  |  |  |  |  |  | N | Not RCT |
| Kaufman M, Cree BA, De Seze J, Fox RJ, Gold R, Hartung HP, et al. Radiologic MS disease activity during natalizumab treatment interruption: findings from RESTORE. J Neurol 2015;262(2):326-336. |  |  |  |  |  | N |  | Exclude  Re-analysis of RESTORE study and others placebo groups |
| Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R. A multinational, multicenter, randomized, placebo-controlled, double-blind study to assess the efficacy, safety, and tolerability of glatiramer acetate 40 mg injection three times a week in subjects with RRMS: Efficacy and safety results of the gala study. Neurology 2013;80 (1 MeetingAbstracts). |  |  |  |  |  |  | N | Exclude  Abstract |
| Kita M, Fox R, Phillips JT, Arnold D, Bar-Or A, Yang M. Clinical and neuroradiologic efficacy of BG-12 (dimethyl fumarate) in us patients with relapsing-remitting multiple sclerosis (RRMS): An integrated analysis of the phase 3 DEFINE and confirm studies. 2013;80. |  |  |  |  |  |  | N | Exclude  Abstract |
| Leist T, Freedman M, Benamor M, Truffinet P, Dukovic D, Comi G. Pooled safety data from four placebo-controlled teriflunomide studies. Neurology 2014;1). |  |  |  |  |  |  | N | Exclude  Abstract |
| Leist T, Freedman M, Kappos L, Olsson T, Miller A, Wolinsky J, et al. Pooled safety data from three placebo-controlled teriflunomide studies. Mult Scler 2013;1):274-275. |  |  |  |  |  |  | N | Exclude  Abstract |
| Leist TP, Freedman MS, Kappos L, Olsson TP, Miller AE, Wolinsky JS, et al. Three placebo-controlled teriflunomide studies: Pooled safety data. Mult Scler 2014;20 (7):933-934. |  |  |  |  |  |  | N | Exclude  Abstract |
| Leist TP, Freedman MS, Kappos L, Olsson TP, Miller AE, Wolinsky JS, et al. Pooled safety analyses from the teriflunomide clinical development program. Mult Scler 2014;1):110-111. |  |  |  |  |  |  | N | Exclude  Abstract |
| Lublin F, Cofield S, Cutter G, Salter A, Wang J, Conwit R, et al. Edss changes in combirx: Blinded, 7-year extension results for progression and improvement. Neurology 2013;80 (1 MeetingAbstracts). |  |  |  |  |  |  | N | Exclude  Abstract |
| Lublin F, Cofield S, Cutter G, Salter A, Wang J, Conwit R, et al. Relapse activity in the combirx trial: Blinded, 7-year extension results. Neurology 2013;80 (1 MeetingAbstracts). |  |  |  |  |  |  | N | Exclude  Abstract |
| Macdonell R, Lublin F, Comi G, Freedman MS, Kappos L, Maurer M, et al. Teriflunomide reduces relapse-related sequelae, severe relapses, hospitalisations and corticosteroid use: Pooled data from the phase 3 TEMSO and TOWER studies. Mult Scler 2013;1):512-513. |  |  |  |  |  |  | N | Exclude  Abstract |
| Mantia LL, Vacchi L, Rovaris M, Di Pietrantonj C, Ebers G, Fredrikson S, et al. Interferon beta for secondary progressive multiple sclerosis: a systematic review. J Neurol Neurosurg Psychiatry 2013;84(4):420-426 |  |  | N |  |  |  | N | Exclude  Review of  Secondary progressive |
| Maurer M, Van Wijmeersch B, De Seze J, Meca-Lallana J, Bozzi S, Vermersch P. Significant and meaningful improvement in treatment satisfaction with teriflunomide versus subcutaneous IFNB-1A in patients with relapsing ms results from Tenere. Value Health 2014;17 (7):A403. |  |  |  |  |  |  | N | Exclude  Abstract |
| Mikol D, Freedman MS, Goldman MD, Hartung HP, Havrdova E, Jeffery D, et al. Correlations between patient-reported ambulatory function (MSWS-12) and objective disability measurements in SPMS: Analysis of ASCEND baseline data. Mult Scler 2014;1):408. |  |  |  |  |  |  | N | Exclude  Abstract |
| Mikol D, Freedman MS, Goldman MD, Hartung HP, Havrdova E, Jeffery D, et al. Ascend study of natalizumab efficacy on disability in patients with secondary progressive multiple sclerosis (SPMS): Baseline demographics and disease characteristics. Ann Neurol 2013;74:S59-S60. |  |  |  |  |  |  | N | Exclude  Abstract |
| Mikol D, Freedman MS, Goldman MD, Hartung HP, et al. ASCEND study of natalizumab efficacy on reducing disability in patients with secondary progressive multiple sclerosis: Baseline demographics and disease characteristics. Mult Scler 2013;1):507-508. |  |  |  |  |  |  | N | Exclude  Abstract |
| Miller A, Kappos L, Comi G, Confavreux C, Freedman M, Olsson T. Teriflunomide efficacy and safety in patients with relapsing multiple sclerosis: Results from tower, a second, pivotal, phase 3 placebo-controlled study. 2013;80. |  |  |  |  |  |  | N | Exclude  Abstract |
| Miller A, Wolinsky J, Kappos L, Comi G, Freedman M, Olsson T, et al. Topic: Efficacy and safety of once-daily oral teriflunomide in patients with first clinical episode consistent with multiple sclerosis. Neurology 2014;1). |  |  |  |  |  |  | N | Exclude  Abstract |
| Miller A, Wolinsky J, Kappos L, Comi G, Freedman MS, Olsson T, et al. TOPIC main outcomes: Efficacy and safety of once-daily oral teriflunomide in patients with clinically isolated syndrome. Mult Scler 2013;1):25-26. |  |  |  |  |  |  | N | Exclude  Abstract |
| Miller AE, Wolinsky JS, Kappos L, Comi G, Freedman MS, Olsson TP, et al. Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): A randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Neurology 2014;13(10):977-986. | Y |  |  |  |  |  |  | Exclude  TOPIC  Not RRMS patients |
| Montalban X, Barkhof F, Comi G, Hartung HP, Kappos L, Khatri B, et al. Long term efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis previously treated with interferon b-1a or disease modifying therapies: A post hoc analysis of the TRANSFORMS 4.5 year extension study. J Neurol 2013;260:S124-S125. |  |  |  |  |  |  | N | Exclude  Abstract |
| Moses H, Freedman M, Kappos L, Miller A, Olsson T, Wolinsky J. Pre-DEFINEd subgroups analyses of tower, a placebo-controlled phase 3 trial of teriflunomide in patients with relapsing multiple sclerosis. 2013;80. |  |  |  |  |  |  | N | Exclude  Abstract |
| Nabavi M, Abolfazli R, Beladimoghadam N, Shahriari S, Hatami-Sadabadi F, Shati M, et al. A randomized double blind non-inferiority study of efficacy, safety and tolerability of actorif versus rebif in patients with relapsing remitting ms. Neuroepidemiology 2013;41 (3-4):259. |  |  |  |  |  |  | N | Exclude  Abstract |
| Nagtegaal GJA, Pohl C, Wattjes MP, Hulst HE, Freedman MS, Hartung HP, et al. Interferon beta-1b reduces black holes in a randomised trial of clinically isolated syndrome. Mult Scler 2014;20(2):234-242. | Y |  | N |  |  | N |  | Exclude  Not RRMS patients |
| O'Connor P, Lublin F, Wolinsky J, Comi G, Confavreux C, Freedman M. Teriflunomide reduces relapse-related sequelae, hospitalizations and corticosteroid use: A post-HOC analysis of the phase 3 tower study. 2013;80. |  |  |  |  |  |  | N | Exclude  Abstract |
| Olsson T, Comi G, Freedman M, Miller A, Wolinsky J, Truffinet P, et al. Patients free of clinical ms activity in temso and tower: Pooled analyses of two phase 3 placebo-controlled trials. Neurology 2014;1). |  |  |  |  |  |  | N | Exclude  Abstract |
| Pakpoor J, Disanto G, Altmann DR, Pavitt S, Turner B, Calado-Marta M, et al. Is there an increased cancer risk in people with relapsing multiple sclerosis taking cladribine? Mult Scler 2014;1):455. |  |  |  |  |  |  | N | Exclude  Abstract |
| Phillips JT, Fox RJ, Gold R, Havrdova E, Kappos L, Raghupathi K, et al. An integrated analysis of safety and tolerability of BG-12 (dimethyl fumarate) in patients with relapsing-remitting multiple sclerosis from phase 2 and 3 placebo-controlled studies. J Neurol 2013;260:S75. |  |  |  |  |  |  | N | Exclude  Abstract |
| Stefano N, Comi G, Kappos L, Freedman MS, Polman CH, Uitdehaag BMJ, et al. Efficacy of subcutaneous interferon beta-1a on MRI outcomes in a randomised controlled trial of patients with clinically isolated syndromes. J Neurol Neurosurg Psychiatry 2014;85(6):647-653. | Y |  | N |  |  |  |  | Exclude  Not RRMS patients |
| Svenningsson A, Sundstrom P, Salzer J, Vagberg M. MS disease activity in RESTORE: a randomized 24-week natalizumab treatment interruption study. Neurology 2014;83(22):2099-2100. |  |  |  |  |  |  | N | Exclude |
| Tenenbaum N, Schofield L, Meng X, Kern R. The preferms study: Evaluating real-world patient retention on oral fingolimod compared with injectable disease modifying therapies in relapsing-remitting multiple sclerosis. Neurology 2014;1). |  |  |  |  |  |  | N | Exclude  Abstract |
| Tolley K, Hutchinson M, Pachner A, Kinter ET, Sperling B, You X, et al. Systematic literature review and network meta-analysis of peg-interferon beta-1a and injectable therapies for relapsing-remitting multiple sclerosis. Mult Scler 2014;1):209. |  |  |  |  |  |  | N | Exclude  Abstract |
| Tunde C. [Natalizumab retreatment: effectiveness and long-term safety in multiple sclerosis in the STRATA study]. Ideggyogyaszati Szemle 2014;67(7-8):277-279. |  |  |  |  | N |  |  | Exclude  Everybody get Natalizumab |
| Twyman C, Montalban X, Arnold D, Cohen J, Coles A, Confavreux C, et al. Relapse outcomes with alemtuzumab vs IFNB-1A in active relapsing-remitting multiple sclerosis patients who experienced disease activity while on prior therapy (CARE-MS II). Neurology 2013;80 (1 MeetingAbstracts). |  |  |  |  |  |  | N | Exclude  Abstract |
| White JT, Kieseier BC, Newsome SD, Zhu Y, Cui Y, Seddighzadeh A, et al. Immunogenicity with peg-interferon beta-1a in patients with relapsing-remitting multiple sclerosis: 2-year data from the randomised phase 3, multicentre ADVANCE study in relapsing-remitting multiple sclerosis. J Neurol 2014;261:S234. |  |  |  |  |  |  | N | Exclude  Abstract |
| Wolinsky JS, Narayana PA, Nelson F, Datta S, O'Connor P, Confavreux C, et al. Magnetic resonance imaging outcomes from a phase III trial of teriflunomide. Mult Scler 2013;19(10):1310-1319. |  |  |  |  |  | N |  | Exclude  Not our outcome |
| Wolinsky JS, Truffinet P, Bauer D, Miller AE. Efficacy of teriflunomide in patients with early stage MS: Analysis of the TOPIC study using 2010 McDonald diagnostic criteria. Mult Scler 2014;1):109-110. |  |  |  |  |  |  | N | Exclude  Abstract |
| Wolinsky JS, Borresen TE, Dietrich DW, Wynn D, Sidi Y, Steinerman JR, Knappertz V, Kolodny S; GLACIER Study Group. GLACIER: An open-label, randomized, multicenter study to assess the safety and tolerability of glatiramer acetate 40 mg three-times weekly versus 20 mg daily in patients with relapsing-remitting multiple sclerosis. Mult Scler Relat Disord. 2015 Jul;4(4):370-6 |  |  |  | N |  |  |  | All patients used glatiramer acetate 20 mg some of them switched to glatiramer acetate 40 mg |
| Zagmutt F, Carroll C. A network meta-analysis assessing the rate of adverse events and drop outs of alternative treatments for relapsing forms of multiple sclerosis. Neurology 2013;80 (1 MeetingAbstracts). |  |  |  |  |  |  | N | Exclude  Abstract |
| Zagmutt FJ, Carroll CA. Mixed treatment compa rison of adverse events for BG-12, glatiramer, and teriflunomide for the treatment of relapsing forms of multiple sclerosis. Value Health 2013;16 (7):A720. |  |  |  |  |  |  | N | Exclude  Abstract |
| Zagmutt FJ, Carroll CA. Meta-analysis of adverse events in recent randomized clinical trials for dimethil fumarate, glatiramer acetate and teriflunomide for the treatment of relapsing forms of multiple sclerosis. Int J Neurosci 2014. |  |  |  |  |  |  | N | Exclude  SR. Date of search:  January 2013 |
| Kieseier BC, Arnold DL, Balcer LJ, Boyko AA, Pelletier J, Liu S, Zhu Y, Seddighzadeh A, Hung S, Deykin A, Sheikh SI, Calabresi PA. Peg-interferon beta-1a in multiple sclerosis: 2-year results from ADVANCE. Mult Scler. 2014 |  |  | Y | Y | N | Y | N | Exclude |

## Supplementary material 10 Ongoing studies and other potential relevant literature

Below is the list of randomized control trials identifiend on the WHO ICTRP website. Due to the lack of information, we could not determine whether these studies fit our criteria of selection. These studies may add to the evidence.

1) [Retinal Nerve Fiber Layer (RNFL) as measured by Optical Coherence Tomography (OCT) to Depict axonal loss in Early RRMS treated with difFEreNt dosage of subCutaneous IFN bEta 1a - DEFENCE](http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2009-015007-97-IT)

<http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2009-015007-97-IT>

2) [Long-Term Safety and Efficacy Study of Oral BG00012 Monotherapy in Relapsing-Remitting Multiple Sclerosis](http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2008-004753-14-BE)

<http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2008-004753-14-BE>

3) [ADVANCED MRI STUDY ON INFLAMMATORY AND DEGENRATIVE DAMAGE IN MULTIPLE SCLEROSIS - RMaIDSM](http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2008-007162-32-IT)

<http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2008-007162-32-IT>

4) [A Phase 3 Randomized, Rater- and Dose-Blinded Study Comparing Two Annual Cycles of Intravenous Low- and High-Dose Alemtuzumab to Three-Times Weekly Subcutaneous Interferon Beta-1a (Rebif®) in Patients with Relapsing-Remitting Multiple Scleroris Who Have Relapsed On Therapy - CARE MS-II](http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2007-001162-32-GB)

<http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2007-001162-32-GB>

5) Long-term extension of the multinational, double-blind, placebo controlled study EFC6049 (HMR1726D/3001) to document the safety of two doses of teriflunomide (7 and 14 mg) in patients with multiple sclerosis with relapses

<http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2006-003361-14-FI>

6) A pilot multi-centre randomised controlled trial of sequential treatment with Mitoxantrone and Glatiramer Acetate vs. Interferon Beta-1a in early active relapsing remitting Multiple Sclerosis

<http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2004-004903-39-GB>

7) Study of Montelukast on Gastrointestinal Tolerability in Patients With Relapsing Forms of Multiple Sclerosis Receiving Tecfidera

<http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT02410278>

8) [Impact of Natalizumab versus Fingolimod on Central Nervous System (CNS) Tissue Damage and Recovery in Active Relapsing-Remitting Multiple Sclerosis (RRMS) Subjects](http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2013-004622-29-IT)

<http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2013-004622-29-IT>

10) [A study to evaluate the effect of aspirin on flushing in patients with RRMS treated with Tecfidera](http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2013-001895-40-IE)

<http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2013-001895-40-IE>

9) [Study to investigate the ability of a blood-derived score to select patients with relapsing multiple sclerosis who benefit from treatment with human immune globulin](http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2012-005086-12-AT)

<http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2012-005086-12-AT>

10) [MS Study Evaluating Safety and Efficacy of Two Doses of Fingolimod Versus Copaxone](http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT01633112)

<http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT01633112>

11) A Study of Ocrelizumab in Comparison With Interferon Beta-1a in Patients With Relapsing Multiple Sclerosis

<http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2010-020315-36-BE>

12) A 18-month, open-label, rater-blinded, randomized, multi-center, active-controlled, parallel-group pilot study to assess efficacy and safety of fingolimod (Gilenya) in comparison to interferon beta-1b in treating the cognitive symptoms associated to relapsing-remitting multiple sclerosis and to assess possible relationship of these effects to regional brain atrophy

<http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2010-023023-19-IT>

13) A Study of Ocrelizumab in Comparison With Interferon Beta-1a in Patients With Relapsing Multiple Sclerosis

<http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2010-020337-99-GB>

## Supplementary material 11 Trial description, data extraction and Risk of Bias tables for the included trials

**Notes on the following tables:**

* Unless otherwise stated, the baseline characteristics described are those of all participants in the study
* Unless otherwise stated, the statistics presented for age and Expanded Disability Status Scale (EDSS) are means (+/-standard deviation)
* The following tables are presented by alphabetic order of the medicine considered as the intervention of interest.
* List of abbreviations used in tables:

IV= intravenous;

