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Medicines used for Multiple Sclerosis – A Health Technology Assessment

Norwegian Institute of Public Health

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Key messages

This Health Technology Assessment was commissioned by the "National system for the introduction of new health technologies within the specialist health service". The aim of this report was to assess the effect and cost-effectiveness of the disease modifying medicines used in Norway for patients with relapsing remitting multiple sclerosis (dimethyl fumarate, teriflunomide, interferon beta, peg-interferon, glatiramer acetate, natalizumab, fingolimod, and alemtuzumab).

The key results are:

- We identified 37 randomised clinical trials. The quality of the available evidence ranged from very low to high.

- Alemtuzumab 12 mg had the best effect on annual relapse (for medicines we had evidence of high quality). Dimethyl fumarate 240 mg twice daily and fingolimod oral 0.5 mg were the most effective against disability progression (for medicines we had evidence of high quality).

- Our results indicated that interferon beta-1a 44 mcg and peg-interferon beta-1a were associated with more withdrawal due to adverse events than placebo. The examined treatments had no effect on mortality compared to placebo.

- Our health economic analysis, examining all multiple sclerosis treatment alternatives, indicated that alemtuzumab was more effective (in terms of quality-adjusted life-years (QALY)) and less costly than the other treatment alternatives. We did several scenario analyses and the cost-effectiveness results were robust to variations in the model assumptions.

- The results of a scenario analysis that excluded alemtuzumab (the dominant strategy), showed that three treatments alternatives (interferon beta-1b (Extavia), peg-interferon beta-1a and natalizumab) could be cost-effective depending on the willingness-to-pay (WTP) per QALY. Assuming a WTP below NOK 1,000,000, interferon beta-1b

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Type of publication:

Health technology assessment

Health technology assessment (HTA) is a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the development of safe, effective health policies that are patient focused and that seek to achieve best value.

Doesn't answer everything:

- Excludes studies that fall outside of the inclusion criteria
- No recommendations

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(Extavia) was 40% likely to be the most cost-effective treatment, followed by peg-interferon beta-1a (30% likely).

- The results of our model analysis showed that there is some degree of uncertainty regarding the input parameters. More research on efficacy and epidemiological data would have the greatest impact on reducing decision uncertainty.

- Our bugdet impact analysis based on the results of our cost-effectiveness analysis, the drugs' adverse events profile, and current clinical practice showed that there is a substantial potential for cost saving.

Executive summary

Background

Several disease-modifying therapies are available for the treatment of multiple sclerosis, but the comparative clinical effectiveness of these medicines is unclear. Furthermore, the cost-effectiveness of the different treatments has not been investigated in a Norwegian setting. To ensure the most appropriate multiple sclerosis management, it is important to assess effectiveness and cost-effectiveness of disease modifying medicines used for multiple sclerosis.

Objective

The aim of this project was to compare the effect and cost-effectiveness of the disease modifying medicines used for multiple sclerosis in Norway.

Methods

We conducted a systematic review based on the following conditions: Evidence should come from randomised controlled trials (RCTs) with study populations that included men and women aged 18 years or older were eligible. Modifying medicines used for multiple sclerosis were our intervention of interest (dimethyl fumarate, teriflunomide, interferon beta, peg-interferon, glatiramer acetate, natalizumab, fingolimod, and alemtuzumab). We included studies that compared these medicines to placebo or to each other. We examined the following endpoints: annual relapse, disability progression, mortality, serious adverse events, withdrawal from the study due to adverse events, hospitalisations, and health related quality of life.

We systematically searched the literature for previously published health technology assessment reports or systematic reviews that answered our objectives, and met our inclusion criteria. We conducted a systematic review of randomised controlled trials to supplement the evidence of previously published health technology assessments.

Two persons independently examined the risk of bias of included studies using the Norwegian Knowledge Centre for the Health Services methods. These are based on Cochrane methodology.

We summarised the evidence from the randomised clinical trials quantitavely through network meta-analyses of data on direct and indirect evidence on all relevant comparisons.

Two persons independently assessed the quality of the evidence for each selected endpoint. We used GRADE (Grading of recommendations Assessment, Development, and Evaluation) to assess our confidence in the effect estimates.

In order to assess the cost-effectiveness of disease-modifying therapies in patients diagnosed with relapsing-remitting multiple sclerosis, we developed a decision analytic model. The economic model was developed in the form of a cost-utility analysis and included treatments approved and available in Norway. The model structure and all assumptions were adapted to the Norwegian setting based on Norwegian clinical practice. Efficacy estimates were taken from our network meta-analyses. Transitional probabilities were derived from published sources and clinical experts' opinions. Quality of life data were extracted from published studies based on a systematic review of the literature. The costs of medications were based on prices obtained through the Drug procurement cooperation (LIS), and other costs were based on official Norwegian unit prices.

We performed probabilistic sensitivity analyses, designed as a Monte Carlo simulation with 10,000 iterations, to explore the uncertainty surrounding our results.

Results

All examined treatments were more effective than placebo against annual relapse. The effect was best for alemtuzumab 12 mg (based on high quality evidence). Fingolimod oral 0.5 mg and dimethyl fumarate 240 mg twice daily were also associated with a reduction in annualised relapse rate. For disability progression, dimethyl fumarate 240 mg twice daily and fingolimod 0.5 mg were more effective than placebo (high quality evidence).

For withdrawal due to adverse events, the conclusion is unclear due to the low quality of the available evidence. However, our results indicate that interferon beta-1a 44 mcg, and peg-interferon beta-1a are associated with more withdrawal due to adverse events than placebo.

For the outcomes change in expanded disability status scale, serious adverse events, and mortality; we did not assess the quality of the available evidence. Our results indicate that interferon beta-1a 30 mcg is associated with a reduction in expanded disability status scale. Interferon beta-1a 30 mcg is associated with fewer serious adverse

events. Finally, our results showed that none of the examined treatments increased or decreased mortality compared to placebo.

Our health economic analysis indicated that alemtuzumab dominated all other disease-modifying therapies, as it was more effective in terms of quality-adjusted life-years (QALY) and less costly than the other treatment alternatives.

A scenario analysis that excluded alemtuzumab (the dominant strategy) showed that three treatment alternatives (interferon beta-1b (Extavia), peg-interferon beta-1a and natalizumab) could be cost-effective depending on the willingness-to-pay (WTP) threshold. Interferon beta-1b was likely to be the cost-effective choice for a WTP per QALY below NOK 1,658,000. Peg-interferon was the cost-effective option for a WTP from NOK 1,658,450 to NOK 10,619,960, and natalizumab was the cost-effective alternative for a WTP above NOK 10,619,960. Assuming a WTP below NOK 1,000,000 per QALY, interferon beta-1b (Extavia) was approximately 40% likely to be the most cost-effective treatment, followed by peg-interferon beta-1a (approximately 30% likely).

The results of probabilistic analysis showed that there is some degree of uncertainty regarding the input parameters. More research on efficacy and epidemiologic input parameters would have the greatest impact on reducing decision uncertainty.

We performed several scenario analyses to test the uncertainty around the model assumptions. The results showed that, while there were numerical changes to the incremental cost-effectiveness ratio, the cost-effectiveness results were robust to variations in the model assumptions and the conclusions of the analysis would not change.

Our bugdet impact analysis based on the results of our cost-effectiveness analysis, the drugs' adverse events profile, and current clinical practice showed that there is a substantial potential for cost saving.

Discussion

We used a systematic methodology to search for evidence, extract data, and assess the risk of bias of studies and quality of evidence for important outcomes. The systematic review included evidence on both established and emerging treatments. We examined the effect of these treatments on clinical endpoints relevant for patients with multiple sclerosis. We have analysed direct and indirect evidence through network meta-analyses. The consistency of results using different methods indicates that our results are robust.

Our systematic review has some limitations, due more to the weakness of the available evidence than to the methods used in this report. These limitations are related to the

paucity and quality of the available evidence, and to the methodologies used in the included randomised controlled trials.

We used a probabilistic Markov-model, considered the appropriate approach for simulating the natural history of multiple sclerosis. The model structure and all assumptions have been adapted to the Norwegian setting based on Norwegian clinical practice with close assistance of experts in this field.

For transitional probabilities, we did not find Norwegian data that were compatible with the developed model, so these were based on estimates reported in the published literature.

Study designs of published trials did not permit separate analyses of first and second line treatments, or conclusions regarding the sequential use of first and second line treatments. Therefore, we did not perform separate cost-effectiveness analyses for first or second line treatments. In addition, based on expert opinion, we did not include combination therapy in our model, as it is not relevant to current Norwegian clinical practice.

Conclusion

Alemtuzumab 12 mg had the best effect against annual relapse. Dimethyl fumarate 240 mg twice daily and fingolimod oral 0.5 mg were the most effective against disability progression. Results indicate that some treatments are associated with more withdrawals due to adverse events than placebo. Our results showed that the examined treatments had no effect on mortality.

Our health economic analysis indicated that alemtuzumab was more effective and less costly than the other treatment alternatives. A scenario analysis that excluded alemtuzumab indicated that three treatment alternatives (interferon beta-1b (Extavia), peg-interferon beta-1a and natalizumab) could be cost-effective depending on the WTP. For a WTP below NOK 1,000,000 per QALY, interferon beta-1b (Extavia) was approximately 40% likely to be the most cost-effective treatment, followed by peg-interferon beta-1a (approximately 30% likely).

The results of probabilistic analysis showed that there is some degree of uncertainty regarding the input parameters. More research on efficacy and epidemiologic input parameters would have the greatest impact on reducing decision uncertainty.

Our budget impact analysis showed that there is a substantial potential for cost saving.

Hovedfunn (norsk)

Denne fullstendige metodevurderingen ble bestilt av «Nasjonalt system for innføring av nye metoder i spesialisthelsetjenesten». Målet var å sammenligne effekt, sikkerhet og kostnadseffektivitet av sykdomsmodifiserende legemidler som brukes for multippel sklerose i Norge (dimetylfumarat, teriflunomid, interferon beta, peginterferon, glatirameracetat, natalizumab, fingolimod og alemtuzumab).

Hovedfunnene er:

- Vi identifiserte 37 randomiserte kontrollerte studier og kvaliteten på dokumentasjon varierte fra veldig lav til høy.

- Basert på sammenligninger hvor kvaliteten på dokumentasjonen var høy kan vi si at alemtuzumab 12 mg hadde den beste effekten mot årlig tilbakefall, og at dimetylfumarat 240 mg to ganger om dagen og fingolimod 0.5 mg var de mest effektive mot sykdomsprogresjon.

- Våre resultater indikerer at interferon beta-1a 44 mcg, og peginterferon beta-1a var assosiert med høyere frafall på grunn av bivirkninger enn placebo. Våre resultater viste ingen av behandlingene hadde effekt på dødelighet.

- Vår helseøkonomiske analyse indikerte at alemtuzumab var bedre og mindre kostnadskrevende enn de andre behandlingsalternativene. Vi utførte flere scenarioanalyser for å teste usikkerheten rundt forutsetninger ved modellen, men konklusjonene endret seg ikke.

- En scenarioanalyse hvor alemtuzumab (den dominante strategien) ble ekskludert, viste at tre behandlingsalternativer (interferon beta-1b (Extavia), peginterferon beta-1a og natalizumab) kunne være kostnadseffektive, avhengig av betalingsvilje per vunnet kvalitetjustert leveår (QALY). Ved å anta en betalingsvilje under en million kroner per vunnet QALY, var interferon beta-1b (Extavia) trolig den mest kostnadseffektive behandlingen (ca. 40 %), etterfulgt av peginterferon beta-1a (ca. 30 %).

Tittel:
Fullstendig metodevurdering av legemidler ved multippel sklerose

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Publikasjonstype:

Metodevurdering

En metodevurdering er resultatet av å
- innhente
- kritisk vurdere og
- sammenfatte
relevante forskningsresultater ved hjelp av forhåndsdefinerte og eksplisitte metoder.

Minst ett av følgende tillegg er også med:
helseøkonomisk evaluering, vurdering av konsekvenser for etikk, jus, organisasjon eller sosiale forhold

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Svarer ikke på alt:

- Ingen studier utenfor de eksplisitte inklusjonskriteriene
- Ingen anbefalinger

Hvem står bak denne rapporten?

Folkhelseinstuttet har skrevet rapporten på oppdrag fra Nasjonalt system for innføring av nye metoder i spesialisthelsetjenesten

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Når ble litteratursøket utført?

Søk etter studier ble avsluttet november 2015

- Vår modellanalyse viste at det er en viss grad av usikkerhet knyttet til parameterne brukt i analysen. Mer forskning på effekt av legemidlene eller bedre epidemiologiske data fra norske registre ville hatt størst innvirkning på å redusere beslutningsusikkerhet.

- Vår budsjettkonsensanalyse basert på resultatene av vår kostnadseffektivitetsanalyse, bivirkninger knyttet til behandlingsalternativene og dagens kliniske praksis viste at det er et betydelig potensial for å redusere kostnadene knyttet til MS-behandling i spesialisthelsetjenesten.

Sammendrag (norsk)

Fullstendig metodevurdering av legemidler ved multippel sklerose

Bakgrunn

Det finnes flere sykdomsmodifiserende legemidler godkjent til bruk ved multippel sklerose, men en fullstendig sammenligning av den kliniske effektiviteten på tvers av alle disse har ikke vært gjort. Kostnadseffektiviteten av de ulike behandlingene er heller ikke blitt undersøkt i en norsk setting.

Problemstilling

Målet vårt var å sammenligne effekt, sikkerhet og kostnadseffektivitet av sykdomsmodifiserende legemidler som brukes for multippel sklerose i Norge.

Metode

Vi utførte en systematisk oversikt, hvor vi inkluderte randomiserte kontrollerte studier på personer over 18 år med multippel sklerose behandlet med følgende legemidler: dimetylfumarat, teriflunomid, interferon beta, peginterferon, glatirameracetat, natalizumab, fingolimod og alemtuzumab. Vi inkluderte studier som sammenlignet disse medisinene med placebo eller med hverandre. Vi undersøkte følgende kliniske endepunkt: årlig attakk, sykdomsprogresjon, dødelighet, alvorlige bivirkninger, frafall fra studien på grunn av bivirkninger, sykehusinnleggelser og helserelatert livskvalitet.

Vi søkte etter publiserte Health Technology Assessment (HTA) rapporter og systematiske oversikter som besvarte vår problemstilling. Deretter søkte vi etter randomiserte kontrollerte studier for å supplere kunnskapsgrunnlaget med informasjon publisert etter søkedato i den nyeste, mest omfattende HTA rapporten vi identifiserte.

To personer undersøkte uavhengig av hverandre kvaliteten på den inkluderte HTA-rapporten og risiko for systematiske skjevheter i de supplerende studiene. Vi oppsummerte kliniske resultater gjennom nettverks meta-analyser som baserer seg på både

direkte og indirekte sammenligninger. Til slutt brukte vi GRADE (Grading av anbefalinger Assessment, Development, and Evaluation) for å vurdere kvaliteten på dokumentasjonen og vår vår tillit til effektestimatene.

For å vurdere kostnadseffektiviteten av de sykdomsmodifiserende legemidlene hos pasienter med relapsing-remitting multippel sklerose, utviklet vi en helseøkonomisk modell (Markov-modell). Modellstruktur og alle forutsetninger ble tilpasset norsk klinisk praksis. Effektestimatene ble tatt fra vår systematiske gjennomgang av klinisk effekt og sikkerhet. Overgangssannsynligheter ble hentet fra publiserte kilder og supplert med opplysninger fra kliniske eksperter. Livskvalitetsdata ble hentet fra publiserte studier indentifisert gjennom en systematisk gjennomgang av litteratur. Kostnader på medisiner ble basert på priser fra Legemiddelinnkjøpssamarbeidet (LIS), og andre kostnader var basert på norske kilder. Vi utførte probabilistiske sensitivitetsanalyser, utformet som en Monte Carlo-simulering med 10,000 gjentakelser, for å analysere usikkerheten i våre resultater.

Resultat

Alle undersøkte legemidler var mer effektive enn placebo mot årlig attakk. Effekten var best for alemtuzumab 12 mg (basert på evidens av høy kvalitet). For sykdomsprogresjon var dimetylfumarat og fingolimod mer effektivt enn placebo (evidens av høy kvalitet).

For frafall på grunn av bivirkninger var det lavere kvalitet på tilgjengelig dokumentasjon, noe som knytter mer usikkerhet til resultatene. Men våre resultater indikerer at både interferon beta-1a 44 mcg, og peginterferon beta-1a begge er assosiert med høyere frafall på grunn av bivirkninger enn placebo.

Vi vurderte ikke kvaliteten på tilgjengelig dokumentasjon om endring i uførhetsstatusskalaen EDSS (expanded disabliltity symptom scale), alvorlige bivirkninger og dødsfall. Våre resultater tyder på at interferon beta-1a 30 mcg var relatert til en reduksjon i EDSS nivå. Interferon beta-1a 30 mcg var assosiert med færre alvorlige bivirkninger. Til slutt, viser våre resultater at ingen av de undersøkte behandlinger ga økt dødelighet sammenlignet med placebo.

Vår helseøkonomiske analyse indikerte at alemtuzumab dominerte alle andre sykdomsmodifiserende behandlinger. Alemtuzumab var både mer effektiv og mindre kostnadskrevende enn de andre behandlingsalternativene.

Resultatene av en scenarioanalyse hvor alemtuzumab (den dominante strategien) ble ekskludert, viste at tre behandlingsalternativer (interferon beta-1b (Extavia), peginterferon beta-1a og natalizumab) kunne være kostnadseffektive, avhengig av betalingsvilje per vunnet kvalitetjustert leveår (quality-adjusted life-years, QALY). Forutsatt en betalingsvilje (Willingness to pay, WTP) lavere enn 1 658 000 kroner per

QALY, vil Interferon beta-1b sannsynligvis være et kostnadseffektivt valg. For en WTP mellom 1 658 450 og 10 619 960 kroner var peginterferon et kostnadseffektivt alternativ, og for en WTP over 10 619 960 kroner var natalizumab et kostnadseffektivt alternativ. Ved å anta en betalingsvilje på under 1 000 000 kroner per vunnet QALY var interferon beta-1b (Extavia) trolig den mest kostnadseffektive behandlingen (ca. 40%), fulgt av peginterferon beta-1a (ca. 30%).

Sannsynlighetsanalyser viste at det er usikkerhet knyttet til parameterne benyttet i modellen. Mer forskning på effekt av legemidlene eller bedre epidemiologiske data fra norske registre ville hatt størst innvirkning på å redusere beslutningsusikkerhet.

Vi utførte flere scenarioanalyser for å teste usikkerheten rundt ulike helseøkonmiske modellforutsetninger. Selv om det var numeriske endringer i resultater, så var resultatene for kostnadseffektivitet robuste og konklusjonene fra analysen endret seg ikke.

Vår budsjettkonsensanalyse basert på resultater av kostnadseffektivitetsanalysen vår, bivirkninger knyttet til behandlingsalternativene og dagens kliniske praksis viste at det er et betydelig potensial for å redusere kostnadene knyttet til MS-behandling i spesialisthelsetjenesten.

Diskusjon

Vi brukte internasjonalt anerkjente metoder for å systematisk oppsummere kunnskapsgrunnlaget og fokuserte på kliniske endepunkter som er relevante for pasienter med multippel sklerose. Konsistente resultater ved bruk av direkte, indirekte eller nettverksanalyser viser at våre resultater er pålitelige.

Vår systematiske gjennomgang har noen begrensninger. De er hovedsakelig knyttet til at det er få studier eller rapporterte utfall for enkelte av sammenligningene og metodiske uklarheter i de inkluderte randomiserte kontrollerte studiene.

Vi brukte en probabilistisk Markov-modell, som er ansett for å være den beste måten å simulere sykdomsforløpet til multippel sklerose på. Modellens struktur og alle forutsetninger er tilpasset norske forhold og klinisk praksis med tett bistand fra eksperter på feltet. Der vi ikke fant norske data som kunne brukes i modellen benyttet vi overgangssannsynligheter fra publisert litteratur.

Måten de publiserte kliniske studiene er utført på gjør det vanskelig å undersøke første- og andrelinje behandlinger hver for seg, eller å konkludere på sekvensiell bruk av ulike behandlinger. Vi utførte derfor ikke separate kostnadseffektivitetsanalyser for første- eller andrelinjebehandlinger. Som følge av ekspertuttalelser, gjorde vi heller ikke analyser for kombinasjonsbehandling siden det ikke er relevant for norsk klinisk praksis i dag.

Konklusjon

Basert på dokumentasjon av høy kvalitet kan vi si at alemtuzumab 12 mg hadde den beste effekten mot årlig tilbakefall og at fingolimod oral 0,5 mg og dimetylfumarat 240 mg to ganger daglig hadde den beste effekten mot sykdomsprogresjon. Resultatene tyder på at noen behandlinger er forbundet med mer frafall på grunn av bivirkninger enn placebo. De inkluderte intervensjonene hadde ingen effekt på dødelighet.

Vår helseøkonomiske analyse indikerte at alemtuzumab var både mer effektiv og mindre kostnadskrevende enn de andre behandlingsalternativene.

En scenarioanalyse hvor alemtuzumab ble ekskludert viste at tre behandlingsalternativer (interferon beta-1b (Extavia), peginterferon beta-1a og natalizumab) kunne være kostnadseffektive, avhengig av betalingsvilje per vunnet QALY. Ved å anta en betalingsvilje under en million kroner per vunnet QALY, var trolig interferon beta-1b (Extavia) den mest kostnadseffektive behandlingen (ca. 40 %), fulgt av peginterferon beta-1a (ca. 30 %).