IM= intra muscular

SC= subcutaneous;

mg = milligram

mcg=micrograms

q.d.= once daily

q.w.= once weekly

t.i.w.= three times weekly

### Alemtuzumab

#### CAMMS223-study 2008, CAMMS223 Trial Investigators (Coles et al 2008), included (incl.) in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT00050778 | |
| **Study setting** | Rater-blinded, randomized controlled trial in 49 centres in Europe and US | |
| **Participants** | *Eligibility criteria*: Diagnosis of RRMS (McDonald criteria) with an onset of symptoms no more than 36 months before the time of screening, EDSS = 0 to 3.0; had one or more enhancing lesions on MRI; with ≥ 2 relapses during the previous 2 years.  *Key exclusion criteria*: Previous disease-modifying treatment; presence of serum antithyrotropin-receptor antibodies.  *Baseline characteristics*: Age 32+/-8; 64% female; EDSS 2,0+/-0.8 | |
| **Intervention group** | Annual alemtuzumab:  - Alemtuzumab 12 mg IV q.d., 5 consecutive days at 1st month, 3 consecutive days at months 12 and 24 (n = 113)  - Alemtuzumab 24 mg IV q.d. (n = 110) | |
| **Comparison group** | Interferon beta-1a 44 mcg SC t.i.w. (n = 111) | |
| **Outcome** | *Primary endpoints*: Sustained accumulation of disability and rate of relapse.  *Secondary endpoints*: Proportion of patients with relapse-free MS, different MRI outcomes.  Definitions used for endpoints: *Relapses*: New or worsening symptoms with an objective change in neurologic examination attributable to MS that lasted 48 hours, that were present at normal body temperature, and that were preceded by at least 30 days of clinical stability.  *Sustained accumulation of disability*: An increase of at least 1.5 points for patients with baseline score of 0, and at least 1.0 point for patients with a baseline score of 1.0 or more; all scores were confirmed twice during a 6-month period. | |
| **Follow-up** | 3 years | |
| **Treatment history** | Treatment-naive (based on inclusion criteria) | |
| **Comments** | In September 2005, alemtuzumab therapy was suspended after immune thrombocytopenic purpura developed in three patients, one of whom died. Treatment with interferon beta-1a continued throughout the study. | |
| **Critical appraisal** | | |
| **Randomization** | | Adequate |
| **Allocation concealment** | | Insufficient reporting |
| **Double-blinding** | | No (rater-blinded) |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 25% |
| **ITT Analysis** | | Yes |
| **Funding** | | Manufacturer |

#### CARE (Comparison of Alemtuzumab and Rebif Effi cacy in Multiple Sclerosis) MS I- study 2012, Cohen et al. (2012), in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT00530348 | |
| **Study setting** | A rater-blinded, randomized controlled trial in 101 centres in 16 countries including Europe, Canada, and US. | |
| **Participants** | *Eligibility criteria*: Age = 18 years to 50 years, diagnosis of RRMS (McDonald criteria) with disease duration up to 5 years, EDSS = 0 to 3.0; had cranial abnormalities on MRI attributable to MS; with ≥ 2 relapses during the previous 2 years.  *Key exclusion criteria*: Progressive disease course, previous MS disease therapy (apart from corticosteroids), previous immunosuppressive; investigational or monoclonal antibody therapy, clinically significant autoimmunity other than MS.  *Baseline characteristics:* Age 33+/-8; 65% female; EDSS 2.0+/-0.8 | |
| **Intervention group** | Alemtuzumab 12 mg IV q.d., 5 consecutive days at month 0, 3 consecutive days at month 12 (n = 386) | |
| **Comparison group** | Interferon beta-1a 44 mcg SC t.i.w. (n = 195) | |
| **Outcome** | *Primary endpoints*: Relapse rate and time to 6 months sustained accumulation of disability.  *Secondary endpoints*: Proportion of patients with relapse-free, change in EDSS, change in MSFC, different MRI outcomes.  Definitions used for endpoints: *Relapses*: New or worsening neurologic symptoms attributable to MS, lasting at least 48 hours, with pyrexia, after at least 30 days of clinical stability, with an objective change on neurological examination assessed by a masked rater.  *Sustained accumulation of disability*: An increase from baseline of at least one EDSS point (or ≥ 1.5 points if baseline EDSS score was 0) confirmed over 6 months. | |
| **Follow-up** | 2 years | |
| **Treatment history** | Treatment-naive (based on inclusion criteria). | |
| **Critical appraisal** | | |
| **Randomization** | | Adequate |
| **Allocation concealment** | | Adequate |
| **Double-blinding** | | No (rater-blinded) |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 9% |
| **ITT Analysis** | | Yes |
| **Funding** | | Manufacturer |

#### CARE (Comparison of Alemtuzu mab and Rebif Effi cacy in Multiple Sclerosis)-MS II study 2012, Coles et al. (2012), in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT00548405 | |
| **Study setting** | Rater-blinded, randomized controlled trial. 194 academic medical centres and clinical practices in 23 countries including Europe, Canada, and US. | |
| **Participants** | *Eligibility criteria*: Age = 18 years to 50 years, diagnosis of RRMS (McDonald criteria) with disease duration up to 5 years, EDSS = 0 to 5.0; had cranial and spinal MRI lesions; with ≥ 2 relapses during the previous 2 years and at least one in the previous year.  *Key exclusion criteria*: Progressive forms of MS, previous cytotoxic drug use or investigational therapy, treatment within the previous 6 months with natalizumab, methotrexate, azathioprine or cyclosporine, and a history of clinically significant autoimmunity other than MS.  *Baseline characteristics:* Age: 35 +/-8, 67 female, EDSS: 2.7 +/-1.2 | |
| **Intervention group** | Alemtuzumab 12 mg IV q.d., 5 consecutive days at month 0, 3 consecutive days at month 12 (n=436)  Alemtuzumab 24 mg IV q.d., 5 consecutive days at month 0, 3 consecutive days at month 12 (n=173) | |
| **Comparison group** | Interferon beta 1a 44 mcg SC t.i.w. (n=231) | |
| **Outcome** | *Primary endpoints*: Relapse rate and time to 6 months sustained accumulation of disability.  *Secondary endpoints*: Proportion of patients with relapse-free, change in EDSS, change in MSFC, different MRI outcomes.  Definitions used for endpoints: *Relapses*: New or worsening neurologic symptoms attributable to MS, lasting at least 48 hours, without pyrexia, after at least 30 days of clinical stability, with an objective change on neurological examination.  *Sustained accumulation of disability*: An increase from baseline of at least one EDSS point (or ≥ 1.5 points if baseline EDSS score was 0) confirmed over 6 months. | |
| **Follow-up** | 2 years | |
| **Treatment history** | Treatment-experienced (based on inclusion criteria). | |
| **Comments** | The 24 mg per day group was discontinued to aid recruitment, but data are included for safety assessments | |
| **Critical appraisal** | | |
| **Randomization** | | Adequate |
| **Allocation concealment** | | Adequate |
| **Double-blinding** | | No (rater blinded) |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 15% |
| **ITT Analysis** | | Yes |
| **Funding** | | Manufacturer |

### Dimetyl fumarate

#### DEFINE (Determination of the Efficacy and Safety of Oral Fumarate in Relapsing–Remitting MS) study, Gold et al. (2012), in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT00420212 | |
| **Study setting** | Randomized, double-blind, placebo controlled trial. 198 sites in 28 countries including Europe, Canada, and US | |
| **Participants** | *Eligibility criteria:* Age = 18 years to 55 years, diagnosis of RRMS (McDonald criteria), EDSS = 0 to 5.0; ≥1 clinically documented relapse within 12 months before randomization, or ≥ 1 gadolinium-enhancing lesion within 6 weeks before randomization  *Key exclusion criteria:* Progressive forms of MS, another major disease that would preclude participation in the clinical trial, abnormal results on the pre-specified laboratory tests, or recent exposure to contraindicated medications  *Baseline characteristics:* Age: 38+/-9 years; 74% female; EDSS 2,4+/-1,2 | |
| **Intervention group** | Dimethyl fumarate 240 mg oral twice daily (480 mg/day) (n = 410) Dimethyl fumarate 240 mg oral 3 times daily (720 mg/day) (n = 416) | |
| **Comparison group** | Placebo (n = 408) | |
| **Outcome** | *Primary endpoint*: Patients’ proportion who had a relapse by 2 years  *Secondary endpoints*: Different MRI outcomes at 2 years, annualized relapse rate, time to progression disability.  Definitions used for endpoints: *Relapses*: New or recurrent neurologic symptoms, not associated with fever or infection, that lasted at least 24 hours and that were accompanied by new objective neurologic findings according to neurologist's evaluation.  *Disability progression*: At least a 1.0-point increase on the EDSS in patients with a baseline score of 1.0 or higher or at least a 1.5-point increase in patients with a baseline score of 0, with the increased score sustained for at least 12 weeks. | |
| **Follow-up** | 2 years | |
| **Treatment history** | Mixed (based on baseline characteristics) | |
| **Comments** | Patients could switch to an approved alternative MS therapy if they had completed 48 weeks of blinded treatment, and had at least 1 confirmed relapse after 24 weeks, or at any time if they had experienced disability progression sustained for 12 weeks. | |
| **Critical appraisal** | | |
| **Randomization** | | Adequate |
| **Allocation concealment** | | Adequate |
| **Double-blinding** | | Yes |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 23% |
| **ITT Analysis** | | Yes |
| **Funding** | | Manufacturer (Biogen) |

CONFIRM (Comparator and an Oral Fumarate in Relapsing–Remitting Multiple Sclerosis) study 2012, Fox et al., (2012), in Tran et al***. (2013)***

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT00451451 | |
| **Study setting** | Rater-blinded, randomized controlled trial. in 200 research sites in 28 countries including Europe and North America | |
| **Participants** | *Eligibility criteria:* RRMS (McDonald criteria), age 18 to 55 years, EDSS 0 to 5 and at least one clinically documented relapse in the previous 12 months or at least one gadolinium-enhancing lesion 0 to 6 weeks before randomization.  *Key exclusion criteria:* Progressive forms of multiple sclerosis,11 other clinically significant illness, prespecified laboratory abnormalities, and prior exposure to glatiramer acetate or contraindicated medications  *Baseline characteristics:* Age: 37 +/-9, 70% female, EDSS score: 2.6 +/-1.2 | |
| **Intervention group** | Dimethyl fumarate 240 mg b.i.d, (n=359)  Dimethyl fumarate 240 mg three times daily (n=345), subcutaneous daily injections of 20 mg of glatiramer acetate for 96 weeks (n=350) | |
| **Comparison group** | Placebo (n=363) | |
| **Outcome** | *Primary endpoint*: Annualized relapse rate at 2 years.  *Secondary endpoints*: Different MRI outcomes at 2 years, disability progression.  *Tertiary endpoints*: Relative benefits and risks of BG-12 or glatiramer acetate versus placebo and the number of gadolinium-enhancing lesions at 2 years.  Definitions used for endpoints: *Relapses*: New or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, accompanied by new objective neurologic findings, and separated from the onset of other confirmed relapses by at least 30 days.  *Disability progression*: An increase in the EDSS score of at least 1.0 point in patients with a baseline score of 1.0 or more or an increase of at least 1.5 points in patients with a baseline score of 0, confirmed at least 12 weeks later. | |
| **Follow-up** | 2 years | |
| **Treatment history** | Mixed (based on reported baseline characteristics) | |
| **Critical appraisal** | | |
| **Randomization** | | Adequate |
| **Allocation concealement** | | Adequate |
| **Double-blinding** | | No |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 21% |
| **ITT Analysis** | | Yes |
| **Funding** | | Manufacturer (Biogen Idec) |

### Fingolimod

#### FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis) study, Kappos et al. (2010), in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT00289978 | |
| **Study setting** | Double-blind, randomized, placebo-controlled trial multi-centre in Australia, Canada, Europe, and South Africa (138 centers in 22 countries) | |
| **Participants** | *Eligibility criteria:* Age = 18 years to 55 years, diagnosis of RRMS (McDonald criteria), EDSS = 0 to 5.5; ≥ 1 relapse in the previous year or ≥ 2 relapses in the previous 2 years.  *Key exclusion criteria:* Relapse or corticosteroid treatment within 30 days before randomization, active infection, macular edema, diabetes mellitus, immune suppression (drug- or disease-induced), or clinically significant systemic disease.  *Baseline characteristics:* Age 37+/-9; 70% female; EDSS 2,4+/-1,4 | |
| **Intervention group** | Fingolimod oral 0.5 mg q.d. (n = 425)  Fingolimod oral 1,25 mg q.d. (n = 429) | |
| **Comparison group** | Placebo (n = 418) | |
| **Outcome** | *Primary endpoint*: Annualized relapse rate.  *Secondary endpoints*: Disability progression, time to a first relapse, EDSS change, MSFC change, different MRI outcomes.  Definitions used for endpoints: *Relapses*: A confirmed relapse constituted symptoms that must have been accompanied by an increase of at least half a point in the EDSS score, of 1 point in each of two EDSS functional system scores, or of 2 points in one EDSS functional system score (excluding scores for the bowel-bladder or cerebral functional systems).  *Disability progression*: An increase of 1 point in the EDSS score (or half a point if the baseline EDSS score was equal to 5.5), confirmed after 3 months, with an absence of relapse at the time of assessment and with all EDSS scores measured during that time meeting the criteria for disability progression. | |
| **Follow-up** | 2 years | |
| **Treatment history** | Mixed (based on reported baseline characteristics) | |
| **Critical appraisal** | | |
| **Randomization** | | Adequate |
| **Allocation concealment** | | Adequate |
| **Double-blinding** | | Yes |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 19% |
| **ITT Analysis** | | Yes |
| **Funding** | | Manufacturer |

#### TRANSFORMS (Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing–Remitting Multiple Sclerosis) study; Cohen et al. (2010), in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT00340834 | |
| **Study setting** | Double-blind, randomized controlled trial. 172 centres in 18 countries including Canada, Australia, Europe, and US. | |
| **Participants** | *Eligibility criteria:* Age = 18 years to 55 years; diagnosis of RRMS (McDonald criteria), EDSS = 0 to 5.5; had ≥ 1 relapse during the previous year or ≥ 2 relapses during the previous 2 years.  *Key exclusion criteria:* Documented relapse or corticosteroid treatment within 30 days before randomization; active infection, macular edema, immunosuppression, and clinically significant coexisting systemic disease.  *Baseline characteristics:* Age: 36+/-9; 67% female; EDSS: 2.2 +/-1.3 | |
| **Intervention group** | Fingolimod oral 0.5 mg q.d. (n=431)  Fingolimod oral 1.25 mg q.d. (n=426) | |
| **Comparison group** | Interferon beta-1a 30 mcg IM q.w. (n=435) | |
| **Outcome** | *Primary endpoint*: Annualized relapse rate.  *Secondary endpoints*: Number of new or enlarged T2-hyperintense lesions, time to confirmed disability progression  Definitions used for endpoints: *Relapses*: New, worsening, or recurrent neurologic symptoms that occurred at least 30 days after the onset of preceding relapse, that lasted at least 24 hours without fever or infection.  *Disability progression*: A one-point increase in the EDSS score (or a half-point increase for patients with a baseline score ≥ 5.5) that was confirmed 3 months later in the absence of relapse. | |
| **Follow-up** | 1 year | |
| **Treatment history** | Mixed (based on reported baseline characteristics) | |
| **Critical appraisal** | | |
| **Randomization** | | Adequate |
| **Allocation concealment** | | Adequate |
| **Double-blinding** | | Yes |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 11% |
| **ITT Analysis** | | Yes |
| **Funding** | | Manufacturer |

#### Saida et al. (2012), included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT00537082 | |
| **Study setting** | Double-blind, randomized controlled trial. Multicentre in Japan | |
| **Participants** | *Eligibility criteria*: Age = 18 years to 60 years, diagnosis of RRMS (McDonald criteria), EDSS = 0 to 6.0; had ≥ 1 relapse in the previous year or ≥ 2 relapses in the previous 2 years; ≥ 1 gadolinium-enhancing lesion within 30 days before study commencement.  *Key exclusion criteria*: Primary-progressive MS; relapse or corticosteroid treatment within 30 days before randomization; malignancy, macular edema, diabetes mellitus, active infection, immunosuppression, or significant systemic disease; received cladribine, cyclophosphamide, mitoxantrone, or other immunosuppressive or immunoglobulin medication in the six months before randomization, or had plasmapheresis immunoadsorption or IFN beta therapy in the three months before randomization.  *Baseline characteristics:* Age: 35 +/-9; 69% female; EDSS: 2.1 +/- 1.8 | |
| **Intervention group** | Fingolimod oral 0.5 mg q.d. (n=57)  Fingolimod oral 1.25 mg q.d. (n=57) | |
| **Comparison group** | Placebo (n=57) | |
| **Outcome** | *Primary endpoint*: Percentage of patients free from gadolinium enhanced lesions at 3 and 6 months.  *Secondary endpoints*: Percentage of patients free from relapse over 6 months, annualized relapse rate, and other MRI outcomes.  Definitions not reported | |
| **Follow-up** | 6 months | |
| **Treatment history** | Unclear (inadequate information to characterise) | |
| **Critical appraisal** | | |
| **Randomization** | | Insufficient reporting |
| **Allocation concealment** | | Not reporting |
| **Double-blinding** | | Yes |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 14% |
| **ITT Analysis** | | No |
| **Funding** | | Manufacturer |

#### FREEDOMS II- study, Calabresi et al. (2014) ), not included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT00355134 | |
| **Study setting** | Double-blind, randomised controlled study. In 117 academic and tertiary referral centres in 8 countries, most patients from USA | |
| **Participants** | *Eligibility criteria:* diagnosed with relapsing-remitting multiple sclerosis according to the 2005 revised McDonald criteria, aged 18–55 years, one or more confirmed relapses during the preceding year (or two or more confirmed relapses during the previous 2 years), EDSS score of 0–5.5, and had no relapse or steroid treatment within 30 days before randomisation. interferon β or glatiramer acetate therapy was stopped at least 3 months before randomisation and natalizumab treatment at least 6 months before randomisation.  *Key exclusion criteria:* clinically significant systemic disease or immune suppression, active infection or macular oedema, diabetes mellitus, or a history of malignancy, and patients with specific cardiac, pulmonary, or hepatic disorders.  Baseline characteristics in placebo group: Age: 40+/-8; 81% female; EDSS: 2.4 +/- 1.3. | |
| **Intervention group** | Fingolimod 0.5 mg oral q.d. (n=358)  Fingolimod 1.25 mg oral q.d. (n=370)  *Note:* The 1.25 mg dose stopped due to absence of clear added benefits and a higher safety events risk (infections,macular oedema). Patients were switched to the 0.5 mg dose in a blinded manner | |
| **Comparison group** | Placebo (n=355) | |
| **Outcome** | *Primary endpoints:* Annualised relapse rates  *Secondary endpoints:* Percent brain-volume change , the time to first relapse and proportion of relapsefree patients; time to disability progression confirmed at6 months, as measured by EDSS; change from baseline to the end of study on the MSFC score; and effect on MRI.  Definitions used for endpoints: *Relapse:* confirmed when accompanied by an increase of at least half a step (0・5) on the EDSS, an increase of 1 point on two different functional systems of the EDSS, or 2 points on one of the functional systems (excluding bowel, bladder, or cerebral functional systems).  *Disability progression:* 1 point EDSS change [0・5 point if baseline EDSS was >5・0]) confirmed at 3 months for up to 24 months. | |
| **Follow-up** | 2 years | |
| **Treatment history** | Unclear (inadequate information to characterise) | |
| **Risk of bias** | | |
| **Random sequence generation** | | Adequate |
| **Allocation concealment** | | Adequate |
| **Blinding of participant and personnel** | | Adequate |
| **Blinding of outcome assessment** | | Adequate |
| **Incomplete outcome data** | | Intention-to-treat analysis  Withdrawals: 28% |
| **Selective reporting** | | None detected |
| **Other sources of bias** | | Funding: Manufacturer |