Resultatene av sannsynlighetsanalysen viste at det er en viss grad av usikkerhet knyttet til de ulike parameterne inkludert i analysen. Mer forskning på effekt og epidemiologiske data vil ha størst innvirkning på å redusere usikkerheten rundt beslutningen.

Vår budsjettkonsensanalyse viste at det er et betydelig potensial for å redusere kostnadene knyttet til MS-behandling i spesialisthelsetjenesten.

Glossary and abbreviations	
CI	**Confidence interval.** A measure of uncertainty around the results of a statistical analysis that describes the range of values within which we can be reasonably sure that the true mean effect lies. Wider intervals indicate lower precision; narrow intervals, greater precision.
CIS	**Clinical isolated syndrome**
CNS	**Central nervous system**
CUA	**Cost-utility analysis.** An economic evaluation where health consequences are measured in **QALY**s.
EDSS	**Expanded disability status scale**
EQ-5D	**European Quality of Life-5 Dimensions.** EQ-5D is a standardized instrument for use as a measure of health outcome.
EVPI	Expected value of partial perfect information
GRADE	**Grading of recommendations Assessment, Development, and Evaluation**
HTA	**Health Technology Assessment**
Healthcare perspective	Economic evaluation from a healthcare perspective will consider only the costs and consequences specifically related to the healthcare sector (direct costs), *e.g.* staff costs, capital costs, drug acquisition costs.
ICER	**Incremental cost-effectiveness ratio**. The ratio of the difference in costs between two alternative health technologies to the difference in effectiveness between these two technologies. $ICER = \frac{Cost_{\text{intervention}} - Cost_{\text{comparator}}}{Effect_{\text{intervention}} - Effect_{\text{comparator}}} = \frac{\Delta C}{\Delta E}$
MRI	**Magnetic resonance imaging**
MS	**Multiple sclerosis**
NHB	**Net Health Benefit.** In a decision-making process, a positive NHB suggests that the intervention represents good value for money $NHB = \Delta E - \frac{\Delta C}{\lambda}$
NMB	**Net Monetary Benefit.** In a decision-making process, a positive NMB suggests that the intervention represents good value for money. $NMB = \lambda \cdot \Delta E - \Delta C$
Odds	The odds of an event happening is defined as the probability that an event will occur divided by the probability that the event will not occur.

OR	**Odds ratio.** The ratio of the odds of an outcome in one treatment group divided by the odds of the same outcome in a different treatment group.
PPMS	**Primary progressive multiple sclerosis**
PSA	**Probabilistic sensitivity analysis.** An analysis of the uncertainty related to all parameters in a decision analytic model. Typically performed by Monte Carlo simulation, hence by drawing values from probability distributions for all parameters simultaneously
QALY	**Quality-adjusted life-year.** A measure of health outcomes that combines quantity and quality of life by assigning to each year of life a weight from 1 (perfect health) to 0 (state judged equivalent to death) dependent on the individual's health related quality of life during that year
RCT	**Randomised controlled trial.** An experiment in which investigators use randomisation to allocate participants into the groups that are being compared. Usually allocation is made at the level of individuals, but sometimes it is done at group level e.g. by schools or clinics. This design allows assessment of the relative effects of interventions.
RRMS	**Relapsing-remitting multiple sclerosis**
RR	**Relative risk / risk ratio.** The relative risk is the absolute risk (AR) in the intervention group divided by the AR in the control group. It is to be distinguished from odds ratio (OR), which is the ratio of events over non-events in the intervention group over the ratio of events over non-events in the control group.
SPMS	Secondary progressive multiple sclerosis
SR	**Systematic review.** A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.
Statistically significant	Means that the findings of a study are unlikely to have arisen because of chance. Significance at the commonly cited 5% level ($P < 0.05$) means that the observed difference or greater difference would occur by chance in only 1/20 similar cases. Where the word "significant" or "significance" is used without qualification in the text, it is being used in this statistical sense.
SUCRA	Surface under the cumulative ranking curve
WTP (λ)	**Willingness to pay**. A pre-specified limit of what society is willing to pay for a given health unit (e.g. QALY or life year). In Norway it is common to use NOK 500 000 per QALY or life year in economic evaluations.

Table of contents

Preface

This project was commissioned by the "National system for the introduction of new health technologies within the specialist health service", that wanted us to examine the effect and cost-utility of the disease modifying medicines used for patients with relapsing remitting multiple sclerosis in Norway. The results will be used as scientific documentation for price negotiations, and guidelines development.

Elisabeth Couto was lead reviewer for the clinical evaluation and Vida Hamidi led the health economic evaluation. Rune Midgard and Torbjørn Wisløff performed peer review of the report. We thank Elisabeth Gulowsen Celius and Elisabeth Farbu for clinical expertise and input in the report, and Bjørn Svendsen for his contribution on cost information.

The project group consisted of:

- Couto, Elisabeth, *(project leader), senior researcher*
- Hamidi Vida, *senior researcher*
- Ringerike Tove, *senior researcher*
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The aim of this report is to support well-informed decisions in health care that lead to improved quality of services. The evidence should be considered together with other relevant issues, such as clinical experience and patients' preferences.

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Objective

Overall objective

- To examine the effect and cost-utility of the disease modifying medicines used for patients with relapsing remitting multiple sclerosis in Norway.

Specific objectives

- To conduct a systematic review to assess the efficacy and safety of the different disease modifying medicines used for multiple sclerosis with regard to clinical important endpoints
- To carry out a health economic evaluation ascertaining cost-utility of the disease modifying medicines used for patients with relapsing remitting multiple sclerosis.

Background

Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system (CNS) with secondary neurodegeneration (1). It affects nerves in the brain and spinal cord by damaging the myelin sheath that covers the axon part of the nerve cells. The myelin sheath protects and aids signal transduction, therefore, when damaged, it affects the transfer of timely and correct information from the CNS to the peripheral part of the nervous system (1-3).

The epidemiology of multiple sclerosis

MS is one of the most common causes of disability in young adults (4). In 2013, a systematic review summarised MS incidence and prevalence estimates reported by 123 studies that used a range of different data sources (5). Prevalence and incidence estimates tended to be higher in Northern countries, and in more recently published studies. Incidence surveys show an increase in MS incidence in later years (6). Reported annual incidence rates are 1.9 (95% confidence interval: 1.2-2.6) for the period 1953 to 1957, and 8.5 (7.3.9.7) for 1978 to 2007 (7). Increase in MS incidence could be due, to some extent, to changes in methods and criteria used for MS diagnosis (6). In Europe, the prevalence of MS is twice as high in women than in men (5). Incidence rates are generally also higher in women (5). A study, using data from the National Patient Registry, the Norwegian MS registry, and Biobank data estimated crude prevalence rates of 203/100,000 (95% confidence interval 199 – 207) overall, 280 (247-287) for women, and 126 (122-130) for men (8).

The disease usually starts around the age of 30 (range 20-40), and prevalence rates peak at around 50 (6). The median time to death is around 30 years from disease onset, representing a reduction in life expectancy of 5 to 10 years (1).

The aetiology of MS is not well understood. Geographical variations in MS prevalence and incidence could be due to differences in genes and environment. To date, most commonly reported risk factors for MS are exposure to Epstein Barr virus, cigarette smoking, low sunlight exposure and vitamin D levels and genetic predisposition (1, 9-11).

The clinical course and diagnosis of multiple sclerosis

Clinical manifestations depend on the affected area of the CNS. Symptoms reflect an involvement of motor, sensory, visual and autonomic systems (1). Symptoms evolve over time. MS appears in several degrees of severity from a mild form (with few attacks) to a more progressive disease that is potentially highly disabling and that impacts on the quality of life of patients and their families (1, 12).

Appropriate MS diagnosis allows early disease management. Different diagnosis criteria have been used over the years, leading to possible differences in MS diagnosis with time. The revised McDonald criteria are the most commonly used for MS diagnosis nowadays. National guidelines, such as British (NICE) and Norwegian guidelines, recommend the use of the revised McDonald criteria for MS diagnosis (12, 13).

To be diagnosed with MS, patients should have at least one clinical attack (demyelinating event in the CNS with duration of symptoms of more than 24 hours in the absence of fever or infection) corroborated by findings on neurological examination, visual evoked potential response or findings on magnetic resonance imaging (MRI) consistent with demyelination in the CNS (T2 lesion or T1 gadolinium-enhancing lesion). In addition, exclusion of other possible diagnoses is essential for the diagnosis of MS.

MS is classified as (1, 13):

- Clinical isolated syndrome (CIS): one attack and objective clinical evidence of one lesion.
- Relapsing-remitting MS (RRMS): objectively established disease as with two or more clinical attacks and localisaton of two or more lesions in the CNS. It is characterised by episodes of acute worsening of function followed by partial or complete recovery (14). 85 to 90% of patients present with RRMS (11). Aproximately half of the patients with RRMS will develop secondary progressive MS (15).
- Secondary progressive MS (SPMS): About 30-40% of the prevalent MS population have SPMS. It is associated with disease progression without clinical attacks and of highly variable degrees (16).
- Primary progressive MS (PPMS): at least one year of disease progression and characteristic findings on MRI and/or positive findings in cerebrospinal fluid.

Disease progression is most commonly assessed by relapse rate and disease progression. The gradual increasing level of disability is often measured with the Expanded Disability Status Scale (EDSS), an ordinal scale ranging from 0 (normal clinical status) to 10 (death due to MS) in steps of 0.5 points (17).

Treatment alternatives

Disease-modifying medicines are the standard treatment for patients with MS. It is possible to treat both the underlying disease, relapses and MS-related symptoms. Disease modifying drugs may inhibit the inflammatory process to prevent progression and reduce disabilities due to the disease. The different treatment options have different mechanisms of action, routes of administration, approved indications and other differences influencing their use. The various medications are presented in Table 1.

Due to safety issues, some of these treatments are used as first line treatments (dimethyl fumarate, teriflunomide, interferon beta, peg-interferon, glatiramer acetate), and others as second line treatments (natalizumab, fingolimod, and alemtuzumab) according to different national guidelines (18).

Disease-modifying treatments are expensive. The use of MS medicines has been described as “uneven” with “questionable effects on the long-term accumulation of disability and disease progression” (1). Currently a number of new disease-modifying therapies are available for the treatment of MS, but it is uncertain whether the new medicines are cost-effective in the Norwegian setting. To insure proper MS management, it is important to assess the effectiveness and cost-effectiveness of disease modifying medicines used for MS.

This report was ordered by the “National system for the introduction of new health technologies within the specialist health service”, and will be used for price negotiations and guidelines development.

Table 1. *Overview of included interventions*

Intervention **Medication name** **First authorisation date in Norway**	**Administration form and recommended dose**	**Approved indication**
Alemtuzumab **(Lemtrada)** **Sept.2013**	- 12 mg concentrate for solution for infusion - 12 mg/day for 5 consecutive days, then after 12 months: 12 mg/day for 3 consecutive days. Diluted and i.v. over approximately 4 hours	Adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features
Dimethyl fumarate **(Tecfidera)** **Jan. 2014**	-120 or 240 mg gastro-resistant hard capsules - 240 mg twice daily	Adult patients with relapsing remitting multiple sclerosis
Fingolimod **(Gilenya)** **March 2011**	- 0,5 mg hard capsules - 0,5 mg once daily	- High disease activity despite treatment with at least one disease modifying therapy - Rapidly evolving severe relapsing remitting multiple sclerosis
Glatiramer acetat **(Copaxone)** **Februar 2004** **April 2015 (40 mg)**	- 20 mg/ml Solution for Injection, Pre-filled Syringe - 20 mg of glatiramer acetate (one pre-filled syringe), administered as a subcutaneous injection once daily - 40 mg of glatiramer acetate administered three times weekly	- Patients experienced a well-defined first clinical episode, determined to be at high risk of developing clinically definite multiple sclerosis - Ambulatory patients with relapsing, remitting multiple sclerosis w/≥2 attacks of neurological dysfunction over the preceding two-year period.
Interferon beta-1a **(Avonex)** **May 2011**	- 30 micrograms (6 million IU) powder and solvent for solution for injection - 30 micrograms (1 ml solution), by intramuscular (IM) injection once a week	-Relapsing multiple sclerosis w/≥2 relapses in the previous three years without evidence of continuous progression between relapses

Interferon beta-1a **(Rebif)** **June 2010**	- 22 micrograms (6 million IU) solution for injection in pre-filled syringe - 44 micrograms given three times per week by subcutaneous injection	Relapsing multiple sclerosis, w/≥2 acute exacerbations in the previous two years
Peg-interferon beta-1a **(Plegridy)** **July 2014**	- 125 micrograms injected subcutaneously every 2 weeks	Adult patients for the treatment of relapsing remitting multiple sclerosis
Interferon beta-1b **(Betaferon)** **August 2008**	- 250 microgram (8.0 million IU) /ml, powder and solvent for solution for injection [300 microgram (9.6 million IU) per vial] - 250 microgram (8.0 million IU), contained in 1 ml of the reconstituted solution, to be injected subcutaneously every other day	- Patients with a single demyelinating event with an active inflammatory process (…)determined to be at high risk of developing clinically definite multiple sclerosis - Patients with relapsing-remitting multiple sclerosis w/≥2 relapses within the last two years -Patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.
Interferon beta-1b **(Extavia)** **June 2006**	See: interferon beta-1b (Betaferon) above	Adults and adolescents from 12-17 years of age. Indication similar to Interferon beta-1b (Betaferon) above
Natalizumab **(Tysabri)** **June 2006**	- 300 mg concentrate for solution for infusion - 300 mg by i.v over approximately 1 hour, once every 4 weeks	- Adult patients with relapsing remitting multiple sclerosis -High disease activity despite treatment with a betainterferon or glatiramer acetate -Rapidly evolving severe relapsing remitting multiple sclerosis
Teriflunomide **(Aubagio)** **Aug.2013**	- 14 mg film-coated tablets - 14 mg once daily, swallowed whole with some water	Adult patients with relapsing remitting multiple sclerosis

Introduction to Economic Evaluations of Health Care Programmes

The basic task of any economic evaluation is to identify, measure and compare costs and consequences of the alternatives under consideration in an incremental analysis—one in which the differences in costs are compared with differences in consequences (19). Results of economic evaluations can be expressed as an incremental cost-effectiveness ratio (ICER), which is defined by the following equation:

$$ICER = \frac{Cost_{\text{intervention}} - Cost_{\text{comparator}}}{Effect_{\text{intervention}} - Effect_{\text{comparator}}} = \frac{\Delta C}{\Delta E}$$

Because the health care sector, like the society in general, is restricted by scarce resources and budget constraints, economic evaluations are important tools for decision makers facing questions of how to prioritize treatments and maximize health benefits using scarce resources. For an economic evaluation to be meaningful in a decision making process, the ICER must be judged with regard to a ceiling ratio that reflects the decision maker's maximum willingness to pay (WTP) for a health gain. The decision rule for an economic evaluation can therefore be expressed as

$$\frac{\Delta C}{\Delta E} < \lambda$$

where λ equals WTP, and means that if the ICER of an intervention is below the ceiling ratio, introducing the intervention represents good value for money. Because the ICER has poor statistical properties, ICERs are often rearranged to express either incremental net monetary benefit (INMB) or incremental net health benefit (INHB), which yields the following decision rules related to INMB or INHB.

INMB: $\lambda \cdot \Delta E - \Delta C > 0$

INHB: $\Delta E - (\Delta C/\lambda) > 0$

An intervention can in other words be considered cost-effective if it yields a positive INHB or INMB.

Economic evaluations are often based on decision models (such as decision trees, Markov models, etc.) that calculate results based on various input parameters in the model. Because there are always uncertainties related to the values of these parameters, sensitivity analysis is an important feature of any economic evaluation based on a decision model framework. In short, sensitivity analysis illustrates how much the results vary when model parameters are changed.

Probabilistic sensitivity analysis (PSA) is a kind of sensitivity analysis. The advantage of PSA is that it makes it possible to take the uncertainties of all of the model-parameters into account simultaneously. The basic approach in PSA is to assign appropriate probability distributions to the model-parameters, which makes it possible to replace the "fixed" values of the parameters with values generated by random draws from the distributions. Doing this repeatedly, with a specified number of iterations, makes it possible to estimate the probabilities that alternative interventions are cost-effective subject to different ceiling values of WTP. The calculation is based on the alternative that renders the highest values of NMB or NHB. Results from PSAs are often presented as scatter plots, which show point estimates of the ICER for all iterations in the cost-effectiveness plane, and also as cost-effectiveness acceptability curves (CEACs), which show the probability of the alternatives being cost-effective subject to changing values of WTP.

Another result from PSA is the expected value of perfect information (EVPI). This number indicates the value to society to have more accurate information about the decision, given a WTP. If EVPI for a given population seems large, it might be of interest to determine for which parameters it would be most useful to obtain additional data. Expected value of perfect information for parameters is a more time-consuming analysis that can help determine for which single parameters or groups of parameters it is most cost-effective to conduct new research.

In short, making a model probabilistic means that it is possible to estimate the uncertainty associated with a decision to implement alternative interventions, and it provides a possibility of estimating the value of collecting additional information from new research.

Priority setting criteria

According to Norwegian policy documents (20) , a treatment should be prioritized if the following criteria are met:

- *The disease is severe:* A disease is considered severe to the degree that it causes pain and discomfort, loss of physical, psychological and social function and if it limits the individual in his or her daily activities. Severity is also evaluated according to the risk increase the disease entails in terms of death, disability and discomfort, if treatment is postponed.

- *The treatment is effective:* The patient should be expected to benefit from treatment in terms of longevity or improved quality of life of certain duration. The treatment effectiveness should also be well documented.

- *The treatment is cost-effective:* The additional costs of the treatment should be reasonable compared to the additional benefits.

It should be mentioned that there is no academic or political consensus regarding what constitutes a reasonable relationship between incremental costs and effects in Norway. For this reason, we use a range of potential willingness-to-pay (WTP) values throughout our report.

Clinical evaluation – Methods

Criteria for considering studies for this review

Type of studies

We searched for published health technology assessment (HTA) reports or systematic reviews (SR) of randomised controlled trials (RCT). We included only reports and reviews of high quality that fitted our inclusion criteria. We supplemented the evidence with data from recently published RCTs.

Type of participants (Population of interest)

Suitable studies included men and women aged 18 and above diagnosed with MS. Eligible MS diagnosis was RRMS. CIS patients were not included in this report; however, Appendix 3 lists identified studies that included CIS patients. We excluded studies with patients with primary progressive MS and radiologically isolated syndrome. Studies that included both eligible patients, and patients from our exclusion criteria were included if results were presented separately for each type of patients (so that we could extract results for patients who fitted our inclusion criteria).

Types of interventions

The following medicines were the interventions of interest: dimethyl fumarate, teriflunomide, interferon beta, peg-interferon, glatiramer acetate, natalizumab, fingolimod, and alemtuzumab.

Comparisons

Eligible comparison groups were either placebo or one of the medicines listed above.

Types of outcome measures

The outcomes of interest were:

Primary outcomes

- Clinical relapses
- Disability progression measured using the EDSS
- Mortality
- Serious adverse events

Secondary outcomes:

- Withdrawal from study due to adverse events
- Stay at hospitals
- Health related quality of life measured with EQ-5D

Literature search

The research librarian (in collaboration with the project team) conducted a peer-reviewed literature search using index terms (Medical Subject Headings and EMTREE terms) and free text terms relating to the population and the interventions of interest. The last date of the literature search was 9/11/2015. Full literature search strategies are presented in Appendix 1. We did not use any language restrictions in the literature search.

We searched 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 searched also 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
- Statens beredning för medicinsk utvärdering (SBU)
- EUnetHTA POP database (POP = Planned and Ongoing Projects)
- PROSPERO – Centre for Reviews and Dissemination

We checked bibliographies of selected articles for additional publications meeting our inclusion criteria. Finally, we searched the WHO ICTRP and ClinicalTrials.gov to identify relevant ongoing or unpublished trials.

We contacted the companies with marketing authorization in Norway for the MS medicines included in order to get additional information.

Selection and assessment of publications

Selection of publications

Unless stated otherwise, two persons independently carried out the selection processes.

Selection of HTA or SR reports

Two persons read titles and abstracts retrieved by the literature search, and excluded obviously irrelevant literature. Based on information provided in abstracts, one person organised the publications depending on how many medicines were apparently examined. Abstracts looking at two, three, or more than three drugs were grouped together. If we lacked information in the abstract to know which medicine were assessed, articles were classified in the "several drugs category" (more than three drugs). One person sorted all abstracts in the "several drugs category" according to the date of publication from the newest to the oldest. Two persons read full-text articles of the "several drugs category" by publication chronological order (from newest to oldest). Hence, we were able to include the most recently published HTA report that met all our inclusion criteria.

Selections of RCT publications

Two persons examined all titles and abstracts retrieved by the literature search for possibly relevant RCTs published after the selected HTA, and excluded obviously irrelevant titles and abstracts. Two persons read full-text articles of selected publications. We included articles that met our inclusion criteria. The same process was used to select publications sent by companies having market authorization for MS medicines in Norway.

Throughout the selection process, any disagreement was discussed to reach an agreement.

Assessment of included publications

Quality assessment of selected HTA

We assessed the quality of the SR part of the identified HTA using the checklist for SR in the handbook of The Norwegian Knowledge Centre for the Health Services (21).