### Glatiramer acetate

#### Johnson et al., (1995 ), included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | Not reported | |
| **Study setting** | Double-blind, randomized, placebo-controlled trial. 11 centres in the US | |
| **Participants** | *Eligibility criteria:* RRMS (Poser-criteria), age 18 to 45 years, EDSS = 0 to 5.0; had ≥ 2 clinically documented relapses in the 2 years before entry; onset of the first relapse at least 1 year before randomization; and a period of neurologic stability and freedom from corticosteroid therapy of at least 30 days prior to entry.  *Key exclusion criteria:* Received Glatiramer acetate 1 or previous immunosuppressive therapy with cytotoxic chemotherapy (azathioprine, cyclophosphamide, or cyclosporine) or lymphoid irradiation; pregnancy or lactation; insulin-dependent diabetes mellitus, positive HIV or HTL V-I serology, evidence of Lyme disease, or required use of aspirin or chronic nonsteroidal antiinflammatory drugs during the course of the trial.  *Baseline characteristics:* Age: 34+/-6; 73% female; EDSS 2.6 +/-1.3 | |
| **Intervention group** | Glatiramer acetate 20 mg SC q.d (n =125) | |
| **Comparison group** | Placebo (n=126) | |
| **Outcome** | *Primary endpoints*: Relapse rate over 24 months, annualized relapse rate, number of relapse over 24 months.  *Secondary endpoints:* Proportion of relapse-free patients, median time to first relapse, number of relapse per patient, proportion of patients with a change in disability, EDSS change, proportion of progression-free patients, ambulation index.  Definitions used for endpoints: *Relapses*: The appearance or reappearance of one or more neurologic abnormalities persisting for at least 48 hours and immediately proceeded by a relatively stable or improving neurologic state of at least 30 days.  *Disability progression*: An increase of at least one full step on the EDSS that persisted of at least 3 months. | |
| **Follow-up** | 2 years | |
| **Treatment history** | Treatment-naive (based on exclusion criteria, year of study, and clinical expert input). | |
| **Critical appraisal** | | |
| **Randomization** | | Insufficient reporting |
| **Allocation concealment** | | Not reporting |
| **Double-blinding** | | Yes |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 14% |
| **ITT Analysis** | | Yes |
| **Funding** | | Manufacturer, public |

#### Comi et al., (2001), included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | Not reported | |
| **Study setting** | Double-blind, randomized controlled study. 29 centres in 6 European countries and Canada. | |
| **Participants** | *Eligibility criteria:* Age = 18 years to 50 years, with relapse-remitting course, a diagnosis of MS for at least 1 year, EDSS = 0 to 5.0; ≥1 documented relapse in the preceding 2 years, ≥ 1 enhancing lesion on screening brain MRI.  *Key exclusion criteria:* previous use of glatiramer acetate, oral myelin, lymphoid irradiation, the use of immunosuppressant or cytotoxic agents in the past 2 years, or the use of azathioprine, cyclosporine, interferons, deoxyspergualine, or chronic corticosteroids during the previous 6 months.  *Baseline characteristics in placebo group:* Age: 34.0+/-8; % female not reported; EDSS: 2,4+/-1.2 | |
| **Intervention group** | Glatiramer acetate 20 mg SC q.d. (n=119) | |
| **Comparison group** | Placebo (n=120) | |
| **Outcome** | *Primary endpoint*: Total number of enhancing lesions.  *Secondary endpoints*: Other different MRI outcomes.  *Tertiary endpoints*: Relapse rate, percentage of patients with relapse-free, steroid courses, relapse-related hospitalizations.  Definitions used for endpoints: *Relapses*: The appearance of one or more new neurological symptoms, or the reappearance of one or more previously experienced ones. An event was counted as a relapse only when the patient’s symptoms were accompanied by objective changes in the neurological examination corresponding to an increase of at least 0.5 points on the EDSS, or one grade in the score of the two or more functional systems, or two grades in one functional system. | |
| **Follow-up** | 9 months | |
| **Treatment history** | Unclear (inadequate information to characterize) | |
| **Critical appraisal** | | |
| **Randomization** | | Adequate |
| **Allocation concealment** | | Adequate |
| **Double-blinding** | | Yes |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 6% |
| **ITT Analysis** | | Yes |
| **Funding** | | Manufacturer |

#### REGARD (REbif vs Glatiramer Acetate in Relapsing MS Disease) study 2008, Mikol et al., (2008), in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT00078338 | |
| **Study setting** | Randomized comparative study. Open-label, rater-masked. 81 centres in 14 countries (e.g. Canada, South America, and Europe) | |
| **Participants** | *Eligibility criteria*: Adult RRMS patients (McDonald criteria), EDSS = 0 to 5.5; had ≥ 1 relapse in the preceding 12 months, and clinically stable or neurologically improving during the 4 weeks before randomization.  *Key exclusion criteria*: Pregnancy or breastfeeding; treatment with steroids or adrenocorticotropic hormone with the previous 4 weeks; previous treatment with interferon beta, glatiramer acetate, or cladribine; total lymphoid irradiation; plasma exchange within the previous 3 months; intravenous gamma-globulin use within the previous 6 months; cytokine or anti-cytokine therapy within the previous 3 months; or immunosuppressant use within the past 12 months.  *Baseline characteristics:* Age: 37+/-10; 71% female; EDSS: 2.3+/-1.3 | |
| **Intervention group** | Glatiramer acetate 20 mg SC q.d. (n=378) | |
| **Comparison group** | Interferon beta-1a 44 mcg SC t.i.w. (n=386) | |
| **Outcome** | *Primary endpoint*: Time to first relapse over 96 weeks.  *Secondary endpoints*: Mean number T2 active lesions, mean number gadolinium-enhancing lesions, change in T2 lesion volume.  *Tertiary endpoint*: Other MRI outcomes, relapse outcomes, disability progression.  Definitions used for endpoints: *Relapses*: New or worsening neurological symptoms, without fever, that lasted for 48 hours or more and accompanied by a change in the Kurtzke Functional Systems Scores.  *Disability progression*: Disability progression at the 6-month follow-up visit was confirmed, as follows — if the EDSS score at the baseline was 0, then a change of 1.5 points or more was required; if the EDSS was 0.5 - 4.5 at baseline, then a change of 1.0 point or more was required; and if the EDSS at baseline was 5 points or more, then the change required was 0.5 points or more. | |
| **Follow-up** | 96 weeks | |
| **Treatment history** | Treatment-naive (based on inclusion criteria, year of study, and clinical expert input). | |
| **Critical appraisal** | | |
| **Randomization** | | Adequate |
| **Allocation concealment** | | Adequate |
| **Double-blinding** | | Yes |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 18% |
| **ITT Analysis** | | Yes |
| **Funding** | | Manufacturer |

#### BECOME (Betaseron vs Copaxone in Multiple Sclerosis with Triple-Dose Gadolinium and 3-Tesla MRI Endpoints) study 2009, Cadavid et al.(2009), included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT00176592 | |
| **Study setting** | Rater-blinded, randomized controlled trial. In one centre in the US. | |
| **Participants** | *Eligibility criteria:* Age = 18 years to 55 years; treatment-naïve patients with RRMS (79%) or CIS (21%) suggestive of MS.  Exclusion criteria: Not reported.  *Baseline characteristics: in interferon beta-1b* *group:* mean (range) age 36(18-49); 75% female; EDSS median(range) 2,0 (0-5). | |
| **Intervention group** | Glatiramer acetate 20 mg SC q.d. (n = 39) | |
| **Comparison group** | Interferon beta-1b 250 mcg SC every other day (n = 36) | |
| **Outcome** | *Primary endpoints:* Different MRI outcomes at 1 and 2 years. Confirmed relapse occurrences (annualized relapse rate, percent relapse-free).  Definitions used for: *Relapses*: All new or worsening symptoms lasting ≥ 24 hours and not explained by fever or infection that were confirmed by a blinded examining neurologist using worsening scores on SNRS or EDSS. : required for relapse confirmation: 1) increase in total EDSS by \_0.5 point; 2) increase in the EDSS score for one system \_2 points; 3) increase in the score of 2 or more EDSS systems \_1 point; | |
| **Follow-up** | 2 years | |
| **Treatment history** | Treatment-naive (based on reported baseline characteristics). | |
| **Critical appraisal** | | |
| **Randomization** | | Insufficient reporting |
| **Allocation concealment** | | Not reported |
| **Double-blinding** | | No (but rater blinded) |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 15% |
| **ITT Analysis** | | Yes |
| **Funding** | | Manufacturer |

#### BEYOND (Betaferon Effi cacy Yielding Outcomes of a New Dose) study 2009, O’Connor et al. (2009), included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT00099502 | |
| **Study setting** | A rater-blinded, randomized controlled trial in 198 centres in 26 countries worldwide. | |
| **Participants** | *Eligibility criteria*: Age = 18 years to 55 years, diagnosis of RRMS (McDonald criteria), EDSS = 0 to 5.0; with >=1 relapse in the year before entry into the study.  *Key exclusion criteria*: Those who had signs or symptoms of other diseases not MS; progressive forms of MS; heart disease; treatment-experienced or participated in the previous trials of drug for MS; history of severe depression; alcohol or drug misuse; suicide attempts; serious or acute live, renal, or bone marrow dysfunction; monoclonal gammaglobulinopathy, or uncontrolled epilepsy; contraindication or allergy to the drug used in the study; unable to have MRI.  *Baseline characteristics in glatiramer acetate group:* median (range) age 35 (27-43); 68% female; EDSS median (range) 2 (1,5-3,0) mean 2,28 | |
| **Intervention group** | Glatiramer acetate 20 mg SC q.d. (n = 448) | |
| **Comparison group** | Interferon beta-1b 250 mcg SC every other day (n = 897)  Interferon beta-1b 500 mcg SC every other day (n = 899) | |
| **Outcome** | *Primary endpoints*: Relapse-based outcomes at year 2 (ARR, days to first relapse, proportion relapse-free).  *Secondary endpoints*: Confirmed EDSS progression; MS-related admission to hospital, MS-related steroid course, different MRI outcomes.  Definitions used for endpoints: *Relapses*: New or recurrent neurological abnormalities that were separated by at least 30 days from the onset of the preceding event, lasted at least 24 hours, and occurred without fever or infection.  *EDSS progression*: Measured as a 1-point change in the score that was sustained for 3 months. | |
| **Follow-up** | 2 to 3,5 years | |
| **Treatment history** | Treatment-naive (based on inclusion criteria). | |
| **Critical appraisal** | | |
| **Randomization** | | Adequate |
| **Allocation concealment** | | Adequate |
| **Double-blinding** | | No [(rater-blinded), IFN doses double-blinded] |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 15% |
| **ITT Analysis** | | Unclear |
| **Funding** | | Manufacturer |

#### Calabrese et al., 2012 (2012), included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | Not reported | |
| **Study setting** | Rater-blinded, randomized controlled trial, single-centre in Italy | |
| **Participants** | *Eligibility criteria:* Age = 18 years to 55 years, diagnosis of RRMS (McDonald/Polman criteria), EDSS = 0 to 5.0  *Key exclusion criteria:* Those previously treated with immunosuppressive drugs.  *Baseline characteristics:* Age: 37+/-10 years; 70% female; EDSS 2,0+/-1,1 | |
| **Intervention group** | Glatiramer acetate 20 mg SC q.d. (n = 55) | |
| **Comparison group** | Interferon beta-1a 44 mcg SC t.i.w. (n = 55)  Interferon beta-1a 30 mcg IM q.w. (n = 55) | |
| **Outcome** | Different MRI outcomes.  Annualized relapse rate.  EDSS change.  Definition not stated | |
| **Follow-up** | 2 years | |
| **Treatment history** | Unclear (inadequate information to characteristics) | |
| **Comments** | The publication also includes a group of disease modifying treated patients, and disease modifying drug untreated controls | |
| **Critical appraisal** | | |
| **Randomization** | | Adequate |
| **Allocation concealment** | | Adequate |
| **Double-blinding** | | No (rater blinded) |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 15% |
| **ITT Analysis** | | No |
| **Funding** | | Manufacturer |

#### GALA (Glatiramer Acetate Low-frequency Administration) study, Khan et al., (2013), not included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | Not reported | |
| **Study setting** | A randomized, double-blind study was conducted in 142 sites in 17 countries, including the United States, Bulgaria, Croatia, Germany, Poland, Romania, and Ukraine | |
| **Participants** | *Eligibility criteria:* 18 to 55 years of age, Confirmed RRMS diagnosis (according to the revised McDonald criteria), had an Expanded Disability Status Scale (EDSS) score of <=5.5, and were relapse-free for >=30 days. Patients also were required to have >=1 documented relapse in the 12 months prior to screening, >=2 documented relapses in the 24 months prior to screening, or 1 documented relapse between 12 and 24 months prior to screening with at least 1 documented T1 gadolinium enhancing lesion in an MRI performed within 12 months of screening.  *Key exclusion criteria:* Several exclusions criteria based on previous and/or concurrent treatments.  *Baseline characteristics in placebo group:* 38+/-9 years; 68% female; EDSS 2.7+/-1.2 | |
| **Intervention group** | Glatiramer acetate sc 40mg (1ml) tiw (n=943) | |
| **Comparison group** | Placebo (n=461) | |
| **Outcome** | *Primary endpoint:* Annualised relapse rate  *Secondary outpoints:* MRI outcomes  Definition used for relapse: A Relapse was defined as the appearance of >=1 new neurological abnormalities or the reappearance of >=1 previously observed neurological abnormalities lasting at least 48 hours and preceded by an improving neurological state of at least 30 days from the onset of previous relapse. An event was counted as a relapse when the patient’s symptoms were accompanied by observed objective neurological changes consistent with an increase of >=0.5 points in the EDSS score compared with previous evaluation, or an increase of 1 grade in the actual score of >=2 or more of the 7 FSs; or an increase of 2 grades in the score of 1 FS, compared with the previous assessment. | |
| **Follow-up** | 12 months (placebo controlled) | |
| **Treatment history** | Mixed (based on exclusion criteria) | |
| **Risk of bias** | | |
| **Random sequence generation** | | Low risk |
| **Allocation concealment** | | Not described, but blinding is adequate. |
| **Blinding of participant and personnel** | | Low risk |
| **Blinding of outcome assessment** | | Low risk |
| **Incomplete outcome data** | | Low risk  Analysis performed as ITT |
| **Selective reporting** | | Not detected |
| **Other sources of bias** | | Funding: Manufacturer |

#### CombiRx study 2013. Lublin et al., (2013), included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT00211887 | |
| **Study setting** | A double-blind, randomized, controlled study. 68 sites, both private practice and academic, in the USA and Canada | |
| **Participants** | *Eligibility criteria:* Patients with a diagnosis of RRMS by Poser or McDonald cirteria, aged 18- 60, EDSS score of 0 to 5.5, at least 2 exacerbations in the prior 3 years, where 1 exacerbation could be an magnetic resonance imaging (MRI) change meeting the 2001 McDonald MRI criteria for dissemination in time  *Key exclusion criteria:* prior history of seizure activity  Prior use of either interferon or glatiramer acetate  *Baseline characteristics:* Age: 38.0 +/- 10, 72% female, EDSS score: 2.0 +/- 1.2 | |
| **Intervention group** | Interferon beta-1a 30µg IM q.d and glatiramer acetate (GA) 20mg q.d (n=499) (This group was outside our scope)  Glatiramer acetate 20mg q.d (n=259)  Interferon beta-1a 30µg IM q.w (n=250) | |
| **Comparison group** | Interventions were compared one with another | |
| **Outcome** | *Primary endpoint*: Annualized relapse rate.  *Secondary endpoints*: Disability progression (EDSS change or MSFC change), different MRI outcomes.  Definitions used for: *Relapses*: New or worsening neurologic symptoms that lasted at least 24 hours without fever or infection, preceded by 30 days of stability.  *Disability progression*: 1.0 increase in the EDSS from baseline, when baseline ≤ 5.0; or an increase of 0.5 from baseline, when baseline ≥ 5.5, sustained for 6 months (2 successive quarterly visits), as assessed by the blinded EDSS examiner and confirmed centrally. | |
| **Follow-up** | 3 years | |
| **Treatment history** | Treatment-naïve (based on exclusion criteria) | |
| **Critical appraisal** | | |
| **Randomization** | | Adequate |
| **Allocation concealement** | | Adequate |
| **Double-blinding** | | Yes |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 18% |
| **ITT analysis** | | Yes |
| **Funding** | | Public, study agents and placebo provided by manufacturer |

### Interferon beta 1a (im)

#### MSCRG (Multiple Sclerosis Collaborative Research Group) study 1996, Jacobs et al.(1996), included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | Not reported | |
| **Study setting** | Double-blind randomized controlled trial. 4 centres in the US | |
| **Participants** | *Eligibility criteria*: Age = 18 years to 55 years, diagnosis of relapsing MS (complete and incomplete remissions) (Poser et al.), EDSS = 1 to 3.5; had ≥ 2 relapses in previous 3 years, no exacerbations for at least 2 months at study entry  *Key exclusion criteria*: Prior immunosuppressant or IFN therapy; adrenocorticotropic hormone or corticosteroid treatment with 2 months of entry; pregnancy or nursing; unwillingness to practice contraception; presence of chronic-progressive MS, or any disease other than MS compromising organ function.  *Baseline characteristics:* Age 37+/-7; 73% female; EDSS: 2.4+/-0.8 | |
| **Intervention group** | Interferon beta-l a 30 mcg IM q.w. (n=158) | |
| **Comparison group** | Placebo (n=143) | |
| **Outcome** | *Primary endpoint*: Time to onset of sustained worsening in disability.  *Secondary endpoints*: Proportion of patients with relapses, annualized relapse rate, different MRI outcomes  *Definitions used for endpoints: Relapses*: The appearance of new neurological symptoms or worsening of pre-existing neurological symptoms lasting at least 48 hours in a patient who had been neurologically stable or improving for the previous 30 days, accompanied by objective change on neurological examination.  *Disability progression*: Deterioration from baseline by at least 1.0 point on the EDSS persisting for at least 6 months. | |
| **Follow-up** | 2 years | |
| **Treatment history** | Treatment-naive (based on exclusion criteria, year of study, and clinical expert input). | |
| **Critical appraisal** | | |
| **Randomization** | | Adequate |
| **Allocation concealment** | | Adequate |
| **Double-blinding** | | Yes |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 8% |
| **ITT Analysis** | | Yes |
| **Funding** | | Public, manufacturer |

#### EVIDENCE (EVidence of Interferon Dose-response: European North American Comparative Efficacy) study 2002, Panitch et al.(2002), included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | Not reported | |
| **Study setting** | Rater-blinded, randomized, placebo-controlled trial in 56 centres in Europe, Canada, and US. | |
| **Participants** | *Eligibility criteria*: Age = 18 years to 55 years, IFN-naive patients with definite RRMS (Poser et al.), EDSS = 0 to 5.5; ≥ 2 exacerbations of MS in the prior 2 years.  *Key exclusion criteria:* use of defined treatments in previous periods.  *Baseline characteristics in-30 mcg IM q.w group:* Age 37,4 years (range 18-55), 74,6%female, EDSS median 2,0 mean 2,3 | |
| **Intervention group** | Interferon beta-1a 30 mcg IM q.w. (n = 338)  Interferon beta-1a 44 mcg SC t.i.w. (n = 339) | |
| **Comparison group** | These drugs were compared one with another | |
| **Outcome** | *Primary endpoint*: Proportion of patients who were relapse-free at 24 weeks.  *Secondary endpoints*: Relapse, disability, and MRI outcomes at 48 weeks.  Definitions used for endpoints: *Relapses*: The appearance of new symptoms or worsening of an old symptom, accompanied by an appropriate objective finding on neurologic examination by the blinded evaluator, lasting at least 24 hours in the absence of fever and preceded by at least 30 days of clinical stability or improvement.  *Disability*: Progression by one point on the EDSS scale confirmed at a visit 3 or 6 months later without an intervening EDSS value that would not meet the criteria for progression. | |
| **Follow-up** | 24 weeks (treatment for 24 weeks, follow-up until 48 weeks) | |
| **Treatment history** | Unclear (inadequate information to characterise) | |
| **Critical appraisal** | | |
| **Randomization** | | Adequate |
| **Allocation concealment** | | Adequate |
| **Double-blinding** | | No (rater-blinded) |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 4% |
| **ITT Analysis** | | Yes |
| **Funding** | | Manufacturer |

#### INCOMIN (INdependent COMparison of INterferons) study, Durelli et al. (2002), included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | Not reported | |
| **Study setting** | Open label, rater-masked, randomized controlled trial in 15 centres in Italy | |
| **Participants** | *Eligibility criteria*: Age = 18 years to 50 years, clinically definite RRMS (Poser et al.), EDSS = 1-3.5; had two clinically documented relapses during the preceding 2 years, and no relapse (and no corticosteroid treatment) for at least 30 days before the study entry.  *Key exclusion criteria*: Previous systemic treatment with IFN beta or treatment with other immunosuppressive or immunomodulatory drugs (except corticosteroids);  *Baseline characteristics:* Age 37+/-8; 65% female; EDSS 2,0+/-0,7 | |
| **Intervention group** | Interferon beta-1a 30 mcg IM q.w. (n = 92) | |
| **Comparison group** | Interferon beta-1b 250 mcg SC every other day (n = 96) | |
| **Outcome** | *Primary endpoint*: Proportions of patients free from relapses during 24 months.  *Secondary endpoints*: Annualized relapse rate, annualized treated relapse rate, proportion of patients free from sustained and confirmed progression from disability, EDSS score, time to sustained and confirmed progression in disability.  Definitions used for endpoints: *Relapses*: The occurrence of new neurological symptoms or worsening of an old one, with an objective change of at least one point in Kurtzke Functional System Scores, lasting at least 24 hours, without fever, and which followed a period of clinical stability or of improvement of at least 30 days.  *Disability progression*: An increase in EDSS of at least 1 point sustained for at least 6 months and confirmed at the end of follow-up. | |
| **Follow-up** | 2 years | |
| **Treatment history** | Treatment-naive (based on exclusion criteria). | |
| **Critical appraisal** | | |
| **Randomization** | | Adequate |
| **Allocation concealment** | | Adequate |
| **Double-blinding** | | No (rater-masked) |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 16% |
| **ITT Analysis** | | Yes |
| **Funding** | | Public |

#### Clanet et al., ( 2002 ), included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | Not reported | |
| **Study setting** | Randomized, double-blind, dose-comparison study. 38 centers in Europe | |
| **Participants** | *Eligibility criteria:* Age = 18 years to 55 years, with a relapsing form of MS (Poser et al.), EDSS = 2.0 to 5.5; had a clinical diagnosis of definite MS; with ≥ 2 relapses within 3 years before randomization.  *Key exclusion criteria*: Progressive forms of MS (defined as a continuous deterioration in neurologic function during the previous 6 months, without superimposed relapses during the previous 1 year); had a relapse within 2 months before randomization; pregnant or breastfeeding; with history of uncontrolled seizure, suicidal ideation, or severe depression; received treatment with IFN beta products within 3 months of randomization; investigational products for MS treatment or non-MS indications; chronic immunosuppressant therapy or chronic steroid therapy.  *Baseline characteristics:* Age; 37+/-8; 68% female; EDSS: 3.6+/- 1.0; | |
| **Intervention group** | Interferon beta-1a 30 mcg IM once weekly (n=402)  Interferon beta-1a 60 mcg IM once weekly N=(400) | |
| **Comparison group** | The two doses of Interferon beta-1a are compared one with another | |
| **Outcome** | *Primary endpoint*: Disability progression.  *Secondary endpoint*: Relapse rate, annualized IV steroid use, percent of patients with relapse-free, different MRI outcomes.  *Definitions* used for endpoints: *Relapses*: Not reported.  *Disability progression*: Time to a sustained increase of ≥ 1.0 point on the EDSS persisting for 6 months for subjects with baseline EDSS scores ≤ 4.5, or a 0.5 point increase for subjects with a baseline EDSS score ≥ 5.0. | |
| **Follow-up** | At least 3 years | |
| **Treatment history** | Unclear (inadequate information to characterise) | |
| **Critical appraisal** | | |
| **Randomization** | | Insufficient reporting |
| **Allocation concealment** | | Insufficient reporting |
| **Double-blinding** | | Yes |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 30% |
| **ITT Analysis** | | Yes |
| **Funding** | | Manufacturer |

#### Kappos et al., (2011), included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT00676715 | |
| **Study setting** | Randomised controlled study. 79 centres in 20 countries in North America, east-central Europe, Asia, western Europe, and Latin America. | |
| **Participants** | *Eligibility criteria*: Age = 18 years to 55 years, diagnosis of RRMS, EDSS = 1-6.0; had ≥ 2 relapses in previous 3 years.  *Key exclusion criteria*: SPMS or PPMS, disease duration more than 15 years in patients with EDSS of 2 or less; history or presence of other neurological systemic autoimmune disorders; treatment with rituximab or lymphocyte-depleting therapies; use of lymphocyte trafficking disorders within previous 24 weeks; use of beta interferons, glatiramer acetate, intravenous immunoglobulin, plasmapheresis, and immunosuppressive treatments within previous 12 weeks, use of systemic glucocorticoids within previous 4 weeks; or intolerance to IFN beta-1a.  Baseline characteristics in placebo group: Age in years: 38 +/9, 65% female, mean EDSS score (-/+ SD): 3.2 +/- 1.4 | |
| **Intervention group** | Ocrelizumab 600 mg IV day 1 and 15 (n=55, not our scope)  Ocrelizumab 600 mg IV day 1 and 15 (n=55, not our scope)  Interferon beta-1a 30 mcg IM q.d. (n=55) | |
| **Comparison group** | Placebo (n=54) | |
| **Outcome** | *Primary endpoint*: MRI outcomes.  *Secondary endpoints*: Annualized relapse rate, proportion of relapse-free patients.  Definitions used for endpoints: *Relapses*: The occurrence of new or worsening neurological symptoms attributable to MS, and immediately preceded by a stable or improving neurological state of at least 30 days.  *Disability progression*: An increase of 1 point or more from baseline EDSS score confirmed at the next scheduled examination 3 months after initial screening. | |
| **Follow-up** | 24 weeks  (up to 96 weeks, but after 24 weeks, comparator groups switched to ocrelizumab) | |
| **Treatment history** | Mixed (based on reported baseline characteristics) | |
| **Critical appraisal** | | |
| **Randomization** | | Insufficient reporting |
| **Allocation concealment** | | Not reporting |
| **Double-blinding** | | No |
| **Baseline characteristic similarity** | | No |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 6% |
| **ITT Analysis** | | Yes |
| **Funding** | | Manufacturer |

#### Mokhber et al., (2014), not included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | Protocol number: 84393-1 | |
| **Study setting** | Double blind randomized trial, single center in Iran | |
| **Participants** | *Eligibility criteria:* Eligible participants were all new cases of definite MS according to the revised McDonald criteria, which include magnetic resonance imaging, detailed neurological history and examination, and paraclinical laboratory tests of cerebrospinal fluid findings and visual-evoked potential  *Key exclusion criteria:* Patients were excluded if they had a history of substance abuse or prior treatment with any type of DMTs  *Baseline characteristics*: Age 29,+/-8; 65% female; EDSS: mean=2.02 | |
| **Intervention group** | Interferon beta-1a (Avonex ) 30 mcg once per week IM injection; (n=23)  Interferon beta-1a (Rebif) 44 mcg t.i.w. SC injection; (n=23)  Interferon beta-1a (Betaferon) 0.25 mg every other day SC injection (n=23) | |
| **Comparison group** | These drugs were compared one with another | |
| **Outcome** | *Primary endpoint:* Cognition status  *Secondary endpoint:* EDSS scale | |
| **Follow-up** | 1 year | |
| **Treatment history** | Treatment-naive | |
| **Risk of Bias** | | |
| **Random sequence generation** | | Adequate “The study neurologist (MRA) enrolled the participants and allocated the subjects using a computer-generated list of random numbers” |
| **Allocation concealment** | | Yes |
| **Blinding of participant and personnel** | | Assessors: yes  Participants: insufficient reporting |
| **Blinding of outcome assessment** | | Adequate |
| **Incomplete outcome data** | | 6% lost to follow-up  Modified analysis based on available data |
| **Selective reporting** | | None detected |
| **Other sources of bias** | | No conflict of interest declared. Funding seem to be public “The study was supported by the Vice Chancellor of Research at Mashhad University of Medical Sciences in Iran (Grant number:84393)” |

#### BRAVO (Benefit-Risk Assessment of AVonex and LaquinimOd ) study, Vollmer et al. (2014), not included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT00605215 | |
| **Study setting** | A randomized placebo-controlled phase III trial in 155 sites in 18 countries (including. USA and several European countries) | |
| **Participants** | *Eligibility criteria:* age 18–55 years, diagnosis of RRMS (revised McDonald criteria), and EDSS scores of 0–5.5. At least one relapse in the previous 12 months, two in the previous 24 months, or one in the previous 12–24 months, plus one gadolinium-enhancing (GdE) lesion in the previous 12 months.  *Key exclusion criteria:* progressive forms of MS; use of glatiramer acetate in the previous 2 months; and prior use of natalizumab, laquinimod, cladribine, or any interferon beta at any time.  *Baseline characteristics (in placebo group):* Age (median and 25-75 percentile) 37,5 (30,3-45,4); 71,3% female; EDSS (median and 25-75 percentile) 2.5 (1.5, 3.5) | |
| **Intervention group** | Laquinimod 0.6 mg capsule q.d. (n=434)[not our scope]  Interferon beta-1a IM 30 mcg once-weekly injection (n = 447) | |
| **Comparison group** | Placebo (matching laquinimod) (n = 450) | |
| **Outcome** | *Primary endpoints:* Annualized relapse rate (ARR)  *Secondary endpoints:* percent change in normalized brain volume from baseline to 24 months; changes in disability measured with EDSS. Disability (MSFC z-score at 24 months/early termination)  *Exploratory endpoints:* confirmed worsening of EDSS scores sustained for 6 months. MRI endpoints: the cumulative numbers at 12, 24 months of GdE lesions and of new or enlarging ([50 % larger than previous scan) T2 lesions  Definitions used for endpoints: *Relapse*= appearance of one or more new neurological abnormalities, or reappearance of one or more previously observed neurological abnormalities, in the absence of fever, persisting for >= 48 h, preceded by > 30 days of a stable or improving condition, and accompanied by at least one of the following: an increase of at least 0.5 point in EDSS score, an increase of one grade in the score of two of the seven functional systems (FS) on the EDSS, or an increase of two grades in one FS.  *Disability progression*: a 1.0 point EDSS increase in EDSS if baseline score 0-5.0, or a 0.5 if baseline score was 5.5, for 3 months. | |
| **Follow-up** | 2 years | |
| **Treatment history** | Mixed (based on exclusion criteria) | |
| **Risk of bias** | | |
| **Random sequence generation** | | Low risk |
| **Allocation concealment** | | Not described. (Assume low risk based on description of sequence generation and blinding) |
| **Blinding of participant and personnel** | | Not for our comparison |
| **Blinding of outcome assessment** | | Adequate |
| **Incomplete outcome data** | | Low risk |
| **Selective reporting** | | None detected |
| **Other sources of bias** | | Differences in mean T2 lesion volume and GdE lesions at baseline between laquinimod or IFNb-1a groups |

### Interferon beta 1a (sc)

#### PRISMS (Prevention of Relapses and Disability by Interferon \_beta 1a Subcutaneously in Multiple Sclerosis) study1998, in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | Not reported | |
| **Study setting** | Double-blind, randomized, controlled trial. 22 centres in 9 countries including Australia, Canada, and Europe. | |
| **Participants** | *Eligibility criteria*: Adult RRMS patients (Poser et al.), EDSS = 0 to 5.0; had ≥ 2 relapses in previous 2 years.  *Key exclusion criteria*: Previous systemic treatment with IFN, lymphoid irradiation, or cyclophosphamide, or with other immunomodulatory or immunosuppressive treatments in the preceding 12 months.  Baseline characteristics: Age: median (interquartile range) 35 (29-40); 69% female; EDSS:2.5+/-1.2 | |
| **Intervention group** | Interferon beta-1a 22 mcg SC t.i.w.(n=189)  Interferon beta-1a 44 mcg SC t.i.w. (n=184) | |
| **Comparison group** | Placebo (n=187) | |
| **Outcome** | *Primary endpoint*: Number of relapses.  *Secondary endpoints*: Times to first and second relapse, proportion of relapse-free patients, disability progression, ambulation index, need for steroid therapy and hospitalization, and disease activity under MRI and burden of disease.  Definitions used for endpoints: *Relapses*: The appearance of a new symptom or worsening of an old symptom over at least 24 hours that could be attributed to MS activity and was preceded by stability or improvement for at least 30 days.  *Disability progression*: An increase in EDSS of at least 1 point sustained over at least 3 months. | |
| **Follow-up** | 2 years | |
| **Treatment history** | Treatment-naive (based on exclusion criteria, year of study, and clinical expert input). | |
| **Critical appraisal** | | |
| **Randomization** | | Adequate |
| **Allocation concealment** | | Adequate |
| **Double-blinding** | | Yes |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 10% |
| **ITT Analysis** | | Yes |
| **Funding** | | Manufacturer |

#### IMPROVE (Investigating MRI Parameters with RebifimprOVEd formulation) study 2010, De Stefano et al.,(2010), included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT00441103 | |
| **Study setting** | Double-blind, randomized, placebo-controlled trial, multi-centre, multi-country in European countries. | |
| **Participants** | *Eligibility criteria*: Age = 18 years to 60 years, diagnosis of RRMS (McDonald criteria), EDSS = 0 to 5.5; active disease (≥ 1 clinical event and ≥ 1 gadolinium-enhancing MRI lesion) within the 6 months period before randomization.  *Exclusion criteria*: Not specified.  Baseline characteristics: Not reported | |
| **Intervention group** | Interferon beta-1a 44 mcg SC t.i.w. (n = 120) | |
| **Comparison group** | Placebo (n = 60) | |
| **Outcome** | *Primary endpoint*: Number of combined unique active MRI brain lesions at week 16.  *Secondary endpoints*: Number of combined unique active lesions/patient/scan, other MRI outcomes, relapse rate. | |
| **Follow-up** | 16 weeks | |
| **Treatment history** | Unclear (inadequate information to characterise) | |
| **Comments** | Double-blind phase:16 weeks. After that, patients received Interferon beta-1a, 44 mg sc tiw, for 24 weeks (rater-blind phase).  The analysis populations for the rater-blind period comprised patients who completed treatment during the double-blind period (Interferon beta-1a, n=12; placebo,n=57). | |
| **Critical appraisal** | | |
| **Randomization** | | Insufficient reporting |
| **Allocation concealment** | | Not reporting |
| **Double-blinding** | | Yes |
| **Baseline characteristic similarity** | | Not reporting |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | Not reporting |
| **ITT Analysis** | | Yes |
| **Funding** | | Manufacturer |