Risk of bias of RCTs

We did not perform risk of bias assessments for the RCTs included in the selected high quality HTA report. Instead, we report the risk of bias assessments conducted by the HTA authors. The domains of risk of bias assessed in the HTA report were similar to the Cochrane Collaboration tool for assessing risk of bias (22) (randomization, allocation concealment, double-blinding, baseline characteristics similarity, outcome measures, withdrawals, use of intention-to-treat analysis, and source of funding).
For the newer RCTs that we supplemented, we used the Norwegian Knowledge Centre for the Health Services tool to assess risk of bias (23). That tool is based on Cochrane risk of bias tool (22).

The assessment of risk of bias of included RCTs was carried out by one person and checked by another. For the evaluation of risk of bias provided by the HTA report, one author extracted the assessment data, and another verified the data. Any disagreements were discussed to reach consensus.

Data collection and analysis

Data extraction

One person extracted predefined data from the selected publications, and a second checked the data extraction for accuracy.

Data extraction from HTA/SR

We extracted the following data from the selected HTA report: publication information (authors, publication details), date of the literature search, characteristics of included studies (study design, origin, setting, comparisons and endpoints investigated, follow-up range of included studies), and information on quality assessment.

Data extraction from RCTs

We extracted the following data from included RCTs: information on publication (authors , publication details); RCT description (clinical trial identification, design and setting, source of funding); participants characteristics (age and gender, MS diagnosis, inclusion and exclusion criteria, and baseline characteristics); description of intervention and comparison groups (numbers of participants in each group, doses, administration method); and outcomes (primary and secondary endpoints assessed, definitions used, length of follow-up, measurements of outcomes such as number of events, means, corresponding standard deviations).

For RCTs included in the HTA, for each individual RCT, we extracted the data reported in the HTA publication. To assess accuracy, one person compared the information given by the HTA report with the original study publication of seven randomly chosen RCTs. All the data presented in the HTA were identical to the original publications. For RCTs identified after the HTA literature search, we extracted the data from the primary publications.

Statistical analyses and presentation of results

Measures of treatment effect

We expressed the comparative effectiveness of the treatments as the relative risk (RR) for dichotomous outcomes, annualised rate ratios (ARR) for count data and the mean difference (MD) for continuous outcomes. For all outcomes 95% confidence intervals (CI) or credible intervals (CrI) were calculated for the RR, ARR, MD. The credible interval is the Bayesian analogue to confidence intervals used in traditional frequentist statistical approaches. We considered a difference to be "significant" if the CrI did not include RR =1 or MD=0.

For count data (number of relapses), we used a Poisson regression based approach to obtain the annualised rate ratios (ARR) from the total number of relapses and patient-years of follow-up.

Dealing with missing data

For the endpoint “number of relapses” we performed imputations to derive needed values where included trials did not report the total number of relapses or exposure time (person-years). Missing number of total relapses were derived using the exposure time (person-years) and the reported mean ARR values. For missing exposure-time (in person-years), the values were imputed using treatment duration and number of patients completing the study (100% was assumed in cases where the percentage of completers was not reported).

For disability progression, measured as a dichotomous outcome, we assumed that participants who dropped out experienced the event (a likely scenario). For all other

endpoints, we did not perform imputations for missing data. We based 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).

The statistical analysis was based on binomial likelihoods (dichotomous outcomes), poisson likelihoods (count 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 used a random effects model. We checked for incoherence between direct and indirect evidence by "node-splitting" (24). We calculated the direct and indirect estimates of effect and the corresponding Bayesian "P-values" for incoherence.

We ranked the different treatments in terms of their likelihood of leading to the best results for each primary endpoint. We based the rankings on the surface under the cumulative ranking curve (SUCRA) (25). We interpreted the rankings cautiously taking into account the quality of evidence.

We performed sensitivity analyses where participants who dropped out were excluded from the analyses of the sustained disability progression, to base the analyses only on the available data.

Data synthesis

First, we conducted pairwise meta-analyses for each available outcome and, for each identified intervention vs. control group comparison. This was done using a traditional frequentist statistical approach assuming random effects models using the software RevMan 5.3. Hereafter, we refer to this method as the “pairwise comparisons method”. Further, we combined direct and indirect evidence, and performed a network-meta-analysis (19). For that, we used a Bayesian method based on Markov Chain Monte Carlo simulation. This method is, hereafter, referred to as the “network meta-analysis approach”. This was done using Winbugs version 1.4.3 (Imperial College and MRC, UK).

Grading the quality of evidence

Two review authors assessed independently the quality of the evidence for each selected outcome. We used Grading of recommendations Assessment, Development, and Evaluation (GRADE) to assess the quality of the direct evidence, indirect evidence, and the combined evidence from the NMA (26).

First, we graded the evidence for all comparisons with available direct evidence. Then, we graded the comparisons for which we had indirect evidence. To grade the indirect evidence, we considered the direct evidence that contributed to that indirect evidence. For example, the indirect evidence comparing a medicine A with a medicine C might have been obtained with direct evidence comparing medicines A and B, and B with C. The grade of the indirect evidence for the comparison A and C was based on the grade of the direct evidence on A and B, and B and C. The grade of the indirect evidence on A versus C was the lowest grade of all the direct evidence that contributed to that comparison.

To select the direct evidence that might have contributed to the indirect evidence, we chose the evidence that involved fewest head-to-head comparisons. For example, for indirect evidence comparing A to C, one might also have evidence comparing A to D, D to E and E to C. This example involves three head-to-head comparisons compared to the two presented above (A with B, and B with C). The indirect evidence with fewer head-to-head comparisons is referred to as first order loops. If more than one first order loops were available, we chose the loop with the lowest available quality. This was a conservative approach.

For a specified comparison, the grade of the network meta-analysis evidence was the highest GRADE between the direct and indirect evidence for that comparison.

Due to time constraint, we graded the quality of the evidence only for annual relapse rate, disability progression (when examining disability progression as a dichotomous variable: considering whether someone had been less disabled or not when using a certain treatment) and withdrawal due to adverse events. The first two outcomes were the two outcomes used in the economic evaluation. Withdrawal due to adverse events is also an important outcome as it measures the risk of adverse event(s) outweighing the benefit of the treatment to the point of causing withdrawal from treatment.

GRADE provides specific criteria to consider when rating the quality of evidence. This includes 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 was classified as high, moderate, low, or very low for each outcome. The definition for each category is described in the following table.

Table 2. *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

Clinical evaluation - Results

Result of literature search

Results of the search and selection process

We selected the evidence for this report in two stages, first identifying relevant SRs or HTA reports (Figure 1), and then supplementing the evidence of the identified HTA with more up to date information (Figure 2).

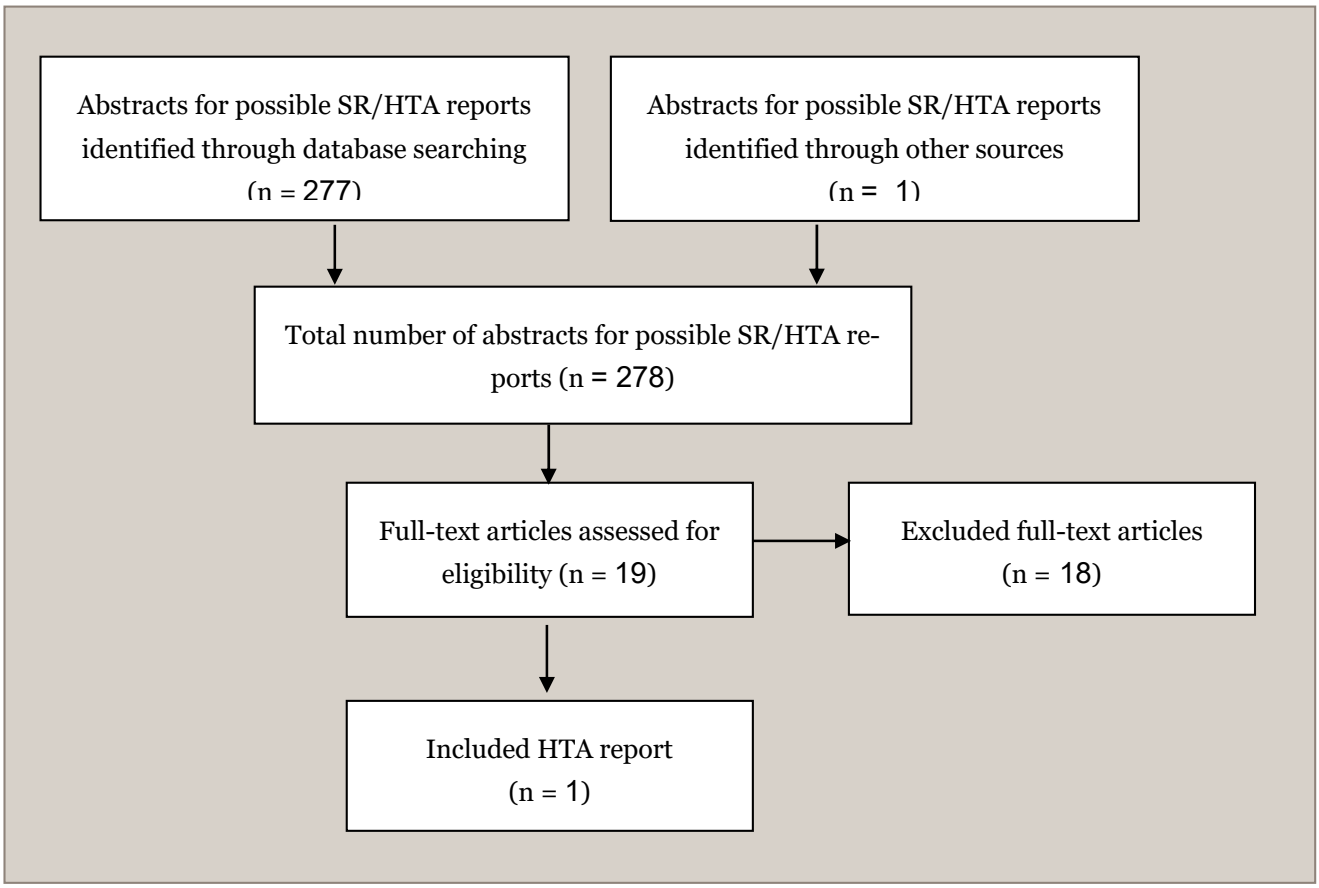


Figure 1. *Flow diagram for the selection of possible systematic reviews (SR) or health technology assessment (HTA) reports*

When looking for possible SR or HTA reports, the literature search retrieved 277 records, and we found one extra record. After abstract selection, and assessing 19 full-text articles, we included one HTA. This was a recent HTA report (literature search carried out in October 2013). To supplement the HTA's information with more up to date evidence, we searched for additional RCTs published from 2013 to the last date of our literature search (9/11/2015).

The literature search for RCTs identified 644 records. We supplemented this search with two records identified in reference lists, and one RCT provided by a pharmaceutical company. After the selection process, we included fifteen publications on eleven RCTs.

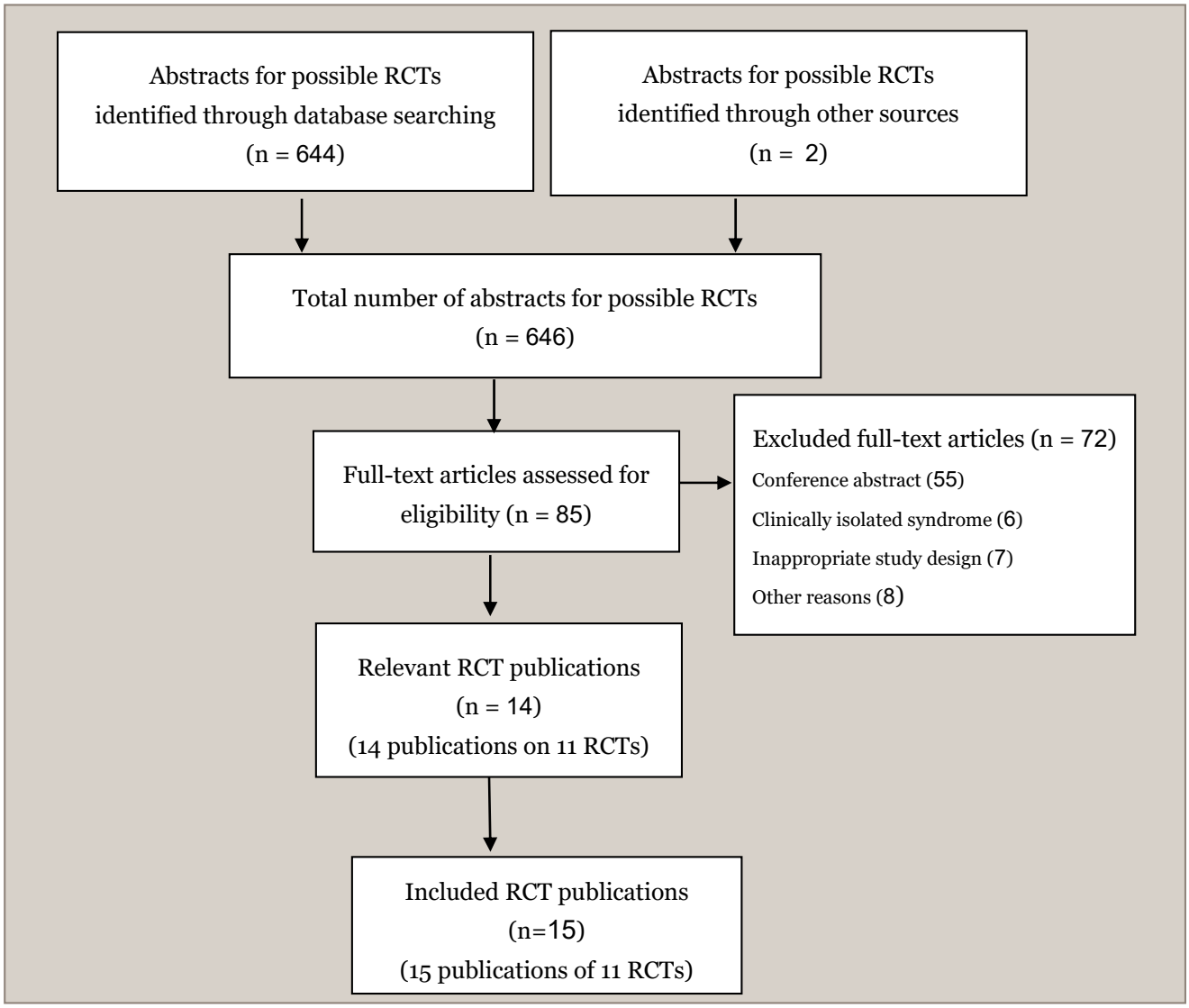


Figure 2. *Flow diagram for the selection of possible randomised clinical trials (RCT) published after the included health technology assessment report*

Included studies

The included health technology assessment report

Some of the evidence presented in this report was extracted from a previously published HTA report (27). This publication is described in Table 3. It summarised evidence from RCTs assessing mono- and combination therapies of MS-medicines. We included data from 26 RCTs (only the RCTs that examined MS monotherapies). The participants were RRMS patients, with a mean age ranging between 29 and 41 years old. They were followed for a period ranging from 16 weeks to 3.5 years, and were in majority women.

Table 3. *Characteristics of the included HTA report*

Date of literature search	October 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

The included primary studies

We present an overview of RCTs that constitute our evidence base in Table 4. Further details on both the primary studies included in the above-mentioned HTA report, and those we identified are provided in Appendix 2.

Altogether, we included 37 studies; 26 from the selected HTA report (27), and 11 RCTs from our supplementary search. All RCTs included RRMS patients. Treatment histories varied, with 11 RCTs confined to treatment-naive patients, 4 included treatment experienced participants, 11 combined treatment naïve and treatment experienced patients, and treatment history was unclear in 9 studies. We had information for 39 comparisons including active treatments versus placebo, and active treatments compared with each other.

Many of the published studies did not examine medications separating first- and second- line treatments. Studies compared first-line treatments and second-line treatments (28-32). Other studies examined first-line treatments in patients who had taken other medications before (33-36). Two studies investigated second-line treatments in a population that comprised treatment naive patients (i.e. patients who had not received a first-line treatment) (37, 38).

Excluded studies

Excluded studies and reasons for exclusion are presented in Appendix 3.

Ongoing studies and other relevant literature

We searched the WHO ICTRP and ClinicalTrials.gov to identify relevant ongoing or unpublished trials. The result of this search is presented in Appendix 4.

Table 4. *Characteristics of included randomised clinical trials*

Name (publication) (reference) Study design	Intervention versus comparison (n=number randomised)	Treatment history	Follow-up
CAMMS223 (2008)(28) 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) (29) 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)(28) 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)(33) 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) (34) 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

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

Name (publication) (reference) Study design	Intervention versus comparison (n=number randomised)	Treatment history	Follow-up
FREEDOMS (2010) (37) 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) (38) 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 et al. (2012) (39) 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)(40, 41) 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 et al. (1995) (42) 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 et al. (2001)(43) Double-blind, in 7 countries	- Glatiramer acetate 20 mg SC q.d. (n=119) - Placebo (n=120)	Unclear	9 months
REGARD (2008)(44) 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) (45) 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

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

Name (publication) (reference) Study design	Intervention versus comparison (n=number randomised)	Treatment history	Follow-up
BEYOND (2009)(46) 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 et al. (2012)(47) 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)(35) 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) (48) 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)(49) 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)(50) 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) (51) 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 et al.* (2002) (52)** 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

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

Name (publication) (reference) Study design	Intervention versus comparison (n=number randomised)	Treatment history	Follow-up
Kappos et al. (2011) (36) 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 et al. (2013) (53) ***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) (54) 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) (55) 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) (56) 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) (57) 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)(58) 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) (59) 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

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

Name (publication) (reference) Study design	Intervention versus comparison (n=number randomised)	Treatment history	Follow-up
AFFIRM (2006) (60) 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 et al (2013) (31) 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) (61) 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 et al.* (2014) (32)** 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) (62) 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) (63, 64) 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) (65) 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) (66) 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

Effects of intervention(s)

We describe here the effects of the examined MS disease modifying medicines on outcomes.

The GRADE evaluation is described in detail in Appendix 5. Results of the full network meta-analysis for all possible comparisons for all outcomes are given in Appendix 6.

Annualised relapse rate

We present here the results obtained using the "network meta-analysis approach" (Bayesian method). We found similar results using the "pairwise comparison method" (Frequentist approach). Those results are presented in Appendix 7.

Figure 3 shows the available network of evidence for annualised relapse rate. The thickness of the line is proportional to the amount of evidence for that comparison. In total, 19 MS treatment strategies and placebo were examined.

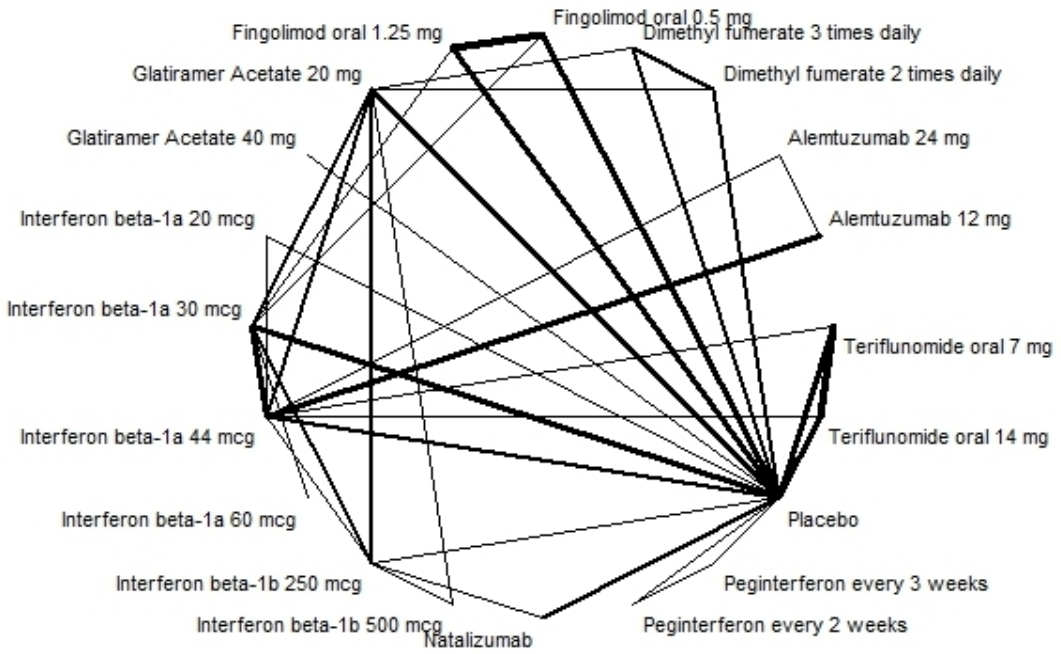


Figure 3. *Evidence network for annualised relapse rate*

Active treatments versus placebo

Fifteen treatments were compared to placebo (Table 5). Results from direct, and indirect evidence, and from the whole network are consistent (except for teriflunomide oral 7 mg). All active treatments examined were more effective than placebo against relapse. The highest effect against annual relapse was seen for alemtuzumab 12 mg IV q.d. When considering results we had high quality evidence for, the relative risk for annual relapse ranged between 0.29 (95% CI: 0.23; 0.35) for alemtuzumab 12 mg IV q.d, and 0.86 (0.7 to 1.06) for interferon beta-1a 60 mcg IM q.w, compared to placebo.