### Interferon beta 1b (sc)

#### IFNB-MS 1993, included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | Not reported | |
| **Study setting** | Randomized, placebo-controlled trial Multi-centre Canada and the US. | |
| **Participants** | *Eligibility criteria*: Age = 18 years to 50 years, diagnosis of RRMS (McDonald criteria), EDSS = 0 to 5.5; had ≥ 2 exacerbations during the previous 2 years; clinically stable for at least 30 days before entry and received no adrenocorticotrophic hormone or prednisone during this period.  *Key exclusion criteria*: Prior treatment with azathioprine or cyclophosphamide.  Baseline characteristics: Age 35+/-7; 70% female; EDSS 2,9+/-1,1 | |
| **Intervention group** | Interferon beta-1b 250 mcg SC every other day (n = 124)  Interferon beta-1b 50 mcg SC every other day (n=125) | |
| **Comparison group** | Placebo (n = 123) | |
| **Outcome** | *Primary endpoints*: Annualized relapse rate, proportion of relapse-free patients  *Secondary endpoints*: Time to first relapse, relapse duration and severity, change in EDSS, MRI outcomes.  Definitions used for endpoints: *Relapses*: The appearance of a new symptoms or worsening of an old symptom, attributable to MS; accompanied by an appropriate new neurologic abnormality; lasting at least 24 hours in the absence of fever; and preceded by stability or improvement for at least 30 days.  *Disability progression*: A patient was considered to have progression in disability when there was a persistent increase of 1 or more EDSS points confirmed on two consecutive evaluations separated by at least 3 months. | |
| **Follow-up** | 3 years | |
| **Treatment history** | Treatment-naive (based on year of study and clinical expert input). | |
| **Critical appraisal** | | |
| **Randomization** | | Insufficient reporting |
| **Allocation concealment** | | Not reporting |
| **Double-blinding** | | Yes |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 33% |
| **ITT Analysis** | | Yes |
| **Funding** | | Not reporting |

#### Etemadifar et al., (2006), included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | Not reported | |
| **Study setting** | Rater-blinded, randomized controlled trial, neurology outpatient clinics in Iran | |
| **Participants** | *Eligibility criteria*: Age = 15 years to 50 years, diagnosis of relapsing MS (Poser et al.), EDSS = 0 to 5.0; ≥ 2 relapses within the 2-year period to treatment initiation documented by a neurologist.  *Key exclusion criteria*: History of severe allergic or anaphylactic reaction to any IFN, or to other components of drug formulation; evidence of neurologic, psychiatric, cardiac, endocrinologic, hematologic, hepatic, renal, active malignancy, autoimmune diseases, or other chronic disease; history of uncontrolled seizure or suicidal ideation or severe depression; lactation and pregnancy.  Baseline characteristics: Age 29+/-7; 76% female; EDSS 2,0+/-0,9 | |
| **Intervention group** | Interferon beta-1b 250 mcg SC every other day (n = 30)  Interferon beta-1a 30 mcg IM q.w. (n = 30)  Interferon beta-1a 44 mcg SC t.i.w. (n = 30) | |
| **Comparison group** | These drugs were compared one with another | |
| **Outcome** | *Endpoints:* Number of relapses, proportion of relapse-free patients, EDSS scores  Definitions used for endpoints: *Relapses*: The appearance of a new neurologic symptom, or severe deterioration in a pre-existing symptom that lasted 24 hours causing the deterioration in the EDSS with 1 point. | |
| **Follow-up** | 2 years | |
| **Treatment history** | Unclear (inadequate information to characterise) | |
| **Critical appraisal** | | |
| **Randomization** | | Insufficient reporting |
| **Allocation concealment** | | Not reporting |
| **Double-blinding** | | No (rater-blinded) |
| **Baseline characteristic similarity** | | No |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 0% |
| **ITT Analysis** | | Yes |
| **Funding** | | Not reporting |

### Natalizumab

#### AFFIRM (Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis) study, Polman et al., (2006 ), in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT00027300 | |
| **Study setting** | Randomized, double-blind, placebo-controlled trial in 99 centres in Europe, North America, Australia, and New Zealand. | |
| **Participants** | *Eligibility criteria*: Age = 18 years to 50 years, diagnosis of RRMS (McDonald criteria), EDSS = 0 to 5.0; had MRI lesions with MS, with ≥1 medially documented relapse within 12 months before the study began.  *Key exclusion criteria*: relapse within 50 days before administration of the first dose of the study drug; treatment with specific named pharmaceuticals (MS related)  Baseline characteristics: Age 36+/-8 years; 70% female; EDSS 2,3+/-1,2 | |
| **Intervention group** | Natalizumab 300 mg IV every 4 weeks (n = 627) | |
| **Comparison group** | Placebo (n = 315) | |
| **Outcome** | *Primary endpoints*: Rate of clinical relapse at 1 year; cumulative probability of sustained progression of disability at 2 years.  *Secondary endpoints*: Different MRI outcomes at 1 and 2 years; proportion of relapse-free patients at 1 year; progression of disability at 2 years, measured by MSFC.  *Tertiary endpoints*: HRQoL was assessed by SF-36 (PCS and MCS) and Subject Global Assessment Visual Analogue Scale.  Definitions used for endpoints: *Relapses*: New or recurrent neurologic symptoms not associated with fever or infection that lasted for at least 24 hours and were accompanied by new neurologic signs found by the examining neurologist.  *Sustained progression of disability*: An increase of 1.0 or more on the EDSS from a baseline score of 1.0 or more or an increase of 1.5 or more from a baseline score of 0 that was sustained for 12 weeks (progression could not be confirmed during a relapse). | |
| **Follow-up** | 2 years | |
| **Treatment history** | Unclear (inadequate information to characterise) | |
| **Critical appraisal** | | |
| **Randomization** | | Adequate |
| **Allocation concealment** | | Adequate |
| **Double-blinding** | | Yes |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 9% |
| **ITT Analysis** | | Yes |
| **Funding** | | Manufacturer |

#### Gobbi et al. (2013), not included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT01144052 | |
| **Study setting** | Randomized controlled study, rater blinded. One centre, Switzerland. | |
| **Participants** | *Eligibility criteria*: Patients with RRMS (2005 McDonald’s criteria), aged between 18 and 60 years, who were on natalizumab (NTZ) and feared or were at significant risk for progressive multifocal leucoencephalopathy (PML) [Risk for PML was defined significant in case of NTZ treatment duration equal to or greater than 12mMonths]. Patients had to be free of disease activity while  on NTZ (free from relapses and disability progression for at least 6 months and no gadolinium enhancing lesions on baseline MRI  *Key exclusion criteria:* relevant neurologic, internistic or psychiatric disorders; treatment with steroids less than 1 month before study entry; treatment with any immunomodulators or immune-suppressors other than steroids, ACTH\* or NTZ in the past year.  *Baseline characterics in NTZ group*: Age median (range): 43 (20-60), 60% female, EDSS score (median (range)): 3 (1.5-3.5) | |
| **Intervention group** | Continue on natalizumab 300 mg IV q.m. (n=10) | |
| **Comparison group** | Switch to interferon beta-1b 250 mcg every other day (n=9) | |
| **Outcome** | *Primary endpoint* was time to first on-study relapse  from randomization.  *Secondary endpoints* included number of relapses, proportion of relapse free patients, severity of relapses (severe relapse was defined by ≥1.5 increase in EDSS score), 3 months confirmed disability progression (defined by ≥1.0 increase in EDSS score), number of new T2-hyperintense lesions (nT2L) and Gd+L per patient at months 3, 6, 9 and 12. | |
| **Follow-up** | 1 year | |
| **Treatment history** | Treatment experienced | |
| **Risk of Bias** | | |
| **Random sequence generation** | | Adequate  A monitoring agency prepared the randomization list and provided sealed envelopes for treatment allocation. |
| **Allocation concealment** | | Adequate |
| **Blinding of participant and personnel** | | No  Rater blinded |
| **Blinding of outcome assessment** | | Adequate  “EDSS and relapses assessment was performed by an examining neurologist blinded to treatment.” |
| **Incomplete outcome data** | | Analysis was based on intention to treat.  Withdrawals: 10.5% |
| **Selective reporting** | | None detected |
| **Other sources of bias** | | Several of the authors report funding from one or several pharmaceutical companies. |

**\****ACTH: this abbreviation was not explained in the publication*

#### RESTORE-study 2014, Fox et al., (2014), not included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT01071083 | |
| **Study setting** | Randomized, partially placebo-controlled study. 31 sites in North America and Europe | |
| **Participants** | *Eligibility criteria:* Patients with RRMS receiving natalizumab, aged 18 and 60 years, who had been treated with natalizumab for at least 12 months prior to randomization and who had no relapses during those 12 months.  *Key exclusion criteria:* presence of gadolinium enhancing lesions; presence of antinatalizumab antibodies; immunosuppressive treatment within 24 months prior to randomization; treatment with IV immunoglobulin, plasmapheresis, or cytapheresis within 12 months prior to randomization; or treatment with systemic corticosteroids within 3 months prior to randomization.  *Baseline characteristics in placebo group:* Age: 40 +/- 10; 74% female; EDSS: 3.3 +/-1.8 | |
| **Intervention group** | Natalizumab 300 mg IV every 4 weeks (n=45)  Alternate immunomodulatory therapy (IM interferon b-1a, glatiramer acetate, or methylprednisolone (n=88) [not included as patients and their neurologist selected the immunomodulatory therapy on an individual basis; as such, the distribution of patients receiving IM IFN-b-1a, GA, and MP was not randomized, and the groups were unbalanced] | |
| **Comparison group** | Placebo IV every 4 weeks (n=42) | |
| **Outcome** | Relapse  Quality of life’  Withdrawal due to adverse events  Deaths  Definition used: Radiographic and clinical disease activity. Quality of life with Visual Analogue Scale, and Modified Fatigue Impact Scale, and cognition (Symbol Digit Modalities Test (SDMT)). Disability progression with EDSS. | |
| **Follow-up** | 24 weeks (52 weeks but at week 28, patients resumed open-label infusions of natalizumab) | |
| **Treatment history** | Treatment experienced ( all groups received natalizumab at day 0) | |
| **Risk of Bias** | | |
| **Random sequence generation** | | Adequate |
| **Allocation concealment** | | Adequate  For arms natalizumab + placebo |
| **Blinding of participant and personnel** | | Adequate  For arms natalizumab + placebo |
| **Blinding of outcome assessment** | | Adequate  For arms natalizumab + placebo |
| **Incomplete outcome data** | | Adequate |
| **Selective reporting** | | Not detected |
| **Other sources of bias** | | Funding: manufacturer. |

#### Zecca et al., (2014), not included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT1144052, | |
| **Study setting** | Randomized, rater-blinded, parallel-group study, single center, Switzerland | |
| **Participants** | *Eligibility criteria:* Age between 18 and 60, being at significant risk for (i.e. NTZ treatment duration equal to or greater than 12 months) or fear of PML, and being free of disease activity (free from relapses and disability progression for at least 6 months and no gadolinium enhancing lesions [Gd + L] on baseline [BL] MRI). RRMS according to 2005 McDonald criteria [13] from 2010 to 2011  *Baseline characteristics in Interferon group:* Mean (range) 39 (24-48) ; 33% female (3/9); EDSS median (range) 3,0 (1,5-3,5) | |
| **Intervention group** | Continue Natalizumab monthly intravenous (i.v.) 300 mg (n=10) | |
| **Comparison group** | De-escalate to interferon beta 1b subcutaneous (s.c.) 250 mcg every other day (n=9) | |
| **Outcome** | Behavioral assessment of patients included Paced Auditory Serial Addition Test, 3 sec (PASAT), Fatigue Scale for Motor and Cognitive functions (FSMC), Functional Assessment of Multiple Sclerosis (FAMS), and EuroQuol visual analogue scale (EQ-VAS) | |
| **Follow-up** | 1 year | |
| **Treatment history** | Treatment experienced (All patients previously treated with natalizumab) | |
| **Risk of bias** | | |
| **Random sequence generation** | | Unclear/Not described |
| **Allocation concealment** | | Unclear/Not described |
| **Blinding of participant and personnel** | | No |
| **Blinding of outcome assessment** | | Adequate (rater-blinded) |
| **Incomplete outcome data** | | No 17/19 completed study (reasons listed) |
| **Selective reporting** | | None detected |
| **Other sources of bias** | | Some of the authors have received compensation from one or several of pharmaceutical companies |

### Peg-interferon

#### ADVANCE study 2014, Calabresi et al.,(2014), not in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT00906399 | |
| **Study setting** | Double-blind, randomized controlled study. 183 neurology practices in 26 countries, including north and south America, Europe, India | |
| **Participants** | *Eligibility criteria*: diagnosis of relapsing-remitting multiple sclerosis as defined by the McDonald criteria, aged 18–65 years, a EDSS score of 0–5 , and at least two clinically documented relapses in the previous 3 years, with at least one having occurred within the past 12 months.  *Key exclusion criteria*: pre-specified laboratory abnormalities, and previous treatment with interferon for multiple sclerosis for more than 4 weeks or discontinuation less than 6 months before baseline  *Baseline characteristics in placebo group:* Age: 36+/- 10; 72% female; EDSS: 2.4 +/-1.2 | |
| **Intervention group** | Peg-interferon beta-1a 125 mcg SC once every 2 weeks (n=512)  Peg-interferon beta-1a 125 mcg SC once every 4 weeks (n=500) | |
| **Comparison group** | Placebo (n=500) | |
| **Outcome** | *Primary endpoints:* Annualised relapse rate at week 48, based on number of relapses.  *Secondary endpoints:* The number of new or newly enlarging hyperintense lesions on T2-weighted images(relative to baseline MRI), proportion of patients who relapsed, and proportion of patients with disability progression at 48 weeks.  *Tertiary endpoints:* Prespecified MRI endpoints at 48 weeks | |
| **Follow-up** | 2 years, but placebo controlled only for 48 weeks | |
| **Treatment history** | Mixed (based on exclusion criteria) | |
| **Risk of bias** | | |
| **Random sequence generation** | | Yes |
| **Allocation concealment** | | Adequate  Patients received either study drug or placebo every 2 weeks to maintain masking; those assigned to receive study drug every 4 weeks received alternate injections of placebo and peg-interferon beta-1a every 2 weeks |
| **Blinding of participant and personnel** | | Adequate “ |
| **Blinding of outcome assessment** | | Adequate |
| **Incomplete outcome data** | | Adequate  Intention to treat |
| **Selective reporting** | | None detected |
| **Other sources of bias** | | Funding: manufacturer |

### Teriflunomide

#### O’connor et al., (2006), included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | Not reported | |
| **Study setting** | Randomized controlled study, double-blind. Centres in Canada | |
| **Participants** | *Eligibility criteria:* Age = 18 years to 65 years, with RRMS (n = 157) or secondary-progressive MS with relapses (n = 22) (Poser et al.), EDSS = 0 to 6.0; had ≥ 2 documented relapses in previous 3 years, and one clinical relapse during the preceding year.  *Key exclusion criteria*: Prior treatment with interferon, gamma-globulin, glatiramer, or other non-corticosteroid immune-modulatory therapies in the 4 months prior to the trial.  Baseline characteristics: Age: 39 +/-; 74% female; , EDSS score: (median) 2.3 | |
| **Intervention group** | Teriflunomide oral 7 mg q.d.(n=61)  Teriflunomide oral 14 mg q.d.(n=57) | |
| **Comparison group** | Placebo (n=61) | |
| **Outcome** | *Primary endpoint*: Number of combined unique active (new and persisting) lesions per MRI scan during 36 weeks.  *Secondary endpoints*: Other MRI outcomes, number of patients experienced relapses, annualized relapse rate, number of relapsing patients required a course of steroids, EDSS change.  Definition used for: *Relapses*: The appearance of a new symptom or worsening of an old symptom due to MS lasting 48 hours in the absence of fever, preceded by period of stability of at least 30 days and accompanied by appropriate changes on neurologic examination. | |
| **Follow-up** | 36 weeks | |
| **Treatment history** | Treatment-naive (based in exclusion criteria, year of study, and clinical expert input). | |
| **Comments** | At baseline 86.9% RRMS, 13.1% secondary progressive | |
| **Critical appraisal** | | |
| **Randomization** | | Insufficient reporting |
| **Allocation concealment** | | Not reporting |
| **Double-blinding** | | Yes |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 11% |
| **ITT Analysis** | | Yes |
| **Funding** | | Manufacturer |

#### TEMSO study 2011, O’Connor et al. (2011, 2013), included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT00134563 | |
| **Study setting** | Double-blind, randomized controlled trial. 127 centres in 21 countries including Canada, Europe, and US. | |
| **Participants** | *Eligibility criteria*: Age = 18 years to 55 years; diagnosis of RRMS (McDonald criteria), EDSS = 0 to 5.5; had ≥ 2 relapses in the previous 2 years or ≥ 1 relapse during the preceding year, but no relapse in the 60 days before randomization.  *Key exclusion criteria*: Had other systemic diseases; pregnant, or planned to conceive during the trial period.  Baseline characteristics: Age 38+/-9; 72% female; EDSS: 2.7+/- 1.3 | |
| **Intervention group** | Teriflunomide oral 7 mg q.d. (n=365)  Teriflunomide oral 14 mg q.d. (n=358) | |
| **Comparison group** | Placebo (n=363) | |
| **Outcome** | *Primary endpoint*: Annualized relapse rate.  *Secondary endpoints*: Disability progression (EDSS change), different MRI outcomes.  Definitions used for endpoints: *Relapses*: The appearance of a new clinical sign or symptom, or clinical worsening of a previous sign or symptom that had been stable for at least 30 days and that persisted for a minimum of 24 hours in the absence of fever.  *Disability progression*: An increase from baseline of at least 1.0 point in the EDSS score (or at least 0.5 points for patients with a baseline EDSS score greater than 5.5) that persisted for at least 12 weeks. | |
| **Follow-up** | 108 weeks | |
| **Treatment history** | Mixed (based on reported baseline characteristics) | |
| **Critical appraisal** | | |
| **Randomization** | | Adequate |
| **Allocation concealment** | | Adequate |
| **Double-blinding** | | Yes |
| **Baseline characteristic similarity** | | Yes |
| **Outcome measures** | | Adequate |
| **Withdrawals** | | 27% |
| **ITT Analysis** | | Yes |
| **Funding** | | Manufacturer |