Table 5. *Relative risk for annual relapse for active MS treatments compared to placebo*

	Direct evidence		Indirect evidence		Network meta-analysis	
Interventions	**RR (95% CI)**	**GRADE**	**RR (95% CI)**	**GRADE**	**RR (95% CI)**	**GRADE**
Interferon beta-1a 22 mcg	0.69 (0.57 to 0.83)	Moderate	NA	NA	0.69 (0.57 to 0.83)	Moderate
Interferon beta-1a 30 mcg	0.76 (0.65 to 0.89)	High	0.87 (0.75 to 1.01)	Moderate	0.82 (0.73 to 0.91)	High
Interferon beta-1a 44 mcg	0.67 (0.54 to 0.80)	High	0.61 (0.52 to 0.72)	Very low	0.64 (0.56 to 0.72)	High
Glatiramer acetate 20mg	0.70 (0.60 to 0.82)	High	0.60 (0.52 to 0.70)	Moderate	0.65 (0.59 to 0.73)	High
Glatiramer acetate 40mg	0.66 (0.52 to 0.82)	High	NA	NA	0.66 (0.52 to 0.82)	High
Dimethyl fumarate 240 mg 2.i.d	0.5 (0.42 to 0.6)	High	NA	NA	0.5 (0.42 to 0.6)	High
Dimethyl fumarate 240 mg t.i.d	0.5 (0.42 to 0.6)	High	NA	NA	0.5 (0.42 to 0.6)	High
Teriflunomide oral 7 mg	0.73 (0.64 to 0.84)	High	1.12 (0.78 to 1.57)	Moderate	0.77 (0.68 to 0.9)	High
Teriflunomide oral 14 mg	0.67 (0.58 to 0.78)	High	0.57 (0.39 to 0.83)	Low	0.67 (0.58 to 0.77)	High
Fingolimod oral 0.5 mg	0.49 (0.41 to 0.57)	High	0.38 (0.27 to 0.51)	Moderate	0.46 (0.39 to 0.54)	High
Fingolimod oral 1.25 mg	0.43 (0.37 to 0.51)	High	0.53 (0.39 to 0.84)	Moderate	0.45 (0.39 to 0.53)	High
Peg-interferon beta-1a 125 mcg 1/ 2 w	0.65 (0.49 to 0.85)	High	NA	NA	0.65 (0.49 to 0.85)	High
Peg-interferon beta-1a 125 mcg 1/4 w	0.73 (0.56 to 0.95)	High	NA	NA	0.73 (0.56 to 0.95)	High
Natalizumab	0.30 (0.25 to 0.36)	Moderate	0.0002 (0.00 to 0.07)	Very low	0.3 (0.24 to 0.36)	Moderate
Interferon beta-1b 250 mcg	0.65 (0.51 to 0.83)	Moderate	0.67 (0.55 to 0.79)	Very low	0.66 (0.57 to 0.76)	Moderate
Alemtuzumab 24 mg IV q.d.	NA	NA	0.16 (0.1 to 0.25)	Low	0.16 (0.1 to 0.25)	Low
Alemtuzumab 12 mg IV q.d	NA	NA	0.29 (0.23 to 0.35)	High	0.29 (0.23 to 0.35)	High
Interferon beta-1b 500mcg SC 1/2 d	NA	NA	0.62 (0.51 to 0.74)	Moderate	0.62 (0.51 to 0.74)	Moderate
Interferon beta-1a 60 mcg IM q.w.	NA	NA	0.86 (0.7 to 1.06)	High	0.86 (0.7 to 1.06)	High

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).

Active treatments compared with each other

We had information on 24 head-to-head comparisons of active treatments (Table 6). Most results (except interferon beta-1a 44mcg versus alemtuzumab 24 mg and interferon beta-1a 22 mcg; and for teriflunomide oral 7 mg versus interferon beta-1a 44 mcg) were similar for direct, and indirect evidence, and for the whole network. When considering statistically significant results for which we had high quality of evidence, we found that some treatments were more effective than others against relapses: interferon beta-1a 44 mcg was less effective than alemtuzumab 12 mg (RR; 95% CI= 2.21; 1.90 to 2.64). Fingolimod oral 0.5 mg and fingolimod oral 1.25 mg performed better than interferon beta-1a 30 mcg, with RRs (95% CI) of 0.57 (0.47 to 0.67) and 0.55 (0.47 to 0.66), respectively. Furthermore, dimethyl fumarate 240 mg two times and three times daily were more effective than glatiramer acetate 20mg, with RRs of 0.77 (0.63 to 0.93) and 0.77 (0.64 to 0.93), respectively.

Table 6. *Relative risk for annual relapse for active MS treatments compared to others for comparisons with available direct evidence*

		Direct evidence		Indirect evidence		Network meta-analysis	
Intervention	**Comparison**	**RR (95% CI)**	**GRADE**	**RR (95% CI)**	**GRADE**	**RR (95% CI)**	**GRADE**
Alemtuzumab 24 mg	Alemtuzumab 12 mg	0.55 (0.35 to 0.86)	Low	NA	NA	0.55 (0.35 to 0.86)	Low
Interferon beta-1a 44 mcg	Alemtuzumab 12 mg	2.21 (1.9 to 2.64)	High	NA	Low	2.21 (1.9 to 2.64)	High
Interferon beta-1a 44 mcg	Interferon beta-1a 22 mcg	0.68 (0.56 to 0.83)	Moderate	0.43 (0.33 to 0.55)	Moderate	0.92 (0.76 to 1.11)	Moderate
Interferon beta-1a 44 mcg	Interferon beta-1a 30 mcg	0.76 (0.63 to 0.93)	High	0.79 (0.65 to 0.95)	Very low	0.78 (0.68 to 0.89)	High
Interferon beta-1a 60 mcg	Interferon beta-1a 30 mcg	1.05 (0.88 to 1.25)	Moderate	NA	NA	1.05 (0.88 to 1.25)	Moderate
Glatiramer acetate 20mg	Interferon beta-1a 30 mcg	0.79 (0.61 to 1.02)	Moderate	0.80 (0.69 to 0.93)	Moderate	0.8 (0.7 to 0.91)	Moderate
Fingolimod oral 0.5 mg	Interferon beta-1a 30 mcg	0.48 (0.35 to 0.64)	High	0.60 (0.50 to 0.73)	Moderate	0.57 (0.47 to 0.67)	High
Fingolimod oral 1.25 mg	Interferon beta-1a 30 mcg	0.63 (0.46 to 0.90)	High	0.52 (0.43 to 0.63)	Moderate	0.55 (0.47 to 0.66)	High
Interferon beta-1b 250 mcg	Interferon beta-1a 30 mcg	0.71 (0.53 to 0.91)	Moderate	0.85 (0.71 to 1.03)	Very low	0.81 (0.69 to 0.93)	Moderate
Glatiramer acetate 20mg	Interferon beta-1a 44 mcg	1.02 (0.83 to 1.28)	Moderate	0.98 (0.82 to 1.18)	Very low	1.02 (0.9 to 1.18)	Moderate
Teriflunomide oral 7 mg	Interferon beta-1a 44 mcg	1.72 (1.24 to 2.44)	Moderate	1.13 (0.93 to 1.34)	Low	1.21 (1.02 to 1.47)	Moderate
Teriflunomide oral 14 mg	Interferon beta-1a 44 mcg	0.91 (0.62 to 1.36)	Low	1.06 (0.89 to 1.31)	Moderate	1.04 (0.87 to 1.27)	Moderate
Interferon beta-1b 250 mcg	Interferon beta-1a 44 mcg	0.81 (0.46 to 1.43)	Very low	1.00 (0.83 to 1.18)	Moderate	1.03 (0.88 to 1.22)	Moderate
Ddimethyl fumarate 240 mg 2.i.d	Glatiramer acetate 20mg	0.59 (0.38 to 0.90)	High	0.63 (0.40 to 0.98)	Moderate	0.77 (0.63 to 0.93)	High
Dimethyl fumarate 240 mg t.i.d	Glatiramer acetate 20mg	0.53 (0.35 to 0.79)	High	0.78 (0.50 to 1.25)	Moderate	0.77 (0.64 to 0.93)	High
Interferon beta-1b 250 mcg	Glatiramer acetate 20mg	1.07 (0.90 to 1.27)	Moderate	0.92 (0.75 to 1.14)	Very low	1.01 (0.88 to 1.16)	Moderate
Interferon beta-1b 500 mcg	Glatiramer acetate 20mg	0.95 (0.8 to 1.12)	Moderate	NA	NA	0.95 (0.8 to 1.12)	Moderate
Dimethyl fumarate 240 mg t.i.d	Dimethyl fumarate 240 mg 2.i.d	1.01 (0.82 to 1.23)	Moderate	NA	NA	1.01 (0.82 to 1.23)	Moderate
Teriflunomide oral 14 mg	Teriflunomide oral 7 mg	0.86 (0.74 to 1.)	Moderate	NA	NA	0.86 (0.74 to 1.)	Moderate
Fingolimod oral 1.25 mg	Fingolimod oral 0.5 mg	0.98 (0.83 to 1.17)	Moderate	NA	NA	0.98 (0.83 to 1.17)	Moderate
Peginterferon beta-1a 125 mcg 1/4 w	Peginterferon beta-1a 125 mcg 1/2 w	1.13 (0.84 to 1.52)	Moderate	NA	NA	1.13 (0.84 to 1.52)	Moderate
Interferon beta-1b 250 mcg	Natalizumab	NE	Very low	2.17 (1.71 to 2.76)	Moderate	2.22 (1.76 to 2.81)	Moderate
Interferon beta-1b 500 mcg	Interferon beta-1b 250 mcg	0.93 (0.8 to 1.1)	Moderate	NA	NA	0.93 (0.8 to 1.1)	Moderate

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.

NE= Not estimable (Estimate of difference for direct evidence is not estimable due to 0 events in the Natalizumab group)

Disability progression

We examined, first, disability progression as a dichotomous variable, considering whether someone had been less disabled or not when using a certain treatment. The results obtained using the "network meta-analysis approach" are presented here. These results are consistent with results found with the "pairwise comparison method". The "pairwise comparison method" results are presented in Appendix 7.

The network of evidence available for disability progression is presented in Figure 4. We had evidence for 18 treatment strategies and placebo.

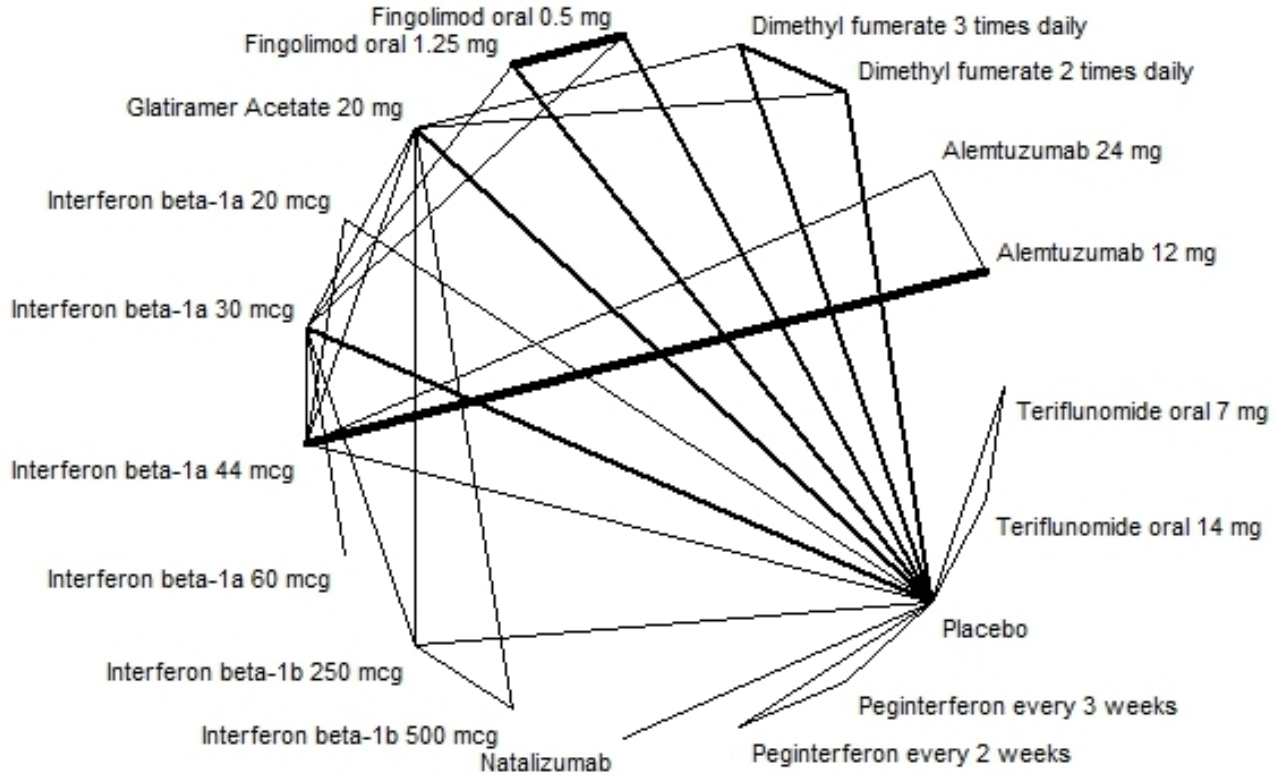


Figure 4. *Evidence network for disability progression*

Active treatments versus placebo

Table 7 compares results obtained when considering direct, indirect evidence and the whole network. It shows that results were similar. Seventeen treatments were compared to placebo. For four of these, we had high quality evidence, and they were all more effective than placebo against disability progression. The network meta-analysis RRs for disability progression were 0.65 (95% CI: 0.49; 0.85) for dimethyl fumarate 240 mg two times daily, 0.68 (0.52; 0.89) for dimethyl fumarate 240 mg three times daily, 0.71 (0.55; 0.90) for fingolimod oral 0.5 mg, and 0.71 (0.56; 0.90) for fingolimod oral 1.25 mg.

Table 7. *Relative risk for disability progression for active MS treatments compared to placebo*

Interventions	Direct evidence		Indirect evidence		Network meta-analysis	
	RR (95% CI)	**GRADE**	**RR (95% CI)**	**GRADE**	**RR (95% CI)**	**GRADE**
Interferon beta-1a 22 mcg	0.84 (0.61 to 1.19)	Low	NA	NA	0.84 (0.61 to 1.19)	Low
Interferon beta-1a 30 mcg	0.68 (0.50 to 0.95)	Moderate	0.88 (0.66 to 1.20)	Low	0.8 (0.65 to 0.99)	Moderate
Interferon beta-1a 44 mcg	0.70 (0.48 to 1.04)	Low	0.86 (0.59 to 1.30)	Low	0.77 (0.6 to 1.01)	Low
Glatiramer acetate 20mg	0.88 (0.61 to 1.21)	Low	0.70 (0.51 to 0.94)	Low	0.78 (0.63 to 0.96)	Low
Dimethyl fumarate 240 mg two times daily	0.65 (0.49 to 0.85)	High	NA	NA	0.65 (0.49 to 0.85)	High
Dimethyl fumarate 240 mg three times daily	0.68 (0.52 to 0.89)	High	NA	NA	0.68 (0.52 to 0.89)	High
Teriflunomide oral 7 mg	0.8 (0.55 to 1.13)	Low	NA	NA	0.8 (0.55 to 1.13)	Low
Teriflunomide oral 14 mg	0.73 (0.51 to 1.05)	Low	NA	NA	0.73 (0.51 to 1.05)	Low
Fingolimod oral 0.5 mg	0.75 (0.56 to 0.98)	High	0.56 (0.32 to 0.91)	Low	0.71 (0.55 to 0.9)	High
Fingolimod oral 1.25 mg	0.70 (0.52 to 0.92)	High	0.81 (0.48 to 1.31)	Low	0.71 (0.56 to 0.9)	High
Peginterferon beta-1a 125 mcg once every 2 wks	0.61 (0.36 to 0.98)	Low	NA	NA	0.61 (0.36 to 0.98)	Low
Peginterferon beta-1a 125 mcg once every 4 wks	0.62 (0.38 to 1.01)	Low	NA	NA	0.62 (0.38 to 1.01)	Low
Natalizumab	0.59 (0.42 to 0.84)	Moderate	NA	NA	0.59 (0.42 to 0.84)	Moderate
Interferon beta-1b 250 mcg	0.77 (0.50 to 1.17)	Low	0.67 (0.43 to 0.95)	Low	0.72 (0.54 to 0.92)	Low
Alemtuzumab 12 mg IV q.d	NA	NA	0.4 (0.27 to 0.6)	Low	0.4 (0.27 to 0.6)	Low
Alemtuzumab 24 mg IV q.d	NA	NA	0.36 (0.16 to 0.74)	Very low	0.36 (0.16 to 0.74)	Very low
Interferon beta-1b 500 mcg SC 1/2 d.	NA	NA	0.79 (0.56 to 1.1)	Low	0.79 (0.56 to 1.1)	Low

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.

Active treatments compared with each other

We obtained similar results when comparing active treatments with each other using direct and indirect evidence, and the evidence from the whole network (except for interferon beta-1b 250 mcg versus interferon beta-1a 30 mcg) (Table 8). We had evidence of very low to moderate quality (Table 8). Only two of the network meta-analysis comparisons showed statistically significant differences between treatments. interferon beta-1a 44 mcg was less effective against disability progression than alemtuzumab 12 mg and 24 mg, with RRs of 1.95 (95% CI: 1.45; 2.59) (evidence of moderate quality) and 2.15 (1.10; 4.55) (evidence of very low quality), respectively.

Table 8. *Relative risk for disability progression for active MS treatments compared to others for comparisons with available direct evidence*

		Direct evidence		Indirect evidence		Network Meta-analysis	
Intervention	**Comparison**	**RR (95% CI)**	**GRADE**	**RR (95% CI)**	**GRADE**	**RR (95% CI)**	**GRADE**
Alemtuzumab 24 mg	Alemtuzumab 12 mg	0.85 (0.4 to 1.65)	Very low	NA	NA	0.85 (0.4 to 1.65)	Very low
Interferon beta-1a 44 mcg	Alemtuzumab 12 mg	1.95 (1.45 to 2.59)	Moderate	NA	NA	1.95 (1.45 to 2.59)	Moderate
Interferon beta-1a 44 mcg	Alemtuzumab 24 mg	2.15 (1.1 to 4.55)	Very low	NA	NA	2.15 (1.1 to 4.55)	Very low
Interferon beta-1a 44 mcg	Interferon beta-1a 22 mcg	0.92 (0.65 to 1.3)	Low	NA	NA	0.92 (0.65 to 1.3)	Low
Interferon beta-1a 44 mcg	Interferon beta-1a 30 mcg	0.89 (0.55 to 1.38)	Low	1.04 (0.72 to 1.50)	Low	0.97 (0.73 to 1.3)	Low
Interferon beta-1a 60 mcg	Interferon beta-1a 30 mcg	0.99 (0.71 to 1.39)	Low	NA	NA	0.99 (0.71 to 1.39)	Low
glatiramer acetate 20mg	Interferon beta-1a 30 mcg	1.18 (0.81 to 1.75)	Low	0.87 (0.64 to 1.17)	Low	0.98 (0.76 to 1.23)	Low
Fingolimod oral 0.5 mg	Interferon beta-1a 30 mcg	0.72 (0.42 to 1.17)	Low	0.96 (0.68 to 1.33)	Low	0.89 (0.65 to 1.16)	Low
Fingolimod oral 1.25 mg	Interferon beta-1a 30 mcg	0.99 (0.58 to 1.60)	Low	0.85 (0.59 to 1.19)	Low	0.89 (0.66 to 1.18)	Low
Interferon beta-1b 250 mcg	Interferon beta-1a 30 mcg	0.44 (0.23 to 0.82)	Low	1.07 (0.81 to 1.43)	Low	0.9 (0.65 to 1.17)	Low
glatiramer acetate 20mg	Interferon beta-1a 44 mcg	0.75 (0.46 to 1.21)	Low	1.17 (0.82 to 1.65)	Low	1.01 (0.75 to 1.33)	Low
dimethyl fumarate 240 mg two times daily	glatiramer acetate 20mg	0.78 (0.52 to 1.18)	Low	0.80 (0.51 to 1.18)	Low	0.83 (0.61 to 1.15)	Low
dimethyl fumarate 240 mg three times daily	glatiramer acetate 20mg	0.79 (0.53 to 1.16)	Low	0.88 (0.59 to 1.36)	Low	0.88 (0.64 to 1.18)	Low
Interferon beta-1b 250 mcg	glatiramer acetate 20mg	1.04 (0.74 to 1.46)	Moderate	0.74 (0.48 to 1.09)	Low	0.92 (0.69 to 1.16)	Moderate
Interferon beta-1b 500 mcg	glatiramer acetate 20mg	1.01 (0.74 to 1.36)	Moderate	NA	NA	1.01 (0.74 to 1.36)	Moderate
dimethyl fumarate 240 mg three times daily	dimethyl fumarate 240 mg two times daily	1.06 (0.78 to 1.42)	Low	NA	NA	1.06 (0.78 to 1.42)	Low
Teriflunomide oral 14 mg	Teriflunomide oral 7 mg	0.92 (0.64 to 1.35)	Low	NA	NA	0.92 (0.64 to 1.35)	Low
Fingolimod oral 1.25 mg	Fingolimod oral 0.5 mg	1.01 (0.78 to 1.32)	Moderate	NA	NA	1.01 (0.78 to 1.32)	Moderate
Peginterferon beta-1a 125 mcg once every 4 wks	Peginterferon beta-1a 125 mcg once every 2 wks	1.02 (0.61 to 1.74)	Low	NA	NA	1.02 (0.61 to 1.74)	Low
Interferon beta-1b 500 mcg	Interferon beta-1b 250 mcg	1.1 (0.84 to 1.51)	Moderate	NA	NA	1.1 (0.84 to 1.51)	Moderate

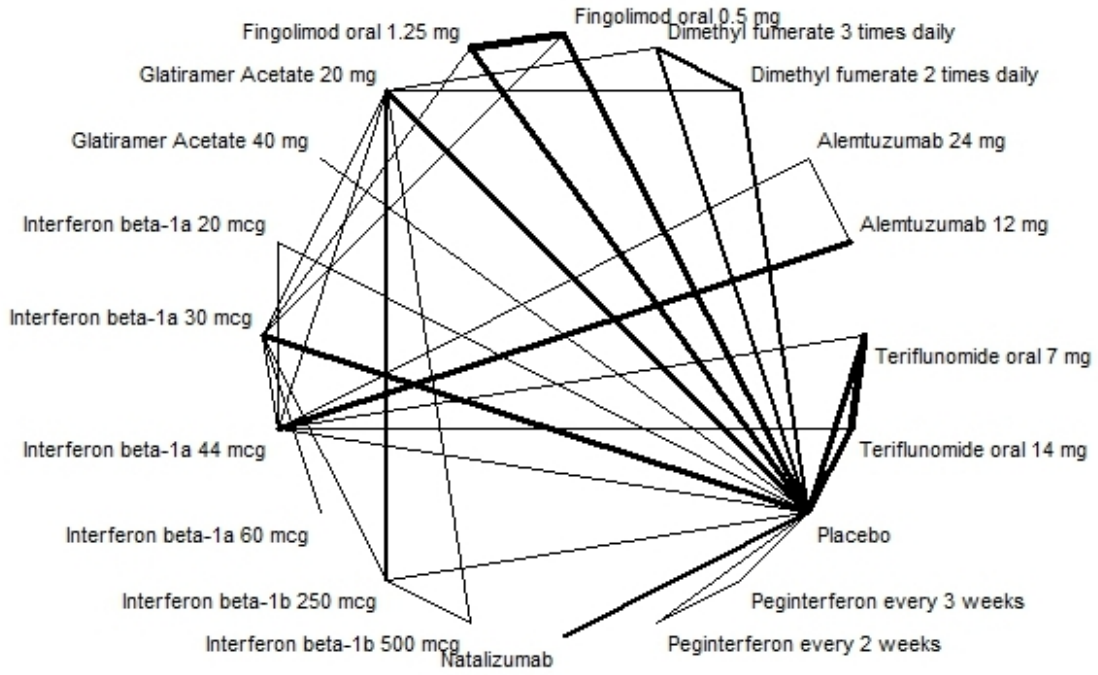
RR= relative ratio, CI= confidence interval, mg= milligrams, mcg= micrograms, SC= subcutaneous, IM= intra muscular, q.d.= once daily, q.w.=once weekly, t.i.w.= three times weekly, 2.i.d= two times daily, t.i.d= three times daily, 1/2 w=once every 2 weeks, 1/4 w=once every 4 weeks.

Withdrawal due to adverse events

We present here the results obtained using the "network meta-analysis approach". Those are consistent with results found with the "pairwise comparison method". The "pairwise comparison method" results are presented in Appendix 7.

Figure 5 presents the network of evidence available for the outcome withdrawal due to adverse events. This network included information on 19 different treatments strategies and placebo.

Figure 5. *Evidence network for withdrawal due to adverse events*



Active treatments versus placebo

Table 9 presents results estimated through direct and indirect evidence, and through the whole network. Results are consistent (except for interferon beta-1b 250 mcg). We had evidence for 19 treatments versus placebo. The quality of the evidence considered for the whole network was of very low to moderate quality. Four treatments were statistically significantly more associated with withdrawal due to adverse events than placebo. We found RRs for withdrawal due to adverse events of 2.20 (95% CI: 1.29-3.97) for interferon beta-1a 44 mcg (low quality evidence), of 2.21 (1.42; 3.58) for fingolimod oral 1.25 mg (moderate quality), and of 3.57 (1.27; 11.14) and 3.47 (1.25 to 10.9) for peg-interferon beta-1a 125 mcg once every 2 and 4 weeks, respectively (low quality evidence).

Table 9. *Relative risk for withdrawal due to adverse events for active MS treatments compared to placebo*

Interventions	Direct evidence		Indiret evidence		Network meta-analysis	
	RR (95% CI)	GRADE	RR (95% CI)	GRADE	RR (95% CI)	GRADE
Interferon beta-1a 22 mcg	1.68 (0.5 to 5.98)	Low	NA	NA	1.68 (0.5 to 5.98)	Low
Interferon beta-1a 30 mcg	1.73 (0.82 to 3.87)	Low	1.12 (0.61 to 2.10)	Low	1.33 (0.85 to 2.17)	Low
Interferon beta-1a 44 mcg	5.32 (1.09 to 41.63)	Low	1.98 (1.10 to 3.61)	Low	2.2 (1.29 to 3.97)	Low
Glatiramer acetate 20mg	1.22 (0.64 to 2.66)	Low	1.15 (0.54 to 2.42)	Low	1.17 (0.74 to 1.94)	Low
Glatiramer acetate 40mg	2.5 (0.86 to 8.29)	Low	NA	NA	2.5 (0.86 to 8.29)	Low
Dimethyl fumarate 240 mg 2.i.d.	1.24 (0.74 to 2.13)	Low	NA	NA	1.24 (0.74 to 2.13)	Low
Dimethyl fumarate 240 mg t.i.d	1.25 (0.74 to 2.13)	Low	NA	NA	1.25 (0.74 to 2.13)	Low
Teriflunomide oral 7 mg	1.54 (0.89 to 2.51)	Low	0.89 (0.32 to 2.44)	Low	1.37 (0.82 to 2.21)	Low
Teriflunomide oral 14 mg	1.70 (1.02 to 3.01)	Low	1.29 (0.47 to 3.44)	Low	1.53 (0.96 to 2.54)	Low
Fingolimod oral 0.5 mg	1.49 (0.86 to 2.50)	Low	1.48 (0.65 to 3.55)	Low	1.54 (0.98 to 2.52)	Low
Fingolimod oral 1.25 mg	1.93 (1.18 to 3.14)	Moderate	3.26 (1.52 to 7.22)	Low	2.21 (1.42 to 3.58)	Moderate
Peginterferon beta-1a 125 mcg 1/2 w	3.57 (1.27 to 11.14)	Low	NA	NA	3.57 (1.27 to 11.14)	Low
Peginterferon beta-1a 125 mcg 1/4 w	3.47 (1.25 to 10.9)	Low	NA	NA	3.47 (1.25 to 10.9)	Low
Natalizumab	1.22 (0.5 to 2.74)	Low	NA	NA	1.22 (0.5 to 2.74)	Low
Interferon beta-1b 250 mcg	0.07 (0.003 to 0.48)	Low	1.64 (0.68 to 4.36)	Low	0.84 (0.4 to 1.87)	Low
Alemtuzumab 24 mg IV q.d	NA	NA	0.54 (0.17 to 1.54)	Very low	0.54 (0.17 to 1.54)	Very low
Alemtuzumab 12 mg IV q.d	NA	NA	0.61 (0.25 to 1.47)	Low	0.61 (0.25 to 1.47)	Low
Interferon beta-1b 500 mcg SC 1/2 d	NA	NA	1.37 (0.52 to 3.92)	Low	1.37 (0.52 to 3.92)	Low
Interferon beta-1a 60 mcg IM q.w	NA	NA	1.9 (0.79 to 4.81)	Low	1.9 (0.79 to 4.81)	Low

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.

Active treatments compared with each other

Results using direct and indirect evidence, and evidence from the whole network were similar in terms of direction of the association and magnitude (Table 10). The quality of the evidence ranged from very low to moderate. Only two of the network meta-analysis comparisons showed statistically significant results. Patients withdrew more due to adverse events with interferon beta-1a 44 mcg than with alemtuzumab 12 and 24 mg (RRs of 3.6 (95% CI: 1.88; 7.33), and 4.08 (1.69; 11.42), respectively). The corresponding quality of the evidence was moderate and very low.

Table 10. *Relative risk for withdrawal due to adverse events for active MS treatments compared to each other*

		Directe evidence		Indirecte evidence		Network meta-analysis	
Intervention	**Comparison**	**RR (95% CI)**	**GRADE**	**RR (95% CI)**	**GRADE**	**RR (95% CI)**	**GRADE**
Alemtuzumab 24 mg	Alemtuzumab 12 mg	0.88 (0.3 to 2.31)	Low	NA	NA	0.88 (0.3 to 2.31)	Low
Interferon beta-1a 44 mcg	Alemtuzumab 12 mg	3.6 (1.88 to 7.33)	Moderate	NA	NA	3.6 (1.88 to 7.33)	Moderate
Interferon beta-1a 44 mcg	Alemtuzumab 24 mg	4.08 (1.69 to 11.42)	Very low	NA	NA	4.08 (1.69 to 11.42)	Very low
Interferon beta-1a 44 mcg	Interferon beta-1a 22 mcg	1.31 (0.4 to 4.36)	Low	NA	NA	1.31 (0.4 to 4.36)	Low
Interferon beta-1a 44 mcg	Interferon beta-1a 30 mcg	1.15 (0.43 to 3.10)	Low	2.09 (0.98 to 4.57)	Low	1.65 (0.91 to 3.08)	Low
Interferon beta-1a 60 mcg	Interferon beta-1a 30 mcg	1.43 (0.66 to 3.11)	Low	NA	NA	1.43 (0.66 to 3.11)	Low
glatiramer acetate 20mg	Interferon beta-1a 30 mcg	0.61 (0.22 to 1.67)	Low	1.02 (0.53 to 2.03)	Low	0.88 (0.51 to 1.55)	Low
Fingolimod oral 0.5 mg	Interferon beta-1a 30 mcg	1.28 (0.52 to 3.44)	Low	1.17 (0.58 to 2.29)	Low	1.16 (0.65 to 2.04)	Low
Fingolimod oral 1.25 mg	Interferon beta-1a 30 mcg	2.44 (1.09 to 5.68)	Low	1.41 (0.73 to 2.59)	Low	1.66 (0.94 to 2.91)	Low
Interferon beta-1b 250 mcg	Interferon beta-1a 30 mcg	6.27 (0.79 to 172.3)	Low	0.41 (0.16 to 0.93)	Low	0.63 (0.28 to 1.44)	Low
glatiramer acetate 20mg	Interferon beta-1a 44 mcg	0.88 (0.36 to 1.94)	Low	0.37 (0.17 to 0.77)	Low	0.53 (0.29 to 0.96)	Low
Teriflunomide oral 7 mg	Interferon beta-1a 44 mcg	0.40 (0.14 to 1.00)	Low	0.75 (0.34 to 1.42)	Low	0.62 (0.31 to 1.12)	Low
Teriflunomide oral 14 mg	Interferon beta-1a 44 mcg	0.54 (0.20 to 1.38)	Low	0.76 (0.35 to 1.57)	Low	0.69 (0.37 to 1.28)	Low
dimethyl fumarate 240 mg two times daily	glatiramer acetate 20mg	1.18 (0.49 to 2.84)	Low	0.96 (0.37 to 2.36)	Low	1.07 (0.56 to 1.92)	Low
dimethyl fumarate 240 mg three times daily	glatiramer acetate 20mg	1.15 (0.52 to 2.56)	Low	0.98 (0.35 to 2.53)	Low	1.07 (0.56 to 1.93)	Low
Interferon beta-1b 250 mcg	glatiramer acetate 20mg	0.91 (0.37 to 2.27)	Low	0.49 (0.14 to 1.63)	Low	0.72 (0.35 to 1.49)	Low
Interferon beta-1b 500 mcg	glatiramer acetate 20mg	1.16 (0.46 to 3.05)	Low	NA	NA	1.16 (0.46 to 3.05)	Low
dimethyl fumarate 240 mg three times daily	dimethyl fumarate 240 mg two times daily	1.01 (0.58 to 1.73)	Low	NA	NA	1.01 (0.58 to 1.73)	Low
Teriflunomide oral 14 mg	Teriflunomide oral 7 mg	1.12 (0.73 to 1.85)	Moderate	NA	NA	1.12 (0.73 to 1.85)	Moderate
Fingolimod oral 1.25 mg	Fingolimod oral 0.5 mg	1.43 (0.94 to 2.21)	Moderate	NA	NA	1.43 (0.94 to 2.21)	Moderate
Peginterferon beta-1a 125 mcg once every 4 wks	Peginterferon beta-1a 125 mcg once every 2 wks	0.98 (0.41 to 2.37)	Low	NA	NA	0.98 (0.41 to 2.37)	Low
Interferon beta-1b 500 mcg	Interferon beta-1b 250 mcg	1.63 (0.66 to 4.11)	Low	NA	NA	1.63 (0.66 to 4.11)	Low

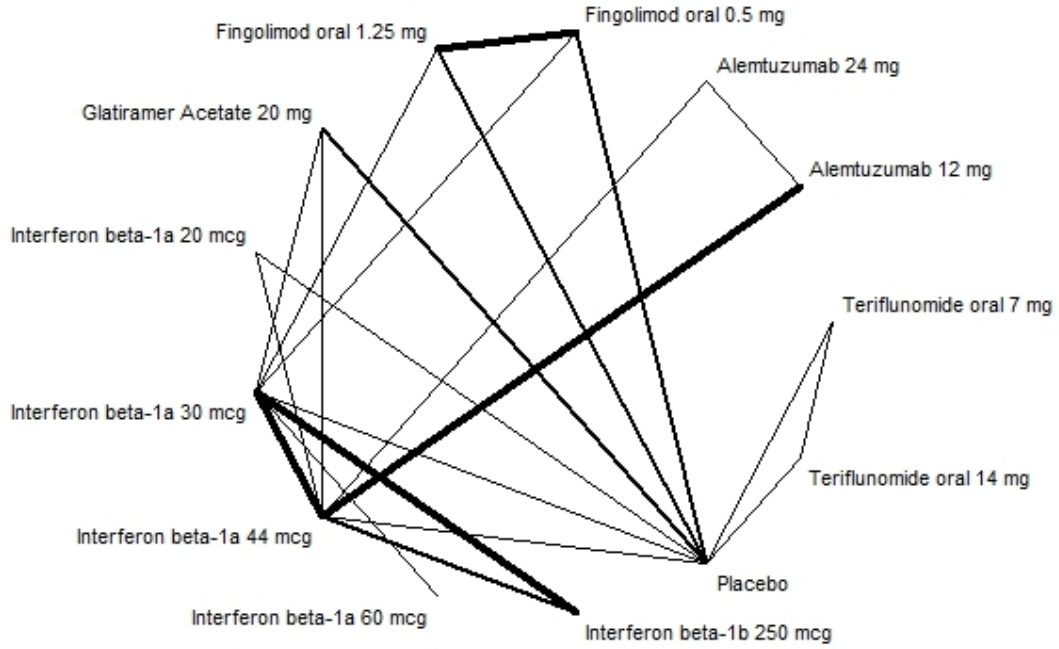
RR= relative ratio, CI= confidence interval, mg= milligrams, mcg= micrograms, SC= subcutaneous, IM= intra muscular, q.d.= once daily, q.w.=once weekly, t.i.w.= three times weekly, 2.i.d= two times daily, t.i.d= three times daily, 1/2 w=once every 2 weeks, 1/4 w=once every 4 weeks.

Change in Expanded Disability Scale

Here, we examined disability progression in a continuous manner; that is by estimating the change in EDSS. We did not grade the quality of the evidence for this outcome. We present here results for active treatments versus placebo. We compare results obtained though the "network meta-analysis approach" and the "pairwise comparison method".

The network of the evidence for change in EDSS included 12 treatment strategies and placebo (Figure 6).

Figure 6. *Network of evidence for change in expanded disability status scale*



Active treatments versus placebo

Twelve different treatments were compared to placebo in the network meta-analysis (Table 11). Four treatments were statistically significantly more effective than placebo against disability progression: alemtuzumab 24 mg (mean difference=-0.91 (95% CI:-1.48; -0.4), alemtuzumab 12 mg (-06 (-1.02; -0.24)), interferon beta-1b 250 mcg every other day (-0.58 (-0.94; -0.22)), and interferon beta-1a 44 mcg three times a week (-0.28 (-0.58; -0.02).

When comparing results obtained through "network meta-analysis approach" and "pairwise comparison method", we found a difference in the magnitude and statistical significance of the effect for the comparison interferon beta-1a 30 mcg versus placebo (Table 11). The mean difference in change in EDSS score was -0.59 (-0.86 to -0.32) when considering pairwise comparisons, and -0.22 (-0.48 to 0.02) for the network meta-analysis estimates. For the other treatments strategies, a similar magnitude of effect was seen.

Table 11. *Change in expanded disability status scale for MS treatments compared to placebo for direct pairwise comparisons and network evidence*

Interventions	Network meta-analysis Mean difference	SUCRA	Pairwise comparison Mean difference
Alemtuzumab 24 mg IV q.d	-0.91 (-1.48 to -0.4)	0.98	
Alemtuzumab 12 mg IV q.d	-0.6 (-1.02 to -0.24)	0.86	
Interferon beta-1b 250 mcg SC every other day	-0.58 (-0.94 to -0.22)	0.85	
Interferon beta-1a 44 mcg SC t.i.w	-0.28 (-0.58 to -0.02)	0.56	-0.24 (-0.48 to 0.00)
Interferon beta-1a 22 mcg SC t.i.w	-0.27 (-0.71 to 0.15)	0.52	-0.25 (-0.51 to 0.01)
Interferon beta-1a 60 mcg IM q.w	-0.25 (-0.76 to 0.24)	0.49	
Fingolimod oral 1.25 mg	-0.22 (-0.47 to 0.04)	0.46	-0.15 (-0.25 to -0.05)
Interferon beta-1a 30 mcg IM q.w	-0.22 (-0.48 to 0.02)	0.46	-0.59 (-0.86 to -0.32)
Teriflunomide oral 14 mg	-0.14 (-0.56 to 0.27)	0.35	-0.14 (-0.27 to -0.01)
Fingolimod oral 0.5 mg	-0.16 (-0.41 to 0.1)	0.35	-0.08 (-0.20 to 0.03)
glatiramer acetate 20mg q.d	-0.13 (-0.4 to 0.11)	0.31	-0.03 (-0.12 to 0.06)
Teriflunomide oral 7 mg	-0.05 (-0.47 to 0.36)	0.23	-0.05 (-0.18 to 0.08)
Placebo	0	0.10	

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.

Serious adverse events

We present here results for active treatments versus placebo. We did not grade the quality of the evidence for this outcome. We compare results obtained though the "network meta-analysis approach" and the "pairwise comparison method".

The evidence network available for serious adverse events is presented in Figure 7.

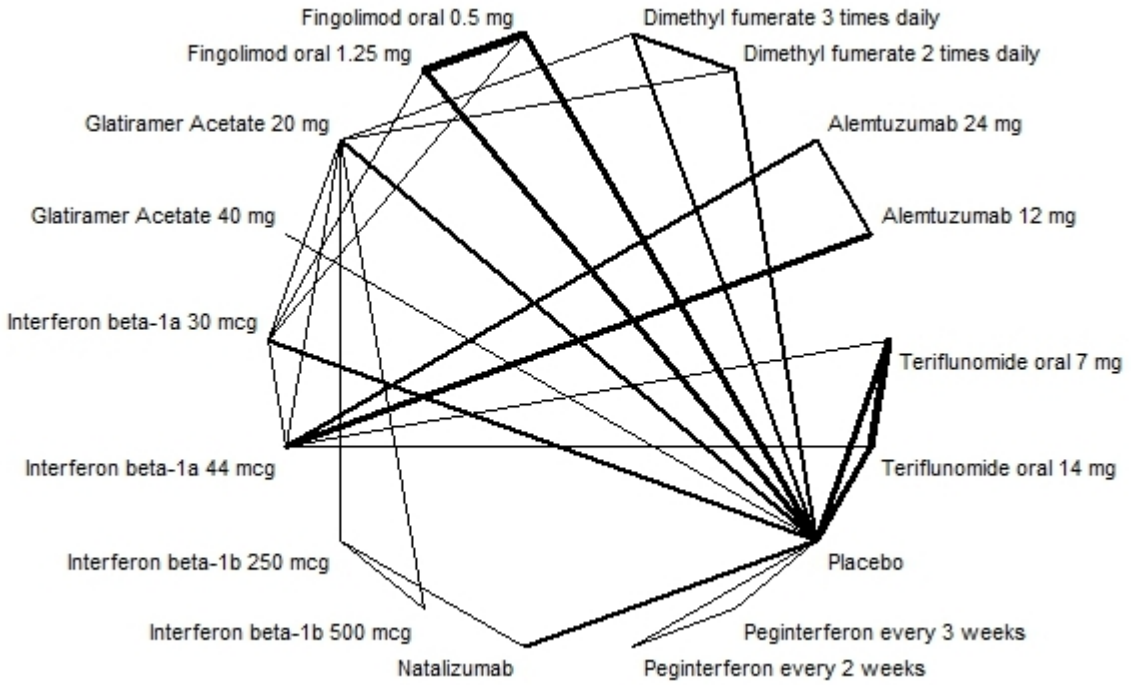


Figure 7. *Network of evidence for serious adverse events*

Active treatments versus placebo

Through the network meta-analysis, we had information for 17 treatments (Table 12). When considering all the available evidence comparing active treatments and placebo, based on the confidence intervals, no statistically significant difference was seen between results obtained through pairwise comparisons and network meta-analysis results. However, for the network meta-analysis results no treatments were found to increase statistically significantly serious adverse events compared to placebo. Results from the "pairwise comparison method" showed that peg-interferon beta-1a 125 mcg once every 4 and 2 weeks were associated with more serious adverse events than placebo, with RRs of 1.55 (95% CI: 1.12-2.14) and 1.66 (1.21- 2.28), respectively.