#### TOWER-(Teriflunomide Oral in people With relapsing multiplE sclerosis) study, Confavreux et al. (2014), not included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT00751881 | |
| **Study setting** | Randomised, double-blind, placebo-controlled in 189 centres mainly hospital-based sites in 26 countries | |
| **Participants** | *Eligibility criteria:* ambulatory patients with RMS, aged 18–55 years, with EDSS scores <=5.5 and >=1 relapse in the previous 12 months or >=2 relapses in the prior 24 months  *Key exclusion criteria:* previously or concomitantly received cytokine therapy, interferon beta, or glatiramer acetate within 3 months of randomisation, or had ever used natalizumab or other immunosuppressive agents  *Baseline characteristics (in placebo group):* Age: 38+/-9; 70% female; EDSS: 2,7+/-1,4 | |
| **Intervention group** | Teriflunomide 14 mg once daily (n=372)  Teriflunomide 7 mg once daily (n=408) | |
| **Comparison group** | Placebo once daily (n=389) | |
| **Outcome** | *Primary endpoints:* Annualised relapse rate (number of relapses per patient-year)  *Secondary endpoints:* time to 12 week sustained accumulation of disability; time to fi rst relapse, proportion of patients free from relapses, proportion of patients free of accumulation of disability, and change from baseline in EDSS score at week 48, and change in Fatigue Impact Scale (FIS) and Short Form-36 (SF-36) scores at week 48 and last study visit.  Definitions used for endpoints: *Relapse* was defined as new or worsening clinical signs or symptoms lasting at least 24 h without fever. Protocol-defined relapse constituted an increase of either 1 point in at least two EDSS functional system scores, or 2 points in one EDSS functional system score (excluding bowel and bladder function, and cerebral function), or 0・5 points in total EDSS score from a previous clinically stable assessment time to 12 week sustained accumulation of disability, defined as an increase from baseline of at least 1 EDSS point (or ≥0・5 points when baseline EDSS score was >5・5 points that persisted for at least 12 weeks | |
| **Follow-up** | Treatment duration in TOWER was variable and ended 48 weeks after the last patient was randomized into the study | |
| **Treatment history** | Mixed (based on exclusion criteria) | |
| **Risk of bias** | | |
| **Random sequence generation** | | Adequate. |
| **Allocation concealment** | | Adequate “After a screening phase (up to 4 weeks), investigators used the allocation sequence to randomly assign eligible patients” |
| **Blinding of participant and personnel** | | Adequate. |
| **Blinding of outcome assessment** | | Adequate |
| **Incomplete outcome data** | | Adequate  Intention to treat analysis |
| **Selective reporting** | | None detected |
| **Other sources of bias** | | Funding: manufacturer |

#### TENERE-((TErifluNomidE and REbifR) )study, Vermersch et al. (2014), not included in Tran et al. (2013)

|  |  |  |
| --- | --- | --- |
| **RCT identification** | NCT00883337 | |
| **Study setting** | Rater-blinded study, randomized multicentre study | |
| **Participants** | *Eligibility criteria:* 18 years of age and older who met McDonald criteria for MS,13 had a relapsing clinical course with or without progression, and an Expanded Disability Status Scale (EDSS) score ≤5.5 at screening.14 Patients had to be relapse free for 30 days prior to randomisation.  *Key exclusion criteria:* several restriction in previous and concomitant medications, and relevant illnesses.  Baseline characteristics (group): Age 37+/-11; 68% female: EDSS 2,0+/-1,2 | |
| **Intervention group** | Teriflunomide 14 mg oral once daily (n=111)  Teriflunomide 7 mg oral once daily (n=109) | |
| **Comparison group** | Interferon beta-1a 44mcg s.c three times/week (n=104) | |
| **Outcome** | *The primary endpoint:* time to failure, defined as first occurrence of confirmed relapse or permanent treatment discontinuation for any cause. Secondary endpoints included ARR, Fatigue Impact Scale (FIS) and Treatment Satisfaction Questionnaire for Medication (TSQM).  Definition used for: *Relapse* criteria a new clinical sign/symptom or clinical worsening of a previous sign/symptom (previously stable for at least 30 days) that persisted for at least 24 hours without fever. required a 1-point increase in each of two FS, a 2-point increase in at least one FS (excluding bowel/bladder and cerebral) or an increase of 0.5 points in EDSS score from the previous stable assessment. | |
| **Follow-up** | 48 weeks after the last patient was randomised, resulting in a variable duration of follow-up | |
| **Treatment history** | Mixed (based on exclusion criteria) | |
| **Risk of bias** | | |
| **Random sequence generation** | | Unclear, not described |
| **Allocation concealment** | | Unclear |
| **Blinding of participant and personnel** | | No. Double blind for teriflunomide, open-label for Interferon beta-1a |
| **Blinding of outcome assessment** | | Adequate |
| **Incomplete outcome data** | | 22.4% discontinued treatment due to AEs  3 patients in IFN did not receive study drug.  Efficacy analyses: intention-to-treat population, The safety analysis included all randomized patients exposed to study medication. |
| **Selective reporting** | | Unclear |
| **Other sources of bias** | | Authors declare conflict of interest in form of collaboration, employment or other with one or several of the pharmaceutical companies |

## Supplementary material 12 Estimates of annual relapse and quality ratings for direct and indirect comparisons from network meta-analysis



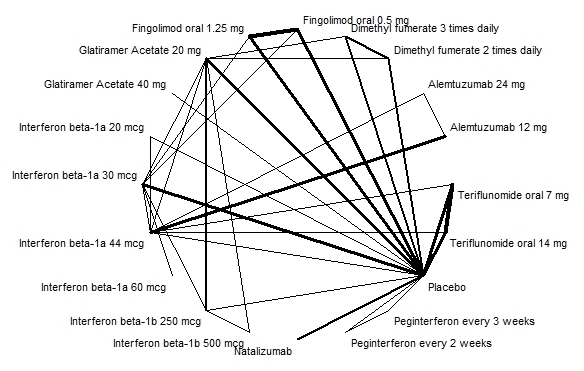
*RR= relative ratio, CI= confidence interval, mg= milligrams, mcg= micrograms, SC= subcutaneous, IM= intra muscular, q.d.= once daily, q.w.=once weekly, t.i.w.= three times weekly, 2.i.d= two times daily, t.i.d= three times daily, 1/2 w=once every 2 weeks, 1/4 w=once every 4 weeks, 1/2 d= once every two days, NA=Not applicable (no available data).*

## Supplementary material 13 Estimates of disability progression and quality ratings for direct and indirect comparisons from network meta-analysis



*RR= relative ratio, CI= confidence interval, mg= milligrams, mcg= micrograms, SC= subcutaneous, IM= intra muscular, q.d.= once daily, q.w.=once weekly, t.i.w.= three times weekly, 2.i.d= two times daily, t.i.d= three times daily, 1/2 w=once every 2 weeks, 1/4 w=once every 4 weeks.*

## Supplementary material 14 Withdrawal due to adverse events from network meta-analysis



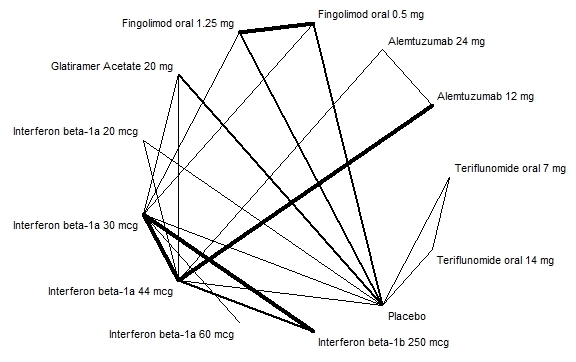
***Figure 14.1.*** *Evidence network for withdrawal due to adverse events*

**Table 14.1.** *Relative risk for withdrawal due to adverse events*



*RR= relative ratio, CI= confidence interval, mg= milligrams, mcg= micrograms, SC= subcutaneous, IM= intra muscular, q.d.= once daily, q.w.=once weekly, t.i.w.= three times weekly, 2.i.d= two times daily, t.i.d= three times daily, 1/2 w=once every 2 weeks, 1/4 w=once every 4 weeks.*

## Supplementary material 15 Change in expanded disability status scale

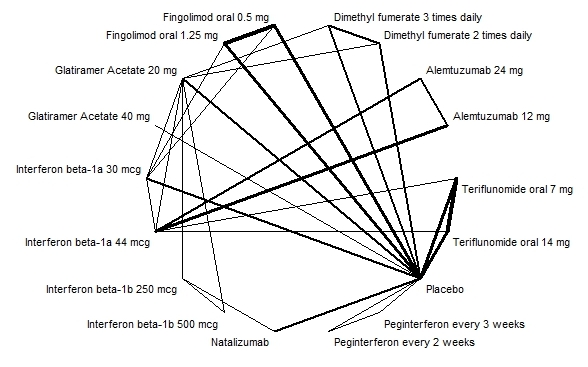


**Figure 15.1.** *Network of evidence for change in expanded disability status scale*

**Table 15.1.** *Relative risk for change in expanded disability status scale* 

*CI= confidence interval, mg= milligrams, mcg= micrograms, SC= subcutaneous, IM= intra muscular, q.d.= once daily, q.w.=once weekly, t.i.w.= three times weekly, 2.i.d= two times daily, t.i.d= three times daily, 1/2 w=once every 2 weeks, 1/4 w=once every 4 weeks. SUCRA= surface under the cumulative ranking curve.*

## Supplementary material 16 Serious adverse events from network meta-analysis



**Figure 16.1.** *Network of evidence for serious adverse events*

**Table 16.1.** *Relative risk for serious adverse events from network meta-analysis*



*RR= relative ratio, CI= confidence interval, mg= milligrams, mcg= micrograms, SC= subcutaneous, IM= intra muscular, q.d.= once daily, q.w.=once weekly, t.i.w.= three times weekly, 2.i.d= two times daily, t.i.d= three times daily, 1/2 w=once every 2 weeks, 1/4 w=once every 4 weeks. SUCRA= surface under the cumulative ranking curve.*

## Supplementary material 17 Mortality from network meta-analysis

**Figure 17.1.** *Network of evidence for withdrawal due to adverse event*

**Table 17.1.** *Relative risk for mortality from network meta-analysis*



*RR= relative ratio, CI= confidence interval, mg= milligrams, mcg= micrograms, SC= subcutaneous, IM= intra muscular, q.d.= once daily, q.w.=once weekly, t.i.w.= three times weekly, 2.i.d= two times daily, t.i.d= three times daily, 1/2 w=once every 2 weeks, 1/4 w=once every 4 weeks. SUCRA= surface under the cumulative ranking curve.*

## Supplementary material 18 Full network meta-analysis results

### Annualised relapse rate



### Disability progression



### Withdrawal due to adverse events



### Change in Expanded Disability Status Scale



### Serious adverse events



### Mortality



## Supplementary material 19 Grade evaluation of comparisons

### Interferon beta-1a 22 mcg compared to Placebo for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Interferon beta-1a 22 mcg** | **Placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious 2 | serious 3 | none | -/189 | -/187 | **RR 0.69** (0.57 to 0.83) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁◯ MODERATE 1 2 3 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious 2 | very serious 4 5 | none | 64/189 (33.9%) | 77/187 (41.2%) | **RR 0.84** (0.61 to 1.19) | 66 fewer per 1000 (from 78 more to 161 fewer) | ⨁⨁◯◯ LOW 1 2 4 5 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious 2 | very serious 4 5 | none | 6/189 (3.2%) | 2/187 (1.1%) | **RR 1.68** (0.50 to 5.98) | 7 more per 1000 (from 5 fewer to 53 more) | ⨁⨁◯◯ LOW 1 2 4 5 |  |

MD – mean difference, RR – relative risk

1. Only one study, not possible to check for inconsistency
2. Patients were treatment naïve.
3. For continuous outcomes, a sample size of approximately 400 may not be sufficient to insure prognostic balance (ref GRADE 6 paper).
4. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).
5. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).

### Interferon beta-1a 30 mcg compared to Placebo for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Interferon beta-1a 30 mcg** | **Placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | not serious 1 | not serious | none | -/659 | -/647 | **RR 0.76** (0.65 to 0.89) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁⨁ HIGH 1 |  |
| Disease Progression | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious 1 | serious 2 | none | 70/605 (11.6%) | 96/593 (16.2%) | **RR 0.68** (0.50 to 0.95) | 52 fewer per 1000 (from 8 fewer to 81 fewer) | ⨁⨁⨁◯ MODERATE 1 2 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | not serious 1 | very serious 2 3 | none | 34/659 (5.2%) | 21/647 (3.2%) | **RR 1.73** (0.82 to 3.87) | 24 more per 1000 (from 6 fewer to 93 more) | ⨁⨁◯◯ LOW 1 2 3 |  |

MD – mean difference, RR – relative risk

1. In the minor contributing study patients were treatment naïve.
2. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).
3. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).

### Interferon beta-1a 44 mcg compared to Placebo for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Interferon beta-1a 44 mcg** | **Placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious 1 | not serious | none | -/204 | -/247 | **RR 0.67** (0.54 to 0.80) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁⨁ HIGH 1 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 2 | not serious 3 | very serious 4 5 | none | 54/184 (29.3%) | 77/187 (41.2%) | **RR 0.70** (0.48 to 1.04) | 124 fewer per 1000 (from 16 more to 214 fewer) | ⨁⨁◯◯ LOW 2 3 4 5 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 2 | not serious 3 | very serious 4 6 | none | 9/184 (4.9%) | 2/187 (1.1%) | **RR 5.32** (1.09 to 41.63) | 46 more per 1000 (from 1 more to 435 more) | ⨁⨁◯◯ LOW 2 3 4 6 |  |

MD – mean difference, RR – relative risk

1. In the major contributing study patients were treatment naïve.
2. Only one study, not possible to check for inconsistency
3. Patients were treatment naïve.
4. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).
5. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).
6. The effect estimate and the confidence interval are not robust. Minor variations in number of events would change the results.

### Glatiramer acetate 20 mg compared to Placebo for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Glatiramer acetate 20 mg** | **Placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | not serious 1 | not serious | none | -/595 | -/609 | **RR 0.70** (0.60 to 0.82) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁⨁ HIGH 1 |  |
| Disease Progression | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious 2 | very serious 3 4 | none | 83/475 (17.5%) | 93/489 (19.0%) | **RR 0.88** (0.61 to 1.21) | 23 fewer per 1000 (from 40 more to 74 fewer) | ⨁⨁◯◯ LOW 2 3 4 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | not serious 1 | very serious 3 4 | none | 43/595 (7.2%) | 41/609 (6.7%) | **RR 1.22** (0.64 to 2.66) | 15 more per 1000 (from 24 fewer to 112 more) | ⨁⨁◯◯ LOW 1 3 4 |  |

MD – mean difference, RR – relative risk

1. In the minor contributing studies, patients were treatment naïve or had an unclear treatment history.
2. In the minor contributing study patients were treatment naïve.
3. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).
4. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).

### Glatiramer acetate 40 mg compared to Placebo for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Glatiramer acetate 40 mg** | **Placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | not serious | none | -/943 | -/461 | **RR 0.66** (0.52 to 0.82) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁⨁ HIGH 1 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | very serious 2 3 | none | 29/943 (3.1%) | 6/461 (1.3%) | **RR 2.50** (0.86 to 8.29) | 20 more per 1000 (from 2 fewer to 95 more) | ⨁⨁◯◯ LOW 1 2 3 |  |

MD – mean difference, RR – relative risk

1. Only one study, not possible to check for inconsistency
2. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).
3. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).

### Dimethyl fumarate 240 mg two times daily compared to Placebo for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Dimethyl fumarate 240 mg two times daily** | **Placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | not serious | none | -/769 | -/771 | **RR 0.50** (0.42 to 0.60) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁⨁ HIGH |  |
| Disease Progression | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | not serious | none | 113/768 (14.7%) | 172/771 (22.3%) | **RR 0.65** (0.49 to 0.85) | 78 fewer per 1000 (from 33 fewer to 114 fewer) | ⨁⨁⨁⨁ HIGH |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | very serious 1 2 | none | 109/769 (14.2%) | 90/771 (11.7%) | **RR 1.24** (0.74 to 2.13) | 28 more per 1000 (from 30 fewer to 132 more) | ⨁⨁◯◯ LOW 1 2 |  |

MD – mean difference, RR – relative risk

1. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).
2. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).

### Dimethyl fumarate 240 mg three times daily compared to Placebo for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Dimethyl fumarate 240 mg three times daily** | **Placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | not serious | none | -/761 | -/771 | **RR 0.50** (0.42 to 0.60) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁⨁ HIGH |  |
| Disease Progression | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | not serious | none | 120/761 (15.8%) | 172/771 (22.3%) | **RR 0.68** (0.52 to 0.89) | 71 fewer per 1000 (from 25 fewer to 107 fewer) | ⨁⨁⨁⨁ HIGH |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | very serious 1 2 | none | 109/760 (14.3%) | 93/771 (12.1%) | **RR 1.25** (0.74 to 2.13) | 30 more per 1000 (from 31 fewer to 136 more) | ⨁⨁◯◯ LOW 1 2 |  |

MD – mean difference, RR – relative risk

1. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).
2. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).

### Teriflunomide oral 7 mg compared to Placebo for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Teriflunomide oral 7 mg** | **Placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | not serious 1 | not serious | none | -/802 | -/806 | **RR 0.73** (0.64 to 0.84) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁⨁ HIGH 1 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 2 | not serious | very serious 3 4 | none | 79/365 (21.6%) | 99/363 (27.3%) | **RR 0.80** (0.55 to 1.13) | 55 fewer per 1000 (from 35 more to 123 fewer) | ⨁⨁◯◯ LOW 2 3 4 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | not serious 1 | very serious 3 4 | none | 97/802 (12.1%) | 57/806 (7.1%) | **RR 1.54** (0.89 to 2.51) | 38 more per 1000 (from 8 fewer to 107 more) | ⨁⨁◯◯ LOW 1 3 4 |  |

MD – mean difference, RR – relative risk

1. In the minor contributing study patients were treatment naïve.
2. Only one study, not possible to check for inconsistency
3. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).
4. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).

### Teriflunomide oral 14mg compared to Placebo for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Teriflunomide oral 14mg** | **Placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | not serious 1 | not serious | none | -/824 | -/806 | **RR 0.67** (0.58 to 0.78) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁⨁ HIGH 1 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 2 | not serious | very serious 3 4 | none | 72/358 (20.1%) | 99/363 (27.3%) | **RR 0.73** (0.51 to 1.05) | 74 fewer per 1000 (from 14 more to 134 fewer) | ⨁⨁◯◯ LOW 2 3 4 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | not serious 1 | very serious 3 5 | none | 100/824 (12.1%) | 57/806 (7.1%) | **RR 1.70** (1.02 to 3.01) | 50 more per 1000 (from 1 more to 142 more) | ⨁⨁◯◯ LOW 1 3 5 |  |

MD – mean difference, RR – relative risk

1. In the minor contributing study patients were treatment naïve.
2. Only one study, not possible to check for inconsistency
3. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).
4. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).
5. The effect estimate and the confidence interval are not robust. Minor variations in number of events would change the results.