Table 12. *Relative risk for serious adverse events for MS treatments compared to placebo for direct pairwise comparisons and network evidence*

Intervention	Network meta-analysis Relative ratio (95% CI)	SUCRA	Pairwise comparison Relative ratio (95% CI)
Alemtuzumab 12 mg IV q.d	0.67 (0.37 to 1.28)	0.80	
Interferon beta-1b 250 mcg SC every other day	0.66 (0.35 to 1.26)	0.80	
Dimethyl fumarate 240 mg three times daily	0.72 (0.49 to 1.07)	0.76	0.73 (0.59 to 0.91)
Interferon beta-1a 30 mcg IM q.w	0.77 (0.54 to 1.13)	0.70	0.65 (0.44 to 0.97)
Glatiramer acetate 20mg q.d	0.78 (0.54 to 1.14)	0.68	0.99 (0.50 to 1.97)
Alemtuzumab 24 mg IV q.d	0.79 (0.42 to 1.53)	0.64	
Dimethyl fumarate 240 mg two times daily	0.81 (0.56 to 1.19)	0.64	0.82 (0.67 to 1.01)
Natalizumab	0.81 (0.49 to 1.39)	0.62	0.80 (0.62 to 1.03)
Interferon beta-1a 44 mcg SC t.i.w	0.86 (0.52 to 1.46)	0.54	
Interferon beta-1b 500 mcg SC every other day	0.93 (0.49 to 1.8)	0.47	
Fingolimod oral 0.5 mg	0.96 (0.68 to 1.39)	0.45	0.98 (0.67 to 1.42)
Glatiramer acetate 40mg t.i.w	0.99 (0.49 to 2.04)	0.44	0.98 (0.59 to 1.63)
Placebo	1	0.39	
Teriflunomide oral 7 mg	1.03 (0.71 to 1.51)	0.37	1.02 (0.79 to 1.32)
Teriflunomide oral 14 mg	1.07 (0.73 to 1.54)	0.33	1.14 (0.89 to 1.46)
Fingolimod oral 1.25 mg	1.22 (0.87 to 1.77)	0.20	1.18 (0.73 to 1.91)
peginterferon beta-1a 125 mcg once every 4 weeks	1.55 (0.88 to 2.74)	0.11	1.55 (1.12 to 2.14)
Peginterferon beta-1a 125 mcg once every 2 weeks	1.67 (0.94 to 2.94)	0.07	1.66 (1.21 to 2.28)

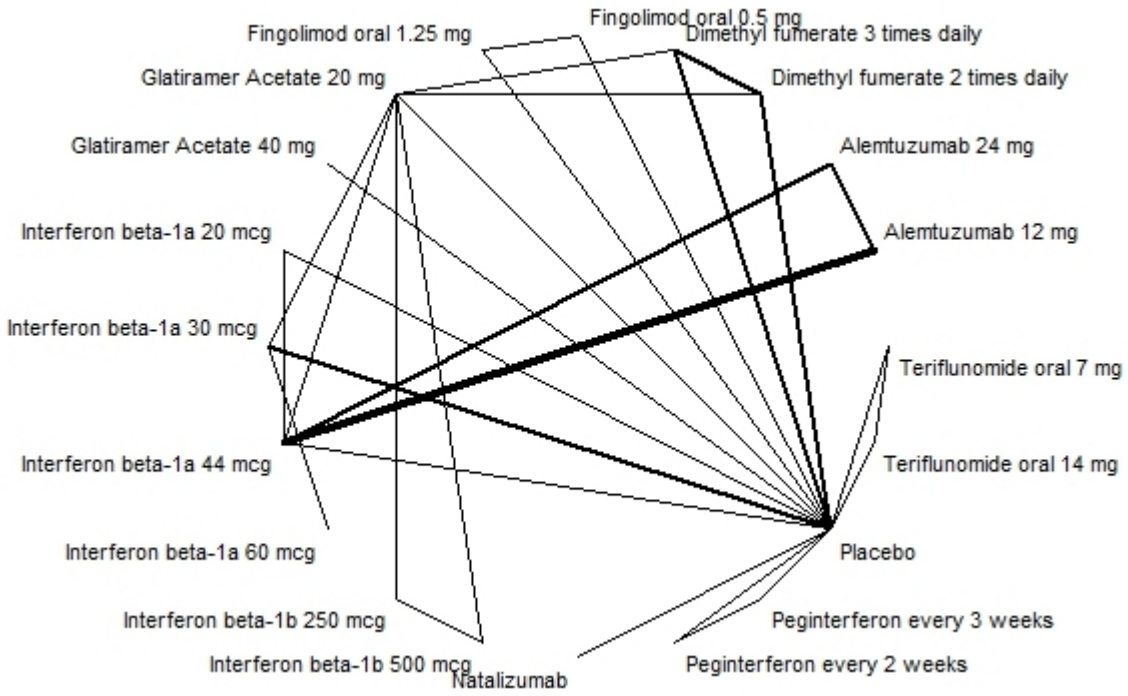
RR= relative ratio, CI= confidence interval, mg= milligrams, mcg= micrograms, SC= subcutaneous, IM= intra muscular, q.d.= once daily, q.w.=once weekly, t.i.w.= three times weekly, 2.i.d= two times daily, t.i.d= three times daily, 1/2 w=once every 2 weeks, 1/4 w=once every 4 weeks. SUCRA= surface under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

Mortality

We present here results for active treatments versus placebo. We compare results obtained though the “network meta-analysis approach” and the “pairwise comparison method”.

Figure 8 illustrates the network of evidence available for mortality. In total, 19 treatment strategies and placebo were examined.

Figure 8. *Evidence network for mortality*



Active treatments versus placebo

Table 13 reports results for nineteen treatments compared to placebo. Estimates obtained through "pairwise comparison method" and "network meta-analysis approach" are statistically consistent. None of the examined treatments were associated with a higher risk for mortality than placebo.

Table 13. *Relative risk for mortality for MS treatments compared to placebo for direct pairwise comparisons and network evidence*

Intervention	Network meta-analysis Relative ratio (95% CI)	SUCRA	Pairwise comparison Relative ratio (95% CI)
Fingolimod oral 0.5 mg	0.1 (0. to 2.57)	0.80	0.20 (0.01 to 4.09)
Interferon beta-1b 500 mcg SC every other day	0.08 (0. to 5.9)	0.79	
Glatiramer acetate 40mg t.i.w	0.08 (0. to 3.54)	0.79	0.16 (0.01 to 4.00)
Interferon beta-1b 250 mcg SC every other day	0.07 (0. to 6.65)	0.79	
Peginterferon beta-1a 125 mcg once every 4 weeks	0.4 (0.01 to 10.22)	0.61	0.50 (0.05 to 5.50)
Peginterferon beta-1a 125 mcg once every 2 weeks	0.41 (0.01 to 8.87)	0.61	0.49 (0.04 to 5.37)
Dimethyl fumarate 240 mg two times daily	0.52 (0.04 to 5.34)	0.59	1.00 (0.10 to 9.62)
Fingolimod oral 1.25 mg	0.52 (0.02 to 6.76)	0.58	0.49 (0.04 to 5.35)
Dimethyl fumarate 240 mg three times daily	0.89 (0.09 to 8.41)	0.47	1.64 (0.20 to 13.27)
Interferon beta-1a 44 mcg SC t.i.w	0.97 (0.06 to 17.15)	0.47	0.34 (0.01 to 8.26)
Glatiramer acetate 20mg q.d	0.9 (0.11 to 7.85)	0.47	1.03 (0.06 to 16.47)
Teriflunomide oral 14 mg	0.94 (0.02 to 37.74)	0.46	0.94 (0.06 to 15.00)
Placebo	1	0.44	
Interferon beta-1a 22 mcg SC t.i.w	1.6 (0.07 to 34.77)	0.37	0.99 (0.06 to 15.70)
Alemtuzumab 24 mg IV q.d	2.08 (0.04 to 125.5)	0.34	
Interferon beta-1a 60 mcg IM q.w	2.28 (0.03 to 222.1)	0.34	
Interferon beta-1a 30 mcg IM q.w	2.1 (0.26 to 24.45)	0.29	2.86 (0.30 to 27.43)
Teriflunomide oral 7 mg	2.59 (0.12 to 82.51)	0.29	2.08 (0.19 to 22.79)
Alemtuzumab 12 mg IV q.d	2.81 (0.08 to 168.2)	0.27	
Natalizumab	4.34 (0.16 to 2761.)	0.22	2.52 (0.12 to 52.25)

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.

Stay at hospitals

Very few studies reported on stay at hospitals. Therefore, we could not summarise quantitatively the results for this endpoint.

Economic evaluation-Methods

General

In order to assess the health economic effectiveness of different disease-modifying medicines for patients with RRMS, we performed a cost-utility analysis (CUA). The relevant costs were expressed in 2015 Norwegian kroner (NOK), and effects were expressed in quality-adjusted life-years (QALYs). Both costs and effects were discounted using an annual discount rate of 4% as recommended by the Norwegian Ministry of Finance and guidelines for health economic evaluation in the health sector (67).

The analysis was carried out from a healthcare perspective. The healthcare perspective is relevant for prioritisation of interventions within a fixed budget if the aim of the decision maker is to maximize health (no expansion of the budget is assumed). The methodological guidelines for economic evaluation in the health sector recommend a societal perspective that includes consequences for all parts of the economy, including time costs, the deadweight loss of taxation, any productivity changes, and excluding transfers such as value added tax. This perspective is more appropriate if an expansion of the budget is assumed and in settings where prioritization of interventions across sectors of the economy is relevant (e.g. for public health interventions).

We expressed the results as mean incremental cost-effectiveness ratio (ICER) from 10,000 runs of the model in base-case. We handled uncertainties in model parameters by performing probabilistic sensitivity analyses, designed as a Monte Carlo simulation, with 10,000 iterations.

Population, interventions and model structure

Population

In the economic evaluation, we assumed that a typical RRMS patient population in Norway has an average age of 30 years at diagnosis, and 68% are female.

Interventions

There are currently 12 disease-modifying therapies approved and available for RRMS patients in Norway (based on clinical experts' opinion). All these active treatment options were included in our analysis (Table 14).

Table 14. *Available treatments included in the health economic analysis*

Interventions
Alemtuzumab 12 mg (Lemtrada)
Dimethyl fumarate 240 mg (Tecifidera)
Fingolimod 0.5 mg (Gilenya)
Glatiramer acetate 20 mg (Copaxone)*
Interferon beta-1a 30 mcg (Avonex)
Interferon beta-1a 22 mcg (Rebif)
Interferon beta-1a 44 mcg (Rebif)
Interferon beta-1b 250 mcg (Betaferon)
Interferon beta-1b 250 mcg (Extavia)
Natalizumab 300 mg/15 mL (Tysabri)
Peg-interferon beta-1a 125 mcg (Plegridy)
Teriflunomide 14 mg (Aubagio)

mg: milligram; mL: millilitre; mcg: microgram

* Glatiramer acetate 40 mg 3 times per week was discussed in the discussion section.

Because of lack of clinical data exploring the sequential use of different treatment options following the failure of first-line treatments or switching, we assumed that patients could not switch between treatments in the model.

Model structure

In order to assess the cost-utility of different disease-modifying therapies in patients diagnosed with RRMS, a decision analytic model was developed in TreeAge pro ® 2015. The model is of the Markov type, in which a cohort of patients is followed over a given period of time. A Markov model was considered appropriate, as multiple sclerosis is a chronic condition requiring continuous treatment (68, 69).

We developed the model based on a previously published report with similar objectives as ours (27). The validity of the model structure and assumptions to the Norwegian context have been discussed and evaluated by two independent clinical experts experienced in treating patients with RRMS in Norway. The model structure and all assumptions were adapted to the Norwegian setting, and took into consideration Norwegian clinical practice.

The model simulates the natural history of MS using the state transition methodology (Figure 9). Health states were defined according to the Kurtzke EDSS (70). EDSS is a clinical rating scale ranging from 0 to 10. EDSS 0-2.5 refers to patients with no or few limitations in mobility, and EDSS 10 refers to death due to MS. Disability status was modelled from 0 to 10 for RRMS and from 2 to 10 for SPMS (70).

During one cycle, all patients could remain in the current health state, progress to the next more severe state, transition to a secondary-progressive health state, or die (Figure 9). Patients with an EDDS scale of five or lower could also improve to a less severe state, and stop treatment. Improvement in lower health states was modelled by assuming that a maximum of 2 EDSS-point improvements could be achieved (71). Patients would discontinue treatment once they progress to an EDSS of six or SPMS (based on clinical experts' opinion).

In the base-case analysis, we assumed no treatment effect once patients progress to an EDDS of six. It is also documented that with advancing disease (EDSS>6) less relapses occur (71). We, therefore, assumed that relapses would occur only in patients with EDSS of five or lower.

We assessed the costs and utilities associated with different treatment options over 20 years for the base case analysis (based on experts' opinion). Alternatives horizons of 10 years and 30 years were considered in scenario analyses. We used a cycle length of the model of one year, meaning that any transitions between different states could happen only once a year. Patients could be in only one of the pre-defined states at any time. Upon completion of each cycle, patients could, depending on transition probabilities, transfer to another state or remain in the same state until death or the end of the simulation. Each state and event is associated with specific health outcomes and costs. Death is modelled as an absorbing state. Once an individual makes a transition into the absorbing state, no further incurred costs or health outcome are included in the analysis.

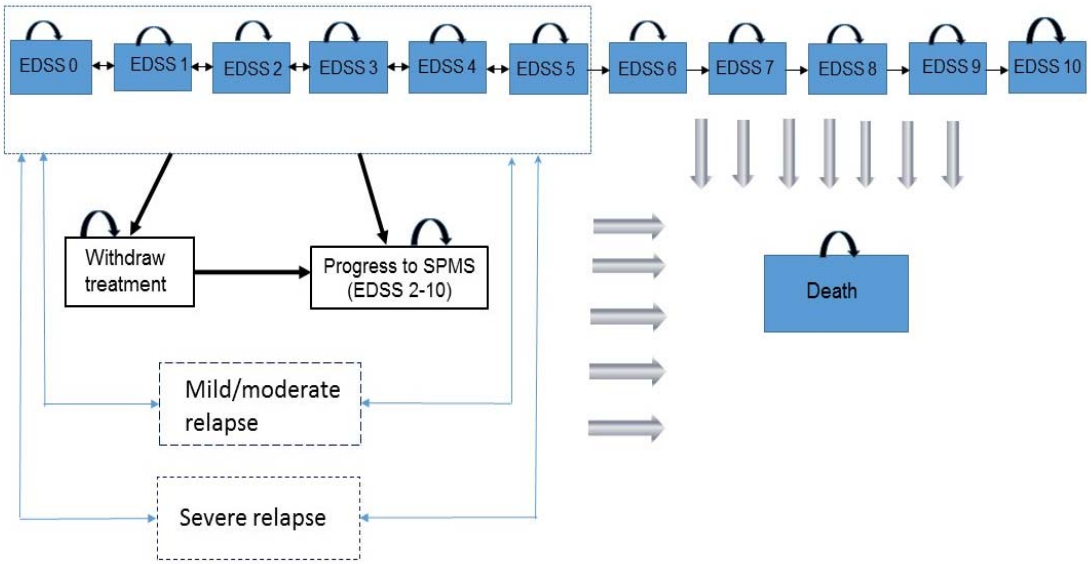


Figure 9. *Model structure*

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.

Disease-modifying therapies are usually initiated in patients with an EDSS score lower than 5, and mostly for patients with an EDSS score between 1 and 3 (clinical expert opinion and (72)). EDSS distributions used in our analysis are presented in Table 15.

Table 15. *EDSS distribution*

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.al* 2014 (72)

Model Parameters

The model was created as a probabilistic model. This means that all uncertain parameters (efficacy, costs, epidemiological data, etc.) were modelled as probability distributions rather than point estimates. This was done to facilitate probabilistic sensitivity analysis. The sources and methods used to derive the model parameters are described below. First, we describe how we estimated the natural history transitional probabilities, then we describe how we incorporated into the model the clinical effect estimates (obtained through the systematic review (SR) and the network meta-analysis). Finally, we describe the methods used to calculate costs, and quality of life estimates.

Key model assumptions

Based on reporting of withdrawals in studies included in our SR, we set annual treatment discontinuation rate at 15% for the first two years in the base case analysis. This rate is also applicable to the Norwegian context according to the experts' opinion. A previous study showed that the proportion of patients who discontinued treatment and the degree of treatment adherence were similar across different treatment options (73). We therefore assumed the same discontinuation rate across all treatment options. We assumed no discontinuation after two years (expert opinion). Any patients who discontinues therapy subsequently progress according to natural history rates with no additional cost of therapy.

We assumed that treatments have no survival benefit. The annual risk of other mortality causes is, therefore, assumed to be the same as the normal population. We collected age and gender specific Norwegian all-cause mortality data from Statistics Norway (74). A weighted average was calculated based on the assumption that 68% of RRMS patients were female.

Natural history transitional probabilities

We did not find Norwegian data that were compatible to the developed model, so the transitional probabilities had to be based on estimates reported in the published literature. However, the transferability of the data to the Norwegian context were critically discussed and modified based on expert advice.

Disability progression

Probabilities for disability progression within RRMS health states, transitioning from RRMS to SPMS, as well as disability progression within SPMS health states were derived from a large 25- year patient-level cohort study (untreated patients) undertaken in London, Ontario, Canada (75, 76). The reported data were eligible for our model and used by the several previously published economic studies (27, 77).

Instantaneous hazard rates for disability progression without disease-modifying therapy were calculated from the Ontario dataset using the formula below (76), and are presented in the Tables 16-18.

$$\lambda i = \frac{\text{Number of people leaving state i}}{\sum_{j=1}^{n} duration\ in\ state\ i}$$

where n *is the number of individuals,* j *is each individual leaving state* i, *and* i= *EDSS sate 0 to 10.*

All rates were transformed into transition probabilities for use in the model (78). All natural history probabilities were incorporated in the model as beta distributions

Table 16. *Progression rates within RRMS health states*

EDSS score	Estimates (per person-year)	Variance
0	0.144	0.00007
1	0.075	0.00003
2	0.152	0.00006
3	0.272	0.00025
4	0.450	0.00166
5	0.485	0.00213
6	0.283	0.00104
7	0.342	0.00450
8	0.105	0.00139
9	0.167	0.02778

EDSS: Expanded Disability Status Scale
Source: (27, 76)

Table 17. *Progression rates from RRMS to SPMS*

EDSS score	Estimates (per person-year)	Variance
0	0.004	0.000002
1	0.002	0.000001
2	0.029	0.000012
3	0.102	0.000094
4	0.199	0.000735
5	0.256	0.001126
6	0184	0.000676
7	0.237	0.000312
8	0.066	0.000866
9	0.167	0.027778

EDSS: Expanded Disability Status Scale; SPMS: Secondary-progressive multiple sclerosis
Source: (27, 76)

Table 18. *Progression rates within SPMS health states*

EDSS score	Estimates (per person-year)	Variance
2	0.370	0.00370
3	0.385	0.00129
4	0.594	0.00280
5	0.349	0.00088
6	0.241	0.00029
7	0.186	0.00024
8	0.107	0.00015
9	0.093	0.00038

EDSS: Expanded Disability Status Scale; SPMS: Secondary-progressive multiple sclerosis
Source: (27, 76)

Improvements in MS disability

Based on a large study, Tremlett and co-workers concluded that improvements in MS disability over one or two years were not unusual (71). The result of the study indicated that 8.3% of patients had an improvement of at least 1 point in the EDDS scale after one year, and 2.2% showed greater than or equal to 2-point improvements. We considered a maximum of two EDSS-point improvements in the model. The rates of annual disability improvements were used in the model only for the EDSS states lower than 6.

Relapse rate

There were no available Norwegian data on annual relapse rate compatible to our model. We considered therefore the best available sources. Annual relapse rates have been estimated based on Ontario cohort data (76), and published evidence suggested that the frequency of relapse is affected by a patient's age and disease duration (a decrease over time) (79, 80). Based on Ontario cohort data, the mean relapse rate after two years since disease onset was reported to be 0.835 and 1.423 for patients in EDSS 0 to 2 and 3+, respectively (76). These estimates were adjusted such that the patients enter the model with an average time since disease onset of five years and onwards (based on the studies included in our systematic review). More detailed information about the estimation of annual relapse rate can be found in the Canadian HTA report (27). These annual relapse rates were judged applicable to the Norwegian context by our clinical experts.

We used a Gamma distribution for annual relapse rates based on the assumption that events with a known average rate occur in a fixed interval of time.

Table 19. *Annual relapse rates*

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: (27)

Based on published literature and expert opinion, we assumed that 23% of relapses were severe (81). In addition, we assumed that the average length of mild or moderate relapses was of 45 days. For severe relapse, it was of 90 days (27, 81).

Clinical efficacy parameters in the model

Clinical efficacy data for the model were the data presented in the "Clinical evaluation-results" section of this report. These were the results obtained through the network meta-analysis of the included trials. In the health economic model, we included the estimates on relapse rates and disability progression. These efficacy estimates were modelled by applying the relative risk for each treatment compared to best supportive care "no treatment", to the transitional probabilities based on the natural history of the disease for untreated patients.

We added the relative risks to the model as probability distributions. We used log-normal distributions, according to the methodology described by Briggs and co-authors (78). Standard errors for the log-normal distributions were calculated based on confidence intervals for efficacy estimates. The estimates of the calculations of distributions for efficacy parameters used in the model are presented in Tables 20 and 21.

Based on expert opinion, we considered a reduction in treatment effect over time. Full effect of treatments is assumed to be 100% for the first four years, 75% from year 5 - 10, and 50% beyond 10 years.

Treatment effect on disability progression

The relative risks of sustained disability progression were multiplied to the transitional probabilities of patients moving to higher health states, as well as to progression to SPMS health states.

We assumed that patients transitioned as natural history of disease transitional probabilities between SPMS health state. That is treatments had no effect on the transition between SPMS states. Patients who withdraw treatment will progress according to transitional probabilities for natural disability progression, but will retain any previously accrued benefits.

Table 20. *Efficacy estimates for disability progression (log-normal distribution)*

Interventions	RR of sustained disability progression	Ln (RR)	SE
Alemtuzumab 12 mg (Lemtrada)	0.36	-1.02	0.39
Dimethyl fumarate 240 mg (Tecifidera)	0.65	-0.43	0.14
Fingolimod 0.5 mg (Gilenya)	0.71	-0.34	0.13
Glatiramer acetate 20 mg * (Copaxone)	0.78	-0.25	0.11
Interferon beta-1a 30 mcg (Avonex)	0.80	-0.22	0.11
Interferon beta-1a 22 mcg (Rebif)	0.84	-0.17	0.17
Interferon beta-1b 250 mcg (Betaferon)	0.72	-0.33	0.14
Interferon beta-1b 250 mcg (Extavia)	0.72	-0.33	0.14
Natalizumab 300 mg/15 mL (Tysabri)	0.59	-0.53	0.18
Peg-interferon beta-1a 125 mcg (Plegridy)	0.61	-0.49	0.26
Teriflunomide 14 mg (Aubagio)	0.73	-0.31	0.18

RR: relative risk; SE: standard error; mg: milligram; mL: millilitre; mcg: microgram

* We did not find any documentation for glatiramer acetate 40 mg.

Treatment effect on relapses

The expected number of relapses for each treatment alternative were estimated in the model by multiplying the treatment effect on the relapse rates for each treatment alternative (Table 21) to the average number of relapses experienced with "no treatment".

Table 21. *Efficacy estimates for annual relapse (log-normal distribution)*

Interventions	RR of annual relapse rate	Ln (RR)	SE
Alemtuzumab 12 mg (Lemtrada)	0.29	-1.24	0.11
Dimethyl fumarate 240 mg (Tecifidera)	0.50	-0.69	0.09
Fingolimod 0.5 mg (Gilenya)	0.46	-0.78	0.08
Glatiramer acetate 20 mg * (Copaxone)	0.65	-0.43	0.05
Interferon beta-1a 30 mcg (Avonex)	0.82	-0.20	0.06
Interferon beta-1a 22 mcg (Rebif)	0.69	-0.37	0.10
Interferon beta-1a 44 mcg (Rebif)	0.64	-0.45	0.06
Interferon beta-1b 250 mcg (Betaferon)	0.66	-0.42	0.07
Interferon beta-1b 250 mcg (Extavia)	0.66	-0.42	0.07
Natalizumab 300 mg/15 mL (Tysabri)	0.30	-1.20	0.10
Peg-interferon beta-1a 125 mcg (Plegridy)	0.65	-0.43	0.14
Teriflunomide 14 mg (Aubagio)	0.67	-0.40	0.07

RR: relative risk; SE: standard error; mg: milligram; mL: millilitre; mcg: microgram

* Glatiramer acetate 40 mg RR: 0.66 SE: 0.11

Treatment-related adverse events

Generally, disease-modifying therapies are well tolerated. Our systematic review showed no statistically significant differences between the therapies for serious adverse events. Moreover, most of the adverse events related to the RRMS treatments were transient, and some of them may potentially be related to the disease process (e.g. depression). We have therefore not included adverse events (except for Progressive multifocal leukoencephalopathy (PML)) in the model based on the assumption that the costs and disutility associated with adverse events would not have a significant impact on the results. However, some of the differences for resource use related to the adverse events have been considered when estimating of monitoring costs associated with each of the treatment strategies. For more information, see Appendix 8.

Natalizumab has been reported to be associated with the development of PML, which is a rare but serious infectious or inflammatory disease. PML is a viral infection (JC-virus) leading to inflammation and finally demyelination, often resulting in severe disability or death (82). A study from 2013 found a risk of developing PML of 2.84 cases per 1000 patients who received natalizumab for MS (83). It was also reported that 22% of the reported natalizumab-associated PML patients died (83). The costs and reduction in quality of life associated with PML is addressed in the next sections.

It should be mentioned that recently PML has also been reported in a small number of patients treated with other disease-modifying therapies, such as dimethyl fumurate and fingolimod. Due to insufficient data, we included PML only for natalizumab in the model.

Costs

An annual cost per patient associated with different treatment alternatives was calculated for each health state and event in the model. The costs included in the model are drug costs, monitoring costs associated with the use of drugs, costs related to MS patients care (excluding drugs) at different EDSS levels, and costs related to the treatments of relapses and PML.

All costs were measured in 2015 Norwegian kroner (NOK) (based on the consumer price index for the first four months of 2015 (74)). The uncertainty surrounding cost parameters were assessed by using gamma distribution.

Annual drug costs

Drug costs were calculated based on the maximum pharmacy retail prices that we received from the Drug procurement cooperation (LIS). The annual drug cost was estimated based on recommended doses (LIS), and are presented in Table 22.

Table 22. *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 autoinjector	7,027.32	12	91,355
Interferon beta-1a (Rebif)	44 mcg/0.5 ml 3 times per week (IM)	Pre-filled syringe or autoinjector	8,904.26	12	115,755
Interferon beta-1b (Betaferon)	250 mcg /mL every other day (SC)	Powder for injec-tion	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 injec-tion	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.

Monitoring costs associated with the use of medicines

Monitoring costs associated with use of medicines were calculated based on the estimates that we received from the drug procurement cooperation (LIS). The monitoring costs were estimated separately for the first and second year. Based on the information from clinical experts, we calculated the monitoring costs beyond the second year. The estimated monitoring costs are summarized in Table 23 and Appendix 8.

Table 23. *Monitoring costs associated with each of the treatments**

Drug	1. year	2. year	Beyond 2. year
Alemtuzumab [a] (Lemtrada)	22,735	14,573	8307 (3.-5.year) 7075 (+5.year)
Dimethyl fumarate (Tecifidera)	11,550	7075	7075
Fingolimod (Gilenya)	17,912	7075	7075
Glatiramer acetate (Copaxone)	11,550	7075	7075
Interferon beta-1a 30 mcg (Avonex)	19,266	14,791	7075
Interferon beta-1a 22 mcg (Rebif)	19,266	14,791	7075
Interferon beta-1a 44 mcg (Rebif)	19,266	14,791	7075
Interferon beta-1b (Betaferon)	19,266	14,791	7075
Interferon beta-1b (Extavia)	19,266	14,791	7075
Natalizumab (Tysabri)	33,240	27,725	27,725
Peg-interferon beta-1a (Plegridy)	19,266	14,791	7075
Teriflunomide (Aubagio)	12,894	7523	7523

* All costs were updated to 2015 costs.

[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) (84).

Costs associated with MS care (exclusive costs associated with interventions)

The costs associated with different health states (EDSS levels) were obtained from a Norwegian study (85). This was a survey study carried out in Hordaland county in 2013 including 546 MS patients. The costs related to diagnosis, treatment, nursing care, assistive devices and equipment were included in the cost calculation.

The costs of mild or moderate and severe relapse were estimated based on the survey carried out by Svendsen in 2013 (85). The difference between the monthly costs for patients who had experienced relapse and for those who had not experienced relapse were estimated to be approximately NOK 14,600.

The cost associated to different EDSS states and relapse are presented in Table 24.

Table 24. *Costs associated to different EDSS states* [a]

EDSS	Direct costs [b] (NOK)
0	18,046
1	36,901
2	51,297
3	126,145
4	147,554
5	329,743
6	564,928
7	689,224
8	1,380,296
9	1,393,636
Cost per relapse [c]	
Mild/ moderate	21,906
Severe	43,812

EDSS: Expanded Disability Status Scale

[a] Estimated costs associated to different EDSS states in Norway (2013) (85). All costs were updated in 2015 NOK (based on the consumer price index for the first four months of 2015 (74)).

[b] Including VAT

c It was assumed that the average length of mild or moderate relapse and severe relapse would be 45 and 90 days, respectively (27, 81).

We assumed that most of the patients who developed PML needed treatment at hospital. The costs were estimated based on prices from the Norwegian DRG system (DRG code 421; personal communication by dr.med Elisabeth Gulowsen Celius). Patients who survived PML also needed 3-6 months extra treatments at rehabilitation centres. We assumed NOK 3,000 cost per day for stay at rehabilitation centre (86).

Health-related Quality of Life

In order to obtain utility weights, we performed a systematic search for published values. For consistency, and as the use of different utility instruments would yield different results, we focused on values based on EQ-5D, the most commonly used instrument (87).

In the base-case, we used the utility values reported by Orme and co-workers (88). The study was a cross sectional study of people comprising all course of MS (RRMS, SPMS and PPMS) from the United Kingdom. Based on the systematic search on health related quality of life data, this is the only study that presented the utility associated with each EDSS state, SPMS and relapse by using the EQ-5D method.

As Orme and colleagues did not make a distinction between mild or moderate and severe relapse, we assumed that the reported disutility was for mild or moderate relapses. Therefore, the ratio between disutility associated with mild or moderate relapse and severe relapse estimated by Prosser and co-workers (81) was applied to estimate the disutility associated with severe relapse. As mentioned, it was assumed that the average length of mild or moderate relapse and severe relapse would be 45 and 90 days, respectively (27, 81).

We assumed a disutility of 0.4 (0.3-0.5) assigned to the year a patient experienced PML (89).

Beta or log-normal distributions were used for utility values used in the model. The mean values and standard errors of the utility (QALY) weights used in our model are presented in the Table 25.

We did not identify reliable data on the probable effect on patients' utility of the different methods of administrating the medication. Therefore, the possible disutility associated with injections is not included in the model.

Table 25. *Quality of life data (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	-0.014	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. (88) and Prosser et al. (81).

[c] Ref:(89)

Economic evaluation – Results

We calculated costs and effectiveness (in terms of QALYs), for all relevant disease modifying therapies used for RRMS based on simulations of the model. We used 10,000 iterations in the Monte Carlo analyses. Our assessment of cost-effectiveness will reflect a range of potential willingness to pay (WTP) values per gained QALY.

Incremental cost–effectiveness estimates

The results of the base-case analysis are presented in Table 26. Over a 20-year time horizon, alemtuzumab dominated all other alternative treatments, *i.e.* it was both more effective and less costly.

Table 26: *Results of the base-case cost-effectiveness analysis (discounted)*

Drugs	Total costs (NOK)	Effects (QALYs)	Incremental cost (NOK)	Incremental effect (QALYs)	ICER (NOK/QALY)
Alemtuzumab (Lemtrada)	4,897,903	8.05			Dominant
Interferon beta-1b (Extavia)	6,031,551	7.40	1,133,647	-0.64	Dominated by alemtuzumab
Interferon beta-1b (Betaferon)	6,088,153	7.40	1,190,250	-0.64	Dominated by alemtuzumab
Glatiramer acetate 20mg (Copax-one)*	6,253,728	7.31	1,355,825	-0.73	Dominated by alemtuzumab
Peg-interferon beta-1a (Plegridy)	6,310,586	7.56	1,412,682	-0.48	Dominated by alemtuzumab
Teriflunomide (Aubagio)	6,337,489	7.38	1,439,586	-0.67	Dominated by alemtuzumab
Interferon beta-1a 22 mcg (Rebif)	6,498,571	7.21	1,600,667	-0.84	Dominated by alemtuzumab

Interferon beta-1a 30 mcg (Avonex)	6,533,915	7.27	1,636,012	-0.77	Dominated by alemtuzumab
Interferon beta-1a 44 mcg (Rebif)	6,574,606	7.32	1,676,702	-0.72	Dominated by alemtuzumab
Dimethyl fumarate (Tecifidera)	6,707,787	7.52	1,809,884	-0.52	Dominated by alemtuzumab
Natalizumab (Tysabri)	6,983,132	7.63	2,085,228	-0.41	Dominated by alemtuzumab
Fingolimod (Gilenya)	7,041,216	7.43	2,143,313	-0.62	Dominated by alemtuzumab

QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio
* 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).

Monte Carlo simulations with 10,000 draws from the input distributions are shown in Figure 10. Simulations for alemtuzumab show that alemtuzumab was more effective and less costly relative to other treatments. All other interventions were dominated by alemtuzumab. The results of the probabilistic sensitivity analysis also showed that alemtuzumab was more likely to be the most cost-effective strategy (above 90%) for all values of WTP.

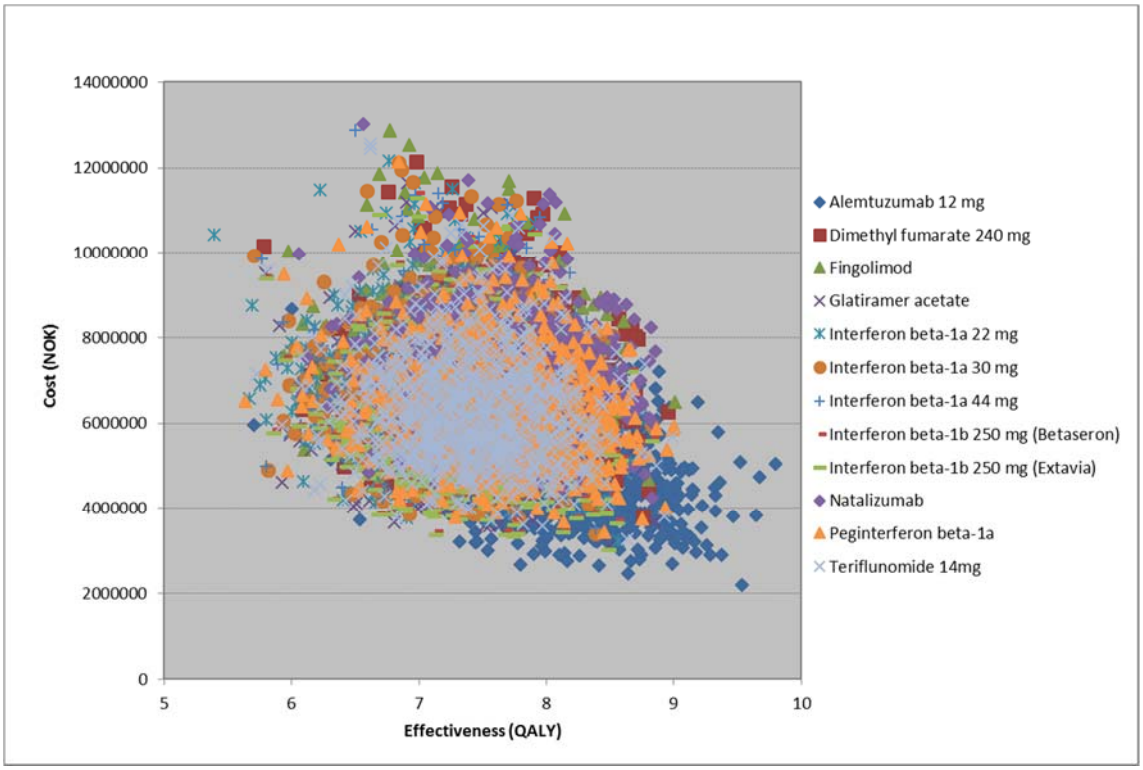


Figure 10. *Cost-effectiveness scatter-plot; mcg: microgram; mg: milligram*

The results presented above show that alemtuzumab was the most cost-effective strategy and dominated all other treatment strategies.

In order to show the cost-effectiveness of other treatment strategies relative to each other, we excluded alemtuzumab (the dominate strategy) and conducted a separate analysis of the remaining interventions. The results (for all treatment strategies, except alemtuzumab) are presented in Table 27 and Figure 11.

Discarding alemtuzumab, natalizumab was the most effective treatment regarding QALYs (7.63), followed by peg-interferon beta-1a (7.56). Interferon beta-1a 22 mcg was the least effective strategy (7.21).

Fingolimod was the most expensive treatment (NOK 7,050,000), followed by natalizumab (NOK 6,984,840). Interferon beta-1b (Extavia) was the least expensive treament (NOK 6,033,330) and was, therefore, used as a reference.

Three treatment strategies were not dominated by the other interventions. The incremental cost per QALY for peg-interferon beta-1a versus interferon beta-1b (Extavia) was NOK 1,658,450. The incremental cost per QALY for natalizumab versus peg-interferon beta-1a was NOK 10,620,000.

Interferon beta-1b (Betaferon) was dominated by interferon-1b (Extavia); glatiramer acetate was dominated by interferon beta-1b (Extavia and Betaferon), while teriflunomide was dominated by interferon beta-1b (Extavia and Betaferon) and peg-interferon beta-1a.

Interferon beta-1a (Rebif and Avonex) was dominated by peg-interferon beta-1a, interferon beta-1b (Extavia and Betaferon), teriflunomide, and glatiramer acetate.
Dimethyl fumarate was dominated by peg-interferon beta-1a, while fingolimod was dominated by natalizumab, peg-interferon beta-1a and dimethyl fumarate.

Table 27. *Results of the base-case cost-effectiveness analysis (all interventions except alemtuzumab) (discounted)*

Drugs	Total costs (NOK)	Effects (QALYs)	Versus Interferon beta-1b 250 mg (Extavia)			Sequential ICER (NOK/QALY)
			Incremental cost (NOK)	Incremental effect (QALYs)	ICER (NOK/QALY)	
Interferon beta-1b (Extavia)	6,033,328	7.40				
Peg-interferon beta-1a (Plegridy)	6,308,924	7.56	275,597	0.17	1,658,451	1,658,451
Natalizumab (Tysabri)	6,984,843	7.63	951,515	0.23	4,140,203	10,619,960

Dominated therapies						
Interferon beta-1b (Betaferon)	6,089,587	7.40	56,259	-	Dominated by interferon beta-1b (Extavia)	Dominated by interferon beta-1b (Extavia)
Glatiramer acetate 20 mg (Copaxone) *	6,256,047	7.31	222,720	-0.09	Dominated	Dominated by interferon beta-1b (Extavia) and interferon beta-1b (Betaferon)
Teriflunomide (Aubagio)	6,332,443	7.38	299,116	-0.02	Dominated	Dominated by interferon beta-1b (Extavia), interferon beta-1b (Betaferon) and peg-interferon beta-1a
Interferon beta-1a 22 mcg (Rebif)	6,497,728	7.21	464,401	-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)	6,539,464	7.27	506,137	-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)	6,573,653	7.32	540,325	-0.08	Dominated	Dominated by interferon beta-1b (Extavia), interferon beta-1b (Betaferon), peg-interferon beta-1a, glatiramer acetate and teriflunomide
Dimethyl fumarate (Tecifidera)	6,710,845	7.52	677,517	0.12	5,746,659	Dominated peg-interferon beta-1a
Fingolimod (Gilenya)	7,040,995	7.42	1,007,668	0.02	43,827,412	Dominated by peg-interferon beta-1a, dimethyl fumarate and natalizumab

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

* 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).

The incremental cost versus incremental effectiveness (QALY), when all treatment strategies, except alemtuzumab are included in the analysis, is presented in Figure 11. As mentioned, three interventions, interferon beta-1b (Extavia), peg-interferon beta-1a and natalizumab were undominated strategies. The line from interferon beta-1b (Extavia) to peg-interferon beta-1a and to natalizumab represent the cost-effectiveness frontier. It means that at different WTP, these three strategies could be considered the most cost-effective. The incremental cost per QALY of peg-interferon beta-1a compared with interferon beta-1b (Extavia) is estimated to be NOK 1,658,000, meaning interferon beta-1b (Extavia) could be considered the cost-effective treatment if WTP for QALY is less than NOK 1,658,000. For WTP between NOK 1,658,000 and NOK 10,620,000, peg-interferon beta-1a is the cost-effective treatment. If WTP is above 10,620,000, then natalizumab is the cost-effective treatment. The other treatments were dominated by the treatment comprising in the frontier. Therefore, they were not considered to be cost-effective.