### Fingolimod oral 0.5 mg compared to Placebo for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Fingolimod oral 0.5 mg** | **Placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | not serious | not serious | none | -/840 | -/830 | **RR 0.49** (0.41 to 0.57) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁⨁ HIGH |  |
| Disease Progression | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | not serious | none | 124/783 (15.8%) | 164/773 (21.2%) | **RR 0.75** (0.56 to 0.98) | 53 fewer per 1000 (from 4 fewer to 93 fewer) | ⨁⨁⨁⨁ HIGH |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | not serious | very serious 1 2 | none | 104/840 (12.4%) | 72/830 (8.7%) | **RR 1.49** (0.86 to 2.50) | 43 more per 1000 (from 12 fewer to 130 more) | ⨁⨁◯◯ LOW 1 2 |  |

MD – mean difference, RR – relative risk

1. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).
2. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).

### Fingolimod oral 1.25 mg compared to Placebo for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Fingolimod oral 1.25 mg** | **Placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | not serious | not serious | none | -/853 | -/830 | **RR 0.43** (0.37 to 0.51) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁⨁ HIGH |  |
| Disease Progression | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | not serious | none | 119/799 (14.9%) | 164/773 (21.2%) | **RR 0.70** (0.52 to 0.92) | 64 fewer per 1000 (from 17 fewer to 102 fewer) | ⨁⨁⨁⨁ HIGH |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | not serious | serious 1 | none | 139/853 (16.3%) | 72/830 (8.7%) | **RR 1.93** (1.18 to 3.14) | 81 more per 1000 (from 16 more to 186 more) | ⨁⨁⨁◯ MODERATE 1 |  |

MD – mean difference, RR – relative risk

1. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).

### Peg-interferon beta-1a 125 mcg once every two weeks compared to Placebo for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Peg-interferon beta-1a 125 mcg once every two weeks** | **Placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | not serious | none | -/512 | -/500 | **RR 0.65** (0.49 to 0.85) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁⨁ HIGH 1 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | very serious 2 3 | none | 31/512 (6.1%) | 50/500 (10.0%) | **RR 0.61** (0.36 to 0.98) | 39 fewer per 1000 (from 2 fewer to 64 fewer) | ⨁⨁◯◯ LOW 1 2 3 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | very serious 2 4 | none | 25/512 (4.9%) | 7/500 (1.4%) | **RR 3.57** (1.27 to 11.14) | 36 more per 1000 (from 4 more to 142 more) | ⨁⨁◯◯ LOW 1 2 4 |  |

MD – mean difference, RR – relative risk

1. Only one study, not possible to check for inconsistency
2. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).
3. The effect estimate and the confidence interval are not robust. Minor variations in number of events would change the results.
4. The effect estimate and the confidence interval are not robust. Minor variations in number of events would change the results.

### Peg-interferon beta-1a 125 mcg once every four weeks compared to Placebo for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Peg-interferon beta-1a 125 mcg once every four weeks** | **Placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | not serious | none | -/500 | -/500 | **RR 0.73** (0.56 to 0.95) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁⨁ HIGH 1 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | very serious 2 3 | none | 31/500 (6.2%) | 50/500 (10.0%) | **RR 0.62** (0.38 to 1.01) | 38 fewer per 1000 (from 1 more to 62 fewer) | ⨁⨁◯◯ LOW 1 2 3 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | very serious 2 4 | none | 24/500 (4.8%) | 7/500 (1.4%) | **RR 3.47** (1.25 to 10.90) | 35 more per 1000 (from 4 more to 139 more) | ⨁⨁◯◯ LOW 1 2 4 |  |

MD – mean difference, RR – relative risk

1. Only one study, not possible to check for inconsistency
2. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).
3. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).
4. The effect estimate and the confidence interval are not robust. Minor variations in number of events would change the results

### Natalizumab 300 mg intravenous every four weeks compared to Placebo for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Natalizumab 300 mg intravenous every four weeks** | **Placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 2 | randomised trials | not serious | serious 1 | not serious 2 | not serious | none | -/673 | -/358 | **RR 0.30** (0.25 to 0.36) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁◯ MODERATE 1 2 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 3 | not serious 4 | serious 5 | none | 107/627 (17.1%) | 91/315 (28.9%) | **RR 0.59** (0.42 to 0.84) | 118 fewer per 1000 (from 46 fewer to 168 fewer) | ⨁⨁⨁◯ MODERATE 3 4 5 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious 2 | very serious 5 6 | none | 38/673 (5.6%) | 15/358 (4.2%) | **RR 1.22** (0.50 to 2.74) | 9 more per 1000 (from 21 fewer to 73 more) | ⨁⨁◯◯ LOW 2 5 6 |  |

MD – mean difference, RR – relative risk

1. Heterogeneity may be explained by differences in study setting. One study compared natalizumab with placebo over a two years period while the other tested treatment interruption in natalizumab users
2. One study compared natalizumab with placebo over a two years period while the other tested treatment interruption in natalizumab users
3. Only one study, not possible to check for inconsistency
4. Patients’ treatment history was unclear.
5. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).
6. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).

### Interferon beta-1b 250 mcg SC every other day compared to Placebo for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Interferon beta-1b 250 mcg SC every other day** | **Placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious 2 | serious 3 | none | -/124 | -/122 | **RR 0.65** (0.51 to 0.83) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁◯ MODERATE 1 2 3 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious 2 | very serious 4 5 | none | 43/122 (35.2%) | 56/122 (45.9%) | **RR 0.77** (0.50 to 1.17) | 106 fewer per 1000 (from 78 more to 230 fewer) | ⨁⨁◯◯ LOW 1 2 4 5 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious 2 | very serious 4 6 | none | 1/124 (0.8%) | 10/122 (8.2%) | **RR 0.070** (0.003 to 0.480) | 76 fewer per 1000 (from 43 fewer to 82 fewer) | ⨁⨁◯◯ LOW 1 2 4 6 |  |

MD – mean difference, RR – relative risk

1. Only one study, not possible to check for inconsistency
2. Patients were treatment naïve.
3. For continuous outcomes, a sample size of approximately 400 may not be sufficient to insure prognostic balance (ref GRADE 6 paper).
4. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).
5. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).
6. The effect estimate and the confidence interval are not robust. Minor variations in number of events would change the results.

### Alemtuzumab 24 mg IV q.d compared to Alemtuzumab 12 mg IV q.d for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Alemtuzumab 24 mg IV q.d** | **Alemtuzumab 12 mg IV q.d** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | serious 2 3 | serious 4 | none | -/110 | -/112 | **RR 0.55** (0.35 to 0.86) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁◯◯ LOW 1 2 3 4 |  |
| Disease Progression (disability sustained for 6 months) | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | serious 2 3 | very serious 5 6 | none | 10/110 (9.1%) | 8/112 (7.1%) | **RR 0.85** (0.40 to 1.65) | 11 fewer per 1000 (from 43 fewer to 46 more) | ⨁◯◯◯ VERY LOW 1 2 3 5 6 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious 7 | very serious 5 6 | none | 7/280 (2.5%) | 16/539 (3.0%) | **RR 0.88** (0.30 to 2.31) | 4 fewer per 1000 (from 21 fewer to 39 more) | ⨁⨁◯◯ LOW 5 6 7 |  |

MD – mean difference, RR – relative risk

1. Only one study, not possible to check for inconsistency
2. Few patients could have received the intended three treatments’s rounds. Alemtuzumab arms were suspended from 2005 as immune thrombocytopenic purpura developed in three patients, and one of them died (patients were recruited from 2002 to 2004).
3. Patients were treatment naïve.
4. For continuous outcomes, a sample size of approximately 400 may not be sufficient to insure prognostic balance (ref GRADE 6 paper).
5. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).
6. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).
7. In the minor contributing study patients were treatment naïve. In the major contributing study patients were treatment experienced.

### Interferon beta-1a 44 mcg compared to Alemtuzumab 12 mg IV q.d for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Interferon beta-1a 44 mcg** | **Alemtuzumab 12 mg IV q.d** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious 1 | not serious 2 3 | not serious | none | -/500 | -/924 | **RR 2.22** (1.89 to 2.63) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁⨁ HIGH 1 2 3 |  |
| Disease Progression | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | not serious 2 3 | serious 4 | none | 113/529 (21.4%) | 102/924 (11.0%) | **RR 1.95** (1.45 to 2.59) | 105 more per 1000 (from 50 more to 176 more) | ⨁⨁⨁◯ MODERATE 2 3 4 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | not serious 2 3 | serious 4 | none | 39/500 (7.8%) | 21/924 (2.3%) | **RR 3.60** (1.88 to 7.34) | 59 more per 1000 (from 20 more to 144 more) | ⨁⨁⨁◯ MODERATE 2 3 4 |  |

MD – mean difference, RR – relative risk

1. Some inconsistency. It might be explained by the fact that in one study alemtuzumab arms were suspended.
2. Included approximately the same proportion of treatment naïve and experienced patients.
3. In the minor contributing study, alemtuzumab arms were suspended from 2005 as immune thrombocytopenic purpura developed in three patients, and one of them died (Patients were recruited from 2002 to 2004).
4. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).

### Interferon beta-1a 44 mcg compared to Alemtuzumab 24 mg IV q.d for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Interferon beta-1a 44 mcg** | **Alemtuzumab 24 mg IV q.d** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | serious 2 3 | serious 4 | none | -/111 | -/110 | **RR 3.33** (1.94 to 5.79) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁◯◯ LOW 1 2 3 4 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | serious 2 3 | very serious 5 6 | none | 24/111 (21.6%) | 10/110 (9.1%) | **RR 2.15** (1.10 to 4.55) | 105 more per 1000 (from 9 more to 323 more) | ⨁◯◯◯ VERY LOW 1 2 3 5 6 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | serious 7 8 | very serious 5 6 | none | 28/313 (8.9%) | 7/280 (2.5%) | **RR 4.08** (1.69 to 11.42) | 77 more per 1000 (from 17 more to 261 more) | ⨁◯◯◯ VERY LOW 5 6 7 8 |  |

MD – mean difference, RR – relative risk

1. Only one study, not possible to check for inconsistency
2. Few patients could have received the intended three treatments’s rounds. Alemtuzumab arms were suspended from 2005 as immune thrombocytopenic purpura developed in three patients, and one of them died (Patients were recruited from 2002 to 2004).
3. Patients were treatment naïve.
4. For continuous outcomes, a sample size of approximately 400 may not be sufficient to insure prognostic balance (ref GRADE 6 paper).
5. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).
6. The effect estimate and the confidence interval are not robust. Minor variations in number of events would change the results.
7. In one of the two studies, few patients could have received the intended three treatments’s rounds. Alemtuzumab arms were suspended from 2005 as immune thrombocytopenic purpura developed in three patients, and one of them died (Patients were recruited from 2002 to 2004).
8. In the minor contributing study patients were treatment naïve. In the major contributing study patients were treatment experienced.

### Interferon beta-1a 44 mcg compared to Interferon beta-1a 22 mcg for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Interferon beta-1a 44 mcg** | **Interferon beta-1a 22 mcg** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious 2 | serious 3 | none | -/184 | -/189 | **RR 0.68** (0.56 to 0.83) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁◯ MODERATE 1 2 3 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious 2 | very serious 4 5 | none | 54/184 (29.3%) | 64/189 (33.9%) | **RR 0.92** (0.65 to 1.30) | 27 fewer per 1000 (from 102 more to 119 fewer) | ⨁⨁◯◯ LOW 1 2 4 5 |  |
| Withdrawal due to advers events | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious 2 | very serious 4 5 | none | 9/184 (4.9%) | 6/189 (3.2%) | **RR 1.31** (0.40 to 4.36) | 10 more per 1000 (from 19 fewer to 107 more) | ⨁⨁◯◯ LOW 1 2 4 5 |  |

MD – mean difference, RR – relative risk

1. Only one study, not possible to check for inconsistency
2. Patients were treatment naïve.
3. For continuous outcomes, a sample size of approximately 400 may not be sufficient to insure prognostic balance (ref GRADE 6 paper).
4. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).
5. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).

### Interferon beta-1a 44 mcg compared to Interferon beta-1a 30 mcg for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Interferon beta-1a 44 mcg** | **Interferon beta-1a 30 mcg** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 3 | randomised trials | not serious 1 | not serious | not serious 2 | not serious | none | -/424 | -/423 | **RR 0.76** (0.63 to 0.93) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁⨁ HIGH 1 2 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 3 | not serious 4 | very serious 5 6 | none | 43/339 (12.7%) | 49/338 (14.5%) | **RR 0.89** (0.55 to 1.38) | 16 fewer per 1000 (from 55 more to 65 fewer) | ⨁⨁◯◯ LOW 3 4 5 6 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 3 | not serious 4 | very serious 5 6 | none | 16/339 (4.7%) | 14/337 (4.2%) | **RR 1.15** (0.43 to 3.10) | 6 more per 1000 (from 24 fewer to 87 more) | ⨁⨁◯◯ LOW 3 4 5 6 |  |

MD – mean difference, RR – relative risk

1. The major contributing study had no risk of bias issue.
2. Patients' treatment history was unclear in all three studies
3. Only one study, not possible to check for inconsistency
4. Patients' treatment history was unclear
5. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).
6. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).

### Interferon beta-1a 60 mcg compared to Interferon beta-1a 30 mcg for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Interferon beta-1a 60 mcg** | **Interferon beta-1a 30 mcg** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious 2 | serious 3 | none | -/400 | -/402 | **RR 1.05** (0.88 to 1.25) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁◯ MODERATE 1 2 3 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious 2 | very serious 3 4 | none | 108/400 (27.0%) | 109/402 (27.1%) | **RR 0.99** (0.71 to 1.39) | 3 fewer per 1000 (from 79 fewer to 106 more) | ⨁⨁◯◯ LOW 1 2 3 4 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious 2 | very serious 3 4 | none | 64/400 (16.0%) | 45/402 (11.2%) | **RR 1.43** (0.66 to 3.11) | 48 more per 1000 (from 38 fewer to 236 more) | ⨁⨁◯◯ LOW 1 2 3 4 |  |

MD – mean difference, RR – relative risk

1. Only one study, not possible to check for inconsistency
2. Patients' treatment history was unclear
3. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).
4. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).

### Glatiramer acetate 20 mg compared to Interferon beta-1a 30 mcg for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Glatiramer acetate 20 mg** | **Interferon beta-1a 30 mcg** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 2 | randomised trials | not serious 1 | not serious | not serious 2 | serious 3 | none | -/314 | -/305 | **RR 0.79** (0.61 to 1.02) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁◯ MODERATE 1 2 3 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 4 | not serious 5 | very serious 3 6 | none | 74/259 (28.6%) | 61/250 (24.4%) | **RR 1.18** (0.81 to 1.75) | 44 more per 1000 (from 46 fewer to 183 more) | ⨁⨁◯◯ LOW 3 4 5 6 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 4 | not serious 5 | very serious 3 6 | none | 11/259 (4.2%) | 17/250 (6.8%) | **RR 0.61** (0.22 to 1.67) | 27 fewer per 1000 (from 46 more to 53 fewer) | ⨁⨁◯◯ LOW 3 4 5 6 |  |

MD – mean difference, RR – relative risk

1. The major contributing study had no risk of bias issue
2. Unclear treatment history in both studies. In the major contributing study patients were excluded if prior use of either interferon or glatiramer acetate.
3. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).
4. Only one study, not possible to check for inconsistency
5. Unclear treatment history, but patients were excluded if prior use of either interferon or glatiramer acetate.
6. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).

### Fingolimod oral 0.5 mg compared to Interferon beta-1a 30 mcg for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Fingolimod oral 0.5 mg** | **Interferon beta-1a 30 mcg** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | not serious | none | -/431 | -/435 | **RR 0.48** (0.35 to 0.64) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁⨁ HIGH 1 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | very serious 2 3 | none | 27/431 (6.3%) | 38/435 (8.7%) | **RR 0.72** (0.42 to 1.17) | 24 fewer per 1000 (from 15 more to 51 fewer) | ⨁⨁◯◯ LOW 1 2 3 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | very serious 2 3 | none | 25/429 (5.8%) | 34/431 (7.9%) | **RR 1.28** (0.52 to 3.44) | 22 more per 1000 (from 38 fewer to 192 more) | ⨁⨁◯◯ LOW 1 2 3 |  |

MD – mean difference, RR – relative risk

1. Only one study, not possible to check for inconsistency
2. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).
3. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).

### Fingolimod oral 1.25 mg compared to Interferon beta-1a 30 mcg for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Fingolimod oral 1.25 mg** | **Interferon beta-1a 30 mcg** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | not serious | none | -/426 | -/435 | **RR 0.63** (0.46 to 0.90) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁⨁ HIGH 1 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | very serious 2 3 | none | 34/426 (8.0%) | 38/435 (8.7%) | **RR 0.99** (0.58 to 1.60) | 1 fewer per 1000 (from 37 fewer to 52 more) | ⨁⨁◯◯ LOW 1 2 3 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | very serious 3 4 | none | 28/420 (6.7%) | 34/431 (7.9%) | **RR 2.44** (1.09 to 5.68) | 114 more per 1000 (from 7 more to 369 more) | ⨁⨁◯◯ LOW 1 3 4 |  |

MD – mean difference, RR – relative risk

1. Only one study, not possible to check for inconsistency
2. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).
3. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).
4. The effect estimate and the confidence interval are not robust. Minor variations in number of events would change the results.

### Interferon beta-1b 250 mcg SC every other day compared to Interferon beta-1a 30 mcg for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Interferon beta-1b 250 mcg SC every other day** | **Interferon beta-1a 30 mcg** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 2 | randomised trials | not serious 1 | not serious | not serious 2 | serious 3 | none | -/126 | -/126 | **RR 0.71** (0.53 to 0.91) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁◯ MODERATE 1 2 3 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 4 | not serious 5 | very serious 6 7 | none | 13/96 (13.5%) | 28/92 (30.4%) | **RR 0.44** (0.23 to 0.82) | 170 fewer per 1000 (from 55 fewer to 234 fewer) | ⨁⨁◯◯ LOW 4 5 6 7 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 4 | not serious 5 | very serious 6 8 | none | 5/96 (5.2%) | 1/92 (1.1%) | **RR 6.27** (0.79 to 172.30) | 57 more per 1000 (from 2 fewer to 1000 more) | ⨁⨁◯◯ LOW 4 5 6 8 |  |

MD – mean difference, RR – relative risk

1. The major contributing study had no risk of bias issue
2. In the major contributing study patients were treatment naïve.
3. For continuous outcomes, a sample size of approximately 400 may not be sufficient to insure prognostic balance (ref GRADE 6 paper).
4. Only one study, not possible to check for inconsistency
5. Patients were treatment naïve.
6. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).
7. The effect estimate and the confidence interval are not robust. Minor variations in number of events would change the results.
8. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).

### Glatiramer acetate 20 mg compared to Interferon beta-1a 44 mcg for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Glatiramer acetate 20 mg** | **Interferon beta-1a 44 mcg** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 2 | randomised trials | not serious 1 | not serious | not serious 2 | serious 3 | none | -/433 | -/441 | **RR 1.02** (0.83 to 1.28) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁◯ MODERATE 1 2 3 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 4 | not serious 5 | very serious 3 6 | none | 33/378 (8.7%) | 45/386 (11.7%) | **RR 0.75** (0.46 to 1.21) | 29 fewer per 1000 (from 24 more to 63 fewer) | ⨁⨁◯◯ LOW 3 4 5 6 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 4 | not serious 5 | very serious 3 6 | none | 19/378 (5.0%) | 23/386 (6.0%) | **RR 0.88** (0.36 to 1.94) | 7 fewer per 1000 (from 38 fewer to 56 more) | ⨁⨁◯◯ LOW 3 4 5 6 |  |

MD – mean difference, RR – relative risk

1. The major contributing study had no risk of bias issue
2. In the major contributing study patients were treatment naïve. Treatment history was unclear in the other
3. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).
4. Only one study, not possible to check for inconsistency
5. Patients were treatment naïve.
6. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).

### Teriflunomide 7 mg oral compared to Interferon beta-1a 44 mcg SC t.i.w. for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Teriflunomide 7 mg oral** | **Interferon beta-1a 44 mcg SC t.i.w.** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | serious 2 | none | -/109 | -/104 | **RR 1.72** (1.24 to 2.44) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁◯ MODERATE 1 2 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | very serious 3 4 | none | 9/110 (8.2%) | 22/101 (21.8%) | **RR 0.40** (0.14 to 1.00) | 131 fewer per 1000 (from 0 fewer to 187 fewer) | ⨁⨁◯◯ LOW 1 3 4 |  |

MD – mean difference, RR – relative risk

1. Only one study, not possible to check for inconsistency
2. For continuous outcomes, a sample size of approximately 400 may not be sufficient to insure prognostic balance (ref GRADE 6 paper).
3. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).
4. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).

### Teriflunomide 14 mg oral compared to Interferon beta-1a 44 mcg SC t.i.w. for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Teriflunomide 14 mg oral** | **Interferon beta-1a 44 mcg SC t.i.w.** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | very serious 2 3 | none | -/111 | -/104 | **RR 0.91** (0.62 to 1.36) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁◯◯ LOW 1 2 3 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | very serious 3 4 | none | 12/110 (10.9%) | 22/101 (21.8%) | **RR 0.54** (0.20 to 1.38) | 100 fewer per 1000 (from 83 more to 174 fewer) | ⨁⨁◯◯ LOW 1 3 4 |  |

MD – mean difference, RR – relative risk

1. Only one study, not possible to check for inconsistency
2. For continuous outcomes, a sample size of approximately 400 may not be sufficient to insure prognostic balance (ref GRADE 6 paper).
3. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).
4. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).

### Interferon beta-1b 250 mcg SC every other day compared to Interferon beta-1a 44 mcg SC t.i.w. for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Interferon beta-1b 250 mcg SC every other day** | **Interferon beta-1a 44 mcg SC t.i.w.** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 1 | randomised trials | serious 1 | not serious 2 | not serious 3 | very serious 4 5 | none | -/30 | -/30 | **RR 0.81** (0.46 to 1.43) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁◯◯◯ VERY LOW 1 2 3 4 5 |  |

MD – mean difference, RR – relative risk

1. Insufficient reporting for randomization, and differences in baseline characteristics between groups
2. Only one study, not possible to check for inconsistency
3. Patients' treatment history was unclear.
4. For continuous outcomes, a sample size of approximately 400 may not be sufficient to insure prognostic balance (ref GRADE 6 paper).
5. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).

### Dimethyl fumarate 240 mg two times daily compared to Glatiramer acetate 20 mg for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Dimethyl fumarate 240 mg two times daily** | **Glatiramer acetate 20 mg** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | not serious | none | -/359 | -/351 | **RR 0.59** (0.38 to 0.90) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁⨁ HIGH 1 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | very serious 2 3 | none | 47/359 (13.1%) | 56/350 (16.0%) | **RR 0.78** (0.52 to 1.18) | 35 fewer per 1000 (from 29 more to 77 fewer) | ⨁⨁◯◯ LOW 1 2 3 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | very serious 2 3 | none | 44/359 (12.3%) | 35/351 (10.0%) | **RR 1.18** (0.49 to 2.84) | 18 more per 1000 (from 51 fewer to 183 more) | ⨁⨁◯◯ LOW 1 2 3 |  |

MD – mean difference, RR – relative risk

1. Only one study, not possible to check for inconsistency
2. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).
3. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).

### Dimethyl fumarate 240 mg three times daily compared to Glatiramer acetate 20 mg for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Dimethyl fumarate 240 mg three times daily** | **Glatiramer acetate 20 mg** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | not serious | none | -/345 | -/350 | **RR 0.53** (0.35 to 0.79) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁⨁ HIGH 1 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | very serious 2 3 | none | 45/345 (13.0%) | 56/350 (16.0%) | **RR 0.79** (0.53 to 1.16) | 34 fewer per 1000 (from 26 more to 75 fewer) | ⨁⨁◯◯ LOW 1 2 3 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | very serious 2 3 | none | 41/344 (11.9%) | 35/351 (10.0%) | **RR 1.15** (0.52 to 2.56) | 15 more per 1000 (from 48 fewer to 156 more) | ⨁⨁◯◯ LOW 1 2 3 |  |

MD – mean difference, RR – relative risk

1. Only one study, not possible to check for inconsistency
2. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).
3. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).

### Interferon beta-1b 250 mcg SC every other day compared to Glatiramer acetate 20mg for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Interferon beta-1b 250 mcg SC every other day** | **Glatiramer acetate 20mg** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious 1 | serious 2 | none | -/933 | -/487 | **RR 1.07** (0.90 to 1.27) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁◯ MODERATE 1 2 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 3 | not serious 1 | serious 2 | none | 188/897 (21.0%) | 90/448 (20.1%) | **RR 1.04** (0.74 to 1.46) | 8 more per 1000 (from 52 fewer to 92 more) | ⨁⨁⨁◯ MODERATE 1 2 3 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious 1 | very serious 2 4 | none | 17/933 (1.8%) | 12/487 (2.5%) | **RR 0.91** (0.37 to 2.27) | 2 fewer per 1000 (from 16 fewer to 31 more) | ⨁⨁◯◯ LOW 1 2 4 |  |

MD – mean difference, RR – relative risk

1. Patients were treatment naïve.
2. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).
3. Only one study, not possible to check for inconsistency
4. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).

### Interferon beta-1b 500 mcg SC every other day compared to Glatiramer acetate 20mg for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Interferon beta-1b 500 mcg SC every other day** | **Glatiramer acetate 20mg** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious 2 | serious 3 | none | -/899 | -/448 | **RR 0.95** (0.80 to 1.12) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁◯ MODERATE 1 2 3 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious 2 | serious 3 | none | 198/899 (22.0%) | 90/448 (20.1%) | **RR 1.01** (0.74 to 1.36) | 2 more per 1000 (from 52 fewer to 72 more) | ⨁⨁⨁◯ MODERATE 1 2 3 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious 2 | very serious 3 4 | none | 20/899 (2.2%) | 8/448 (1.8%) | **RR 1.16** (0.46 to 3.05) | 3 more per 1000 (from 10 fewer to 37 more) | ⨁⨁◯◯ LOW 1 2 3 4 |  |

MD – mean difference, RR – relative risk

1. Only one study, not possible to check for inconsistency
2. Patients were treatment naïve.
3. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).
4. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).

### Dimethyl fumarate 240 mg three times daily compared to Dimethyl fumarate 240 mg two times daily for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Dimethyl fumarate 240 mg three times daily** | **Dimethyl fumarate 240 mg two times daily** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | serious 1 | none | -/760 | -/769 | **RR 1.01** (0.82 to 1.23) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁◯ MODERATE 1 |  |
| Disease Progression | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | very serious 1 2 | none | 120/761 (15.8%) | 113/768 (14.7%) | **RR 1.06** (0.78 to 1.42) | 9 more per 1000 (from 32 fewer to 62 more) | ⨁⨁◯◯ LOW 1 2 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | very serious 1 2 | none | 109/760 (14.3%) | 109/769 (14.2%) | **RR 1.01** (0.58 to 1.73) | 1 more per 1000 (from 60 fewer to 103 more) | ⨁⨁◯◯ LOW 1 2 |  |

MD – mean difference, RR – relative risk

1. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).
2. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).

### Teriflunomide oral 14 mg compared to Teriflunomide oral 7 mg for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Teriflunomide oral 14 mg** | **Teriflunomide oral 7 mg** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 4 | randomised trials | not serious | not serious | not serious 1 | serious 2 | none | -/935 | -/912 | **RR 0.86** (0.74 to 1.00) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁◯ MODERATE 1 2 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 3 | not serious | very serious 2 4 | none | 72/358 (20.1%) | 79/365 (21.6%) | **RR 0.92** (0.64 to 1.35) | 17 fewer per 1000 (from 76 more to 78 fewer) | ⨁⨁◯◯ LOW 2 3 4 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 4 | randomised trials | not serious | not serious | not serious 1 | serious 2 4 | none | 112/934 (12.0%) | 106/912 (11.6%) | **RR 1.12** (0.73 to 1.85) | 14 more per 1000 (from 31 fewer to 99 more) | ⨁⨁⨁◯ MODERATE 1 2 4 |  |

MD – mean difference, RR – relative risk

1. In the minor contributing study, patients were treatment naïve
2. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).
3. Only one study, not possible to check for inconsistency
4. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).

### Fingolimod oral 1.25 mg compared to Fingolomid oral 0.5 mg for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Fingolimod oral 1.25 mg** | **Fingolomid oral 0.5 mg** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 4 | randomised trials | not serious | not serious 1 | not serious 2 | serious 3 | none | -/1273 | -/1269 | **RR 0.98** (0.83 to 1.17) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁◯ MODERATE 1 2 3 |  |
| Disease Progression | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | not serious | serious 3 | none | 153/1225 (12.5%) | 151/1214 (12.4%) | **RR 1.01** (0.78 to 1.32) | 1 more per 1000 (from 27 fewer to 40 more) | ⨁⨁⨁◯ MODERATE 3 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 4 | randomised trials | not serious | not serious | not serious 2 | serious 3 | none | 181/1273 (14.2%) | 128/1269 (10.1%) | **RR 1.43** (0.94 to 2.21) | 43 more per 1000 (from 6 fewer to 122 more) | ⨁⨁⨁◯ MODERATE 2 3 |  |

MD – mean difference, RR – relative risk

1. Some inconsistency. It may be explained by different definitions of relapse in studies
2. In the minor contributing study, patients’ treatment history was unclear.
3. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).

### Peg-interferon beta-1a 125 mcg once every four weeks compared to Peg-interferon beta-1a 125 mcg once every two weeks for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Peg-interferon beta-1a 125 mcg once every four weeks** | **Peg-interferon beta-1a 125 mcg once every two weeks** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | serious 2 | none | -/500 | -/512 | **RR 1.13** (0.84 to 1.52) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁◯ MODERATE 1 2 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | very serious 2 3 | none | 31/500 (6.2%) | 31/512 (6.1%) | **RR 1.02** (0.61 to 1.74) | 1 more per 1000 (from 24 fewer to 45 more) | ⨁⨁◯◯ LOW 1 2 3 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious | very serious 2 3 | none | 24/500 (4.8%) | 25/512 (4.9%) | **RR 0.98** (0.41 to 2.37) | 1 fewer per 1000 (from 29 fewer to 67 more) | ⨁⨁◯◯ LOW 1 2 3 |  |

MD – mean difference, RR – relative risk

1. Only one study, not possible to check for inconsistency
2. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper).
3. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).

### Interferon beta-1b 250 mcg SC every other day compared to Natalizumab 300 mg intravenous every 4 weeks for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Interferon beta-1b 250 mcg SC every other day** | **Natalizumab 300 mg intravenous every 4 weeks** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | serious 2 | very serious 3 4 | none | -/9 | -/10 | not estimable |  | ⨁◯◯◯ VERY LOW 1 2 3 4 |  |

MD – mean difference, RR – relative risk

1. Only one study, not possible to check for inconsistency
2. Study included only patients treated with natalizumab randomised to continue natalizumab or to switch to interferon. Patients selected into the studies may be different from the general MS population.
3. No meaningful information was given to be able to estimate the relative risk (the RR was 1.65\*10^8(4510 to 2.52\*10^9)
4. For continuous outcomes, a sample size of approximately 400 may not be sufficient to insure prognostic balance (ref GRADE 6 paper).

### Interferon beta-1b 500 mcg SC every other day compared to Interferon beta-1b 250 mcg SC every other day for RRMS

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Interferon beta-1b 500 mcg SC every other day** | **Interferon beta-1b 250 mcg SC every other day** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Annualised relapse rate | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious 2 | serious 3 | none | -/899 | -/897 | **RR 0.93** (0.80 to 1.10) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⨁⨁⨁◯ MODERATE 1 2 3 |  |
| Disease Progression | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious 2 | serious 3 | none | 198/899 (22.0%) | 188/897 (21.0%) | **RR 1.10** (0.84 to 1.51) | 21 more per 1000 (from 34 fewer to 107 more) | ⨁⨁⨁◯ MODERATE 1 2 3 |  |
| Withdrawal due to adverse events | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious 1 | not serious 2 | very serious 3 4 | none | 20/899 (2.2%) | 13/897 (1.4%) | **RR 1.63** (0.66 to 4.11) | 9 more per 1000 (from 5 fewer to 45 more) | ⨁⨁◯◯ LOW 1 2 3 4 |  |

MD – mean difference, RR – relative risk

1. Only one study, not possible to check for inconsistency
2. Patients were treatment naïve.
3. The confidence interval (CI) includes both no effect, and the 25% threshold for appreciable benefit or harm. This corresponds to a CI that includes both 1.00, and 0.75 or 1.25 (ref GRADE 6 paper)
4. Optimal information size (OIS) not met. For example, at least 200 events are required to meet OIS, based on a 25% relative risk reduction and control group risks of approximately 50% or greater (ref GRADE 6 paper).

## Supplementary material 20 Results of the cost-effectiveness analysis (all interventions except alemtuzumab) (discounted) a

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Drugs** | **Total costs (EUR)** | **Effects (QALYs)** | **Versus Interferon beta-1b 250 mg (Extavia)** | | | **Sequential ICER**  **(EUR/QALY)** |
| **Incremental cost (EUR)** | **Incremental effect (QALYs)** | **ICER (EUR/QALY)** |
| **Interferon**  **beta-1b (Extavia)** | 673,889 | 7.40 |  |  |  |  |
| **Peg-interferon**  **beta-1a**  **(Plegridy)** | 704,672 | 7.56 | 30,783 | 0.17 | 181,076 | 181,076 |
| **Natalizumab (Tysabri)** | 780,168 | 7.63 | 106,279 | 0.23 | 462,083 | 1,078,514 |
| **Dominated therapies** | | | | | | |
| **Interferon**  **beta-1b (Betaferon)** | 680,173 | 7.40 | 6,284 | - | Dominated by interferon beta-1b (Extavia) | Dominated by interferon beta-1b (Extavia) |
| **Glatiramer acetate 20 mg (Copaxone) b** | 698,765 | 7.31 | 24,876 | -0.09 | Dominated | Dominated by interferon beta-1b (Extavia) and interferon beta-1b (Betaferon) |
| **Teriflunomide (Aubagio)** | 707,298 | 7.38 | 33,409 | -0.02 | Dominated | Dominated by interferon beta-1b (Extavia), interferon beta-1b (Betaferon) and peg-interferon beta-1a |
| **Interferon**  **beta-1a 22 mcg (Rebif)** | 725,760 | 7.21 | 51,871 | -0.19 | Dominated | Dominated by interferon beta-1b (Extavia), interferon beta-1b (Betaferon), peg-interferon beta-1a, glatiramer acetate and teriflunomide |
| **Interferon beta-1a 30 mcg (Avonex)** | 730,422 | 7.27 | 56,533 | -0.13 | Dominated | Dominated by interferon beta-1b (Extavia), interferon beta-1b (Betaferon), peg-interferon beta-1a, glatiramer acetate and teriflunomide |
| **Interferon**  **beta-1a 44 mcg (Rebif)** | 734,240 | 7.32 | 60,351 | -0.08 | Dominated | Dominated by interferon beta-1b (Extavia), interferon beta-1b (Betaferon), peg-interferon beta-1a, glatiramer acetate and teriflunomide |
| **Dimethyl fumarate (Tecifidera)** | 749,564 | 7.52 | 76,675 | 0.12 | 630,625 | Dominated peg-interferon beta-1a |
| **Fingolimod (Gilenya)** | 786,440 | 7.42 | 112,551 | 0.02 | 5,627,550 | Dominated by peg-interferon beta-1a, dimethyl fumarate and natalizumab |

QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; mcg: microgram; mg: milligram

a The results are rounded in accordance to the calculations in the probabilistic model, which operates with several decimals.

b Based on effect estimates and annual drug costs, it is highly probable that glatiramer acetate 40 mg 3 times per week will be as cost-effective as glatiramer acetate 20 mg per day (given all the other parameters are the same).

## Supplementary material 21 Results of expected value of partial perfect information analysis for different groups of parameters

QALY: quality-adjusted life year; WTP: willingness to pay; INMB: incremental net monetary benefit

1. We will use a common comparator in the model based on the results from network analyses. [↑](#footnote-ref-1)