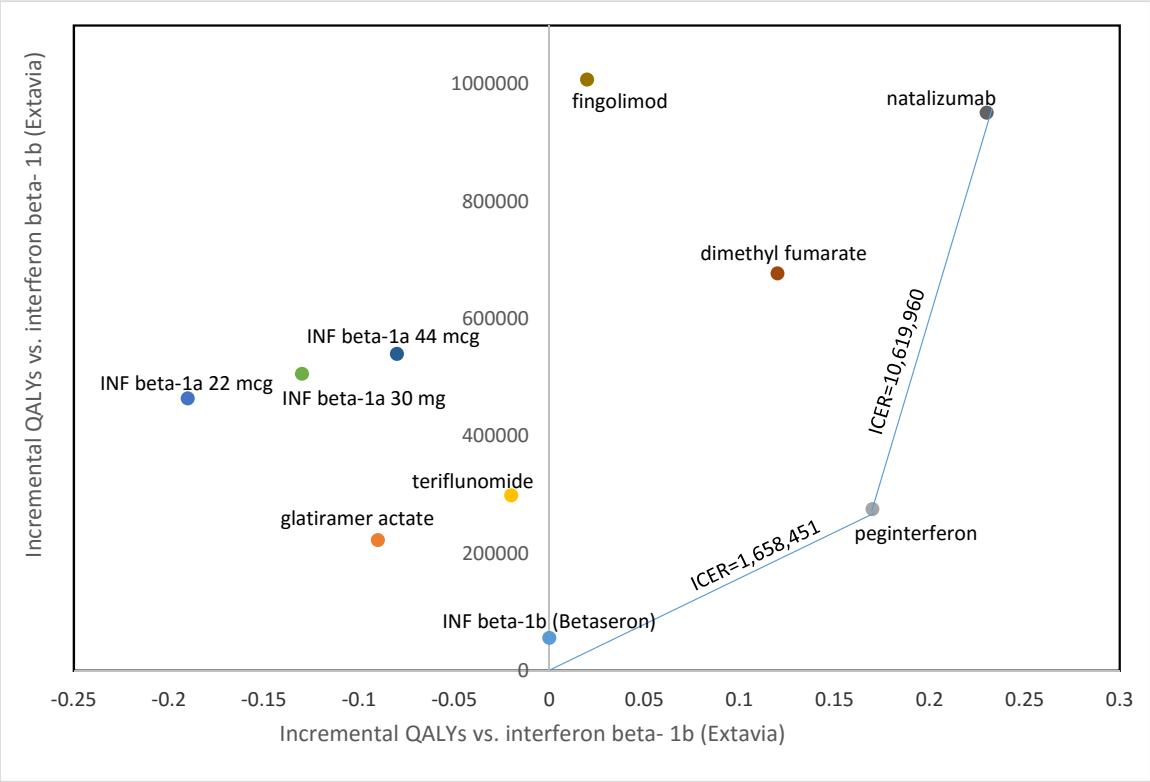


Figure 11. *Cost-effectiveness graph (all interventions except alemtuzumab); mcg: microgram; mg: milligram; INf: interferon*

We performed a Monte Carlo simulation with 10,000 draws from the input distributions and we varied the WTP from NOK 0 to NOK 2,000,000. The cost-effectiveness acceptability curves in Figure 12 show the probability of the alternatives being cost-effective subject to different levels of WTP. If one assumes maximum WTP per QALY is NOK 500,000, interferon beta-1a (Extavia) was the most cost-effective treatment strategy (47%), followed by peg-interferon beta-1a (27%) and teriflunomide (13%). With a WPT per QALY of NOK 1,000,000, interferon beta-1b (Extavia) was the most

cost-effective (36%) followed by peg-interferon beta-1a (34%) and teriflunomide (14%). However, as presented in the cost-effectiveness scatterplot (Figure 10) and Table 27, total QALYs of included interventions (except alemtuzumab) overlapped, which indicates the uncertainty regarding the gain in QALYs.

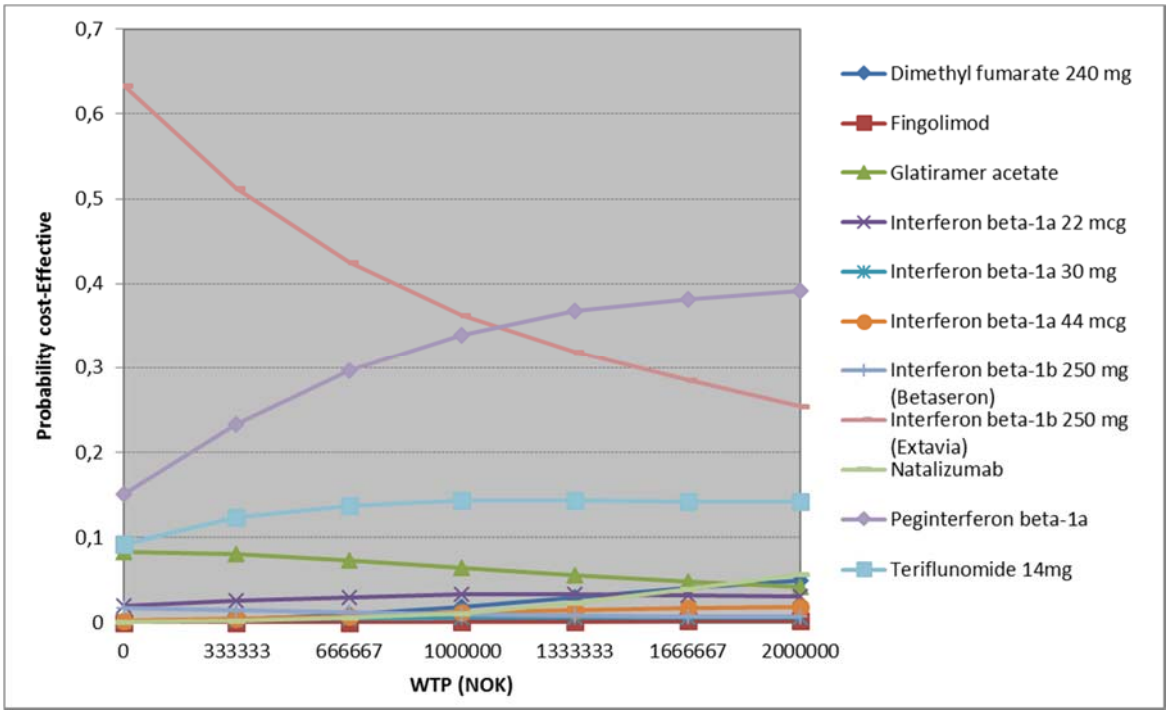


Figure 12. *Cost-effectiveness acceptability curve (all interventions except alemtuzumab)*
WTP willingness to pay; mcg: microgram; mg: milligram

Value of information analysis

We performed an analysis of the expected value of perfect information (EVPI) on all uncertain parameters to explore the uncertainty surrounding specific groups of parameters and show which group has the most impact on the results. EVPI analyses were performed with 100x500 iterations. The EVPI of different groups of parameters (costs, efficacy, QALYs and probabilities) are presented in Figure 13.

At a WTP of NOK 400,000 per QALY, probabilities data (Norwegian epidemiological data) had the highest EVPI. For values of WTP above NOK 1,000,000 per QALY, the results indicate that the treatment efficacy data have the greatest impact on decision uncertainty. These results suggest that if new research is to be undertaken (for WTP above NOK 1,000,000), additional information on efficacy data would contribute most to reducing the uncertainty surrounding the decision about which treatment modality is most cost-effective.

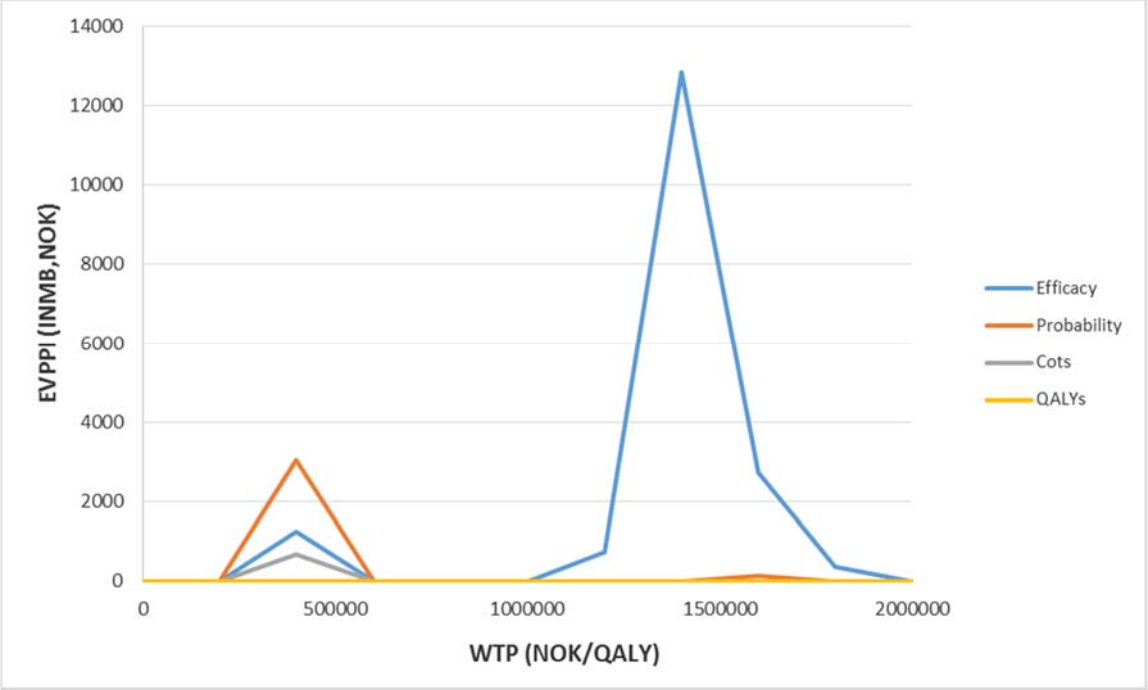


Figure 13. *Expected value of partial perfect information per patient for different groups of parameters; QALY: quality-adjusted life year; WTP: willingness to pay; INMB: incremental net monetary benefit*

Scenario analyses

In addition to the probabilistic sensitivity analysis, we performed several scenario analyses to test the uncertainty around the model assumptions and some of the input parameters.

"No treatment" was our common comparator in the network meta-analyses, and therefore was included in the health economics model. As additional information, we presented the cost-effectiveness of all treatment strategies compared to "no treatment" as a scenario analysis. The results are presented in Table 28. They showed that alemtuzumab remained the dominant strategy (less costly and more effective). Interferon beta-1b (Extavia and Betaferon) had ICERs below NOK 500,000 per QALY. Peginterferon beta-1a had ICER between NOK 500,000-800,000 per QALY. Teriflinomide and glatiramer acetate had ICERs between NOK 1,000,000- 1,500,000 per QALY. Dimethyl fumarate and natalizumab had ICERs between 1,500,000-1,800,000 per QALY. Interferon beta-1a (22mcg, 44 mcg and 30 mcg) and fingolimod had ICERs above NOK 2,000,000 per QALY.

Table 28. *Cost-effectiveness of disease-modifying therapies compared to "no treatment" (discounted)*

Drugs	Total costs (NOK)	Effects (QALYs)	Incremental cost (NOK)	Incremental effect (QALYs)	ICER (NOK/QALY)
No treatment	5,900,815	7.00			
Alemtuzumab (Lemtrada)	4,897,903	8.05	-1,002,911	1.05	Dominant
Interferon beta-1b (Extavia)	6,031,551	7.40	130,736	0.40	326,841
Interferon beta-1b (Beta-feron)	6,088,153	7.40	187,339	0.40	468,346
Glatiramer acetate (Copaxone) *	6,253,728	7.31	352,914	0.31	1,138,431
Peg-interferon beta-1a (Plegridy)	6,310,586	7.56	409,771	0-56	731,734
Teriflunomide (Aubagio)	6,337,489	7.38	436,675	0.38	1,149,144
Interferon beta-1a 22 mcg (Rebif)	6,498,571	7.21	597,756	0.21	2,846,458
Interferon beta-1a 30 mcg (Avonex)	6,533,915	7.27	633,101	0.27	2,344,817
Interferon beta-1a 44 mcg (Rebif)	6,574,606	7.32	673,791	0.32	2,105,598
Dimethyl fumarate (Tecifidera)	6,707,787	7.52	806,973	0.52	1,551,870
Natalizumab (Tysabri)	6,983,132	7.63	1,082,317	0.63	1,717,964
Fingolimod (Gilenya)	7,041,216	7.43	1,140,402	0.43	2,652,097

QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio

* 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).

In the base-case analysis, we assumed that once patients progress to EDSS=6 or SPMS, they would not receive MS treatment anymore. A scenario analysis was conducted varying the EDSS levels where treatment would be discontinued. The results of scenario analysis showed that ICERs were reduced when considering a stopping rule at EDSS=7 (Appendix 9.1). We also assumed a stopping rule without considering SPMS progression. As we did not consider any treatment benefit for SPMS patients in our model, a scenario analysis without considering treatment discontinuation with the progression to SPMS resulted in much higher ICERs.

A time horizon of 20 years was considered in the base-case analysis. We performed a scenario analysis where the time horizon varied within the range of 10 years. A time horizon of 30 years resulted in lower ICERs (Appendix 9.2), and the scenario analysis indicated that a time horizon of 10 years would increase the ICERs.

We also conducted a scenario analysis where the starting age was changed within the range of 10 years. Scenario analysis showed that variation in the starting age had a very small potential impact on the results. However, treating younger patients would slightly decrease the ICERs.

For base-case analysis, we assumed disability improvements (a maximum of 2 EDSS-level). We performed a scenario analysis where no improvement in EDSS were modelled. ICERs were not very sensitive to this assumption. However, “no improvement” in EDSS-level resulted in slightly lower ICERs (Appendix 9.3).

The annual rate of treatment discontinuation was assumed to be 15% in the base-case analysis. Based on our systematic review the rate varied between 0 and 33%. We conducted two scenario-analyses where the annual rate of treatment discontinuation was considered to be 0 and 30%, respectively. The scenario analyses showed that discontinuation rate did not have a significant impact on the results.

Utility values reported by Orme and co-workers (88) were used in the base-case analysis, as it was the only study that presented the utility associated with EDSS-states, SPMS and relapse by using a generic preference-based instrument (EQ-5D). We performed a scenario analysis based on utility values reported by Svendsen and co-worker (90). Utility values were calculated based on data from 423 Norwegian patients by using the EQ-5D method (Table 29).

Table 29. *Quality life data reported by Svendsen et al. (90)*

	EDSS 1	EDSS 2	EDSS 3	EDSS 4	EDSS 5	EDSS 6	EDSS 7	EDSS 8	EDSS 9
Quality of life	0.800	0.757	0.701	0.617	0.536	0.443	0.211	0.142	0.056

The use of different quality of life data resulted in different QALYs gained (higher QALYs for all interventions). However, the conclusion remained the same as in the base-case analysis. The results are presented in Appendix 9.4.

It has been reported that more patients (about 22-28%) than we assumed may need three cycles of alemtuzumab during the 5-year period (and some patients may need four (about 8-10% of patients) or five cycles (1.5%) of alemtuzumab). The scenario analysis was performed by varying the probability of patients who need more than 2 cycles of alemtuzumab. The results showed that alemtuzumab still was the dominant strategy.

Budget impact

The prevalence of MS in Norway is estimated to be 203 per 100,000 people (8). Approximately 85%-90% of patients with MS are estimated to have RRMS from onset of disease (11). We assumed that about 50% of these patients are eligible for disease modifying therapies, based on a Norwegian study (91). Based on these assumptions, we have estimated the number of eligible patients for disease- modifying therapies for the next 5 years (Table 30).

Table 30. *Number of patients eligible for disease-modifying therapies*

	2015 *	2016	2017	2018	2019	2020
Number of patients	4610	4650	4690	4740	4780	4830

*The population used in the analysis was 5,165,802 which was the population in Norway in 1. January 2015. It was assumed that the population of Norway increases about 50,000 annually (74)

The market shares for disease-modifying therapies for the last three years is presented in Figure 14 and Table 31, based on sales data (defined daily dose; DDD) (Farmastat). As results show, in the past few years the oral MS-medicines won market share from non-oral treatment alternatives.

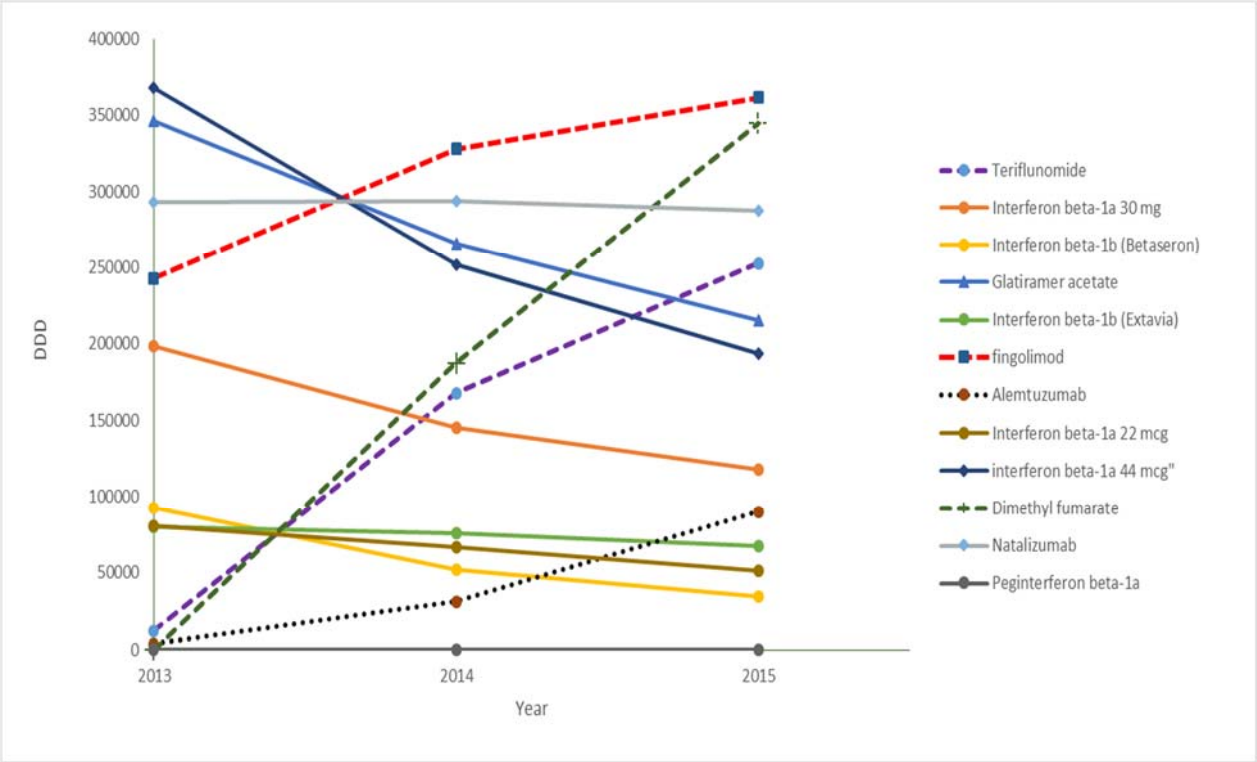


Figure 14. *Sales data for disease-modifying therapies in DDD (Farmastat) DDD: defined daily dose; Sales data for 2015 were estimated based on data from the first half of 2015.*

Table 31. *Current market shares for disease-modifying therapies in DDD (Farmastat)*

Drugs	2013	2014	2015 [a]
Alemtuzumab (Lemtrada)	0%	2%	4%
Dimethyl fumarate (Tecifidera)	0 %	10%	17%
Fingolimod (Gilenya)	14%	18%	18%
Glatiramer acetate (Copaxone)	20%	14%	11%
Interferon beta-1a 30 mcg (Avonex)	12%	8%	6%
Interferon beta-1a 22 mcg (Rebif)	5%	4%	3%
Interferon beta-1a 44 mcg (Rebif)	21%	14%	10%
Interferon beta-1b (Betaferon)	5%	3%	2%
Interferon beta-1b (Extavia)	5%	4%	3%
Natalizumab (Tysabri)	17%	16%	14%
Peg-interferon beta-1a (Plegridy) [b]	0%	0%	0%
Teriflunomide (Aubagio)	1%	9%	13%

DDD: defined daily dose

[a] Estimated based on data from the first half of 2015.

[b] Peg-interfron beta-1a: DDD 2013=0, DDD 2014= 70, DDD 2015=337

The market share forecasts for the next five years were estimated based on the results of our cost-effectiveness analysis and the drugs' adverse events. We also took under consideration the current practice where there is a trend in favour of oral medicines. The results were presented in Table 32.

Table 32: *Forecasted marked shares for disease-modifying therapies*

Drugs	2016	2017	2018	2019	2020
Alemtuzumab (Lemtrada)	15%	19%	24%	31%	33%
Dimethyl fumarate (Tecifidera)	13%	13%	12%	11%	10%
Fingolimod (Gilenya)	13%	12.5%	12%	12%	12%
Glatiramer acetate (Copaxone)	7%	6%	5%	4%	3%
Interferon beta-1a 30 mcg (Avonex)	4%	3%	2%	1%	1%
Interferon beta-1a 22 mcg (Rebif)	2%	1.5%	1%	0%	0%
Interferon beta-1a 44 mcg (Rebif)	8%	5%	3%	1%	1%
Interferon beta-1b (Betaferon)	2%	1%	1%	0%	0%
Interferon beta-1b (Extavia)	9%	9%	9%	9%	9%
Natalizumab (Tysabri)	12%	12%	12%	12%	12%
Peg-interferon beta-1a (Plegridy)	4%	4%	4%	4%	4%
Teriflunomide (Aubagio)	14%	14%	15%	15%	15%

The budget impact was calculated based on the same cost inputs (drug costs, monitoring costs associated with use of drugs) used in the cost-effectiveness model (see Tables 22 and 23). All estimations are based on 2015-price. The results of the budget impact analysis for the next five years (2016 was assumed as a starting point) are shown in Tables 33-35. Table 33 presented estimated costs based on current practice, while Table 34 presented estimated costs based on future practice (based on data from Table 32). Estimated costs based on future practice compared to estimated costs based on current practice were presented in Table 35.

Table 33. *Estimated costs* based on current practice*

Drugs	2016	2017	2018	2019	2020
Alemtuzumab (Lemtrada)	70,957,237	43,384,319	5,405,710	5,381,873	5,488,448
Dimethyl fumarate (Tecifidera)	143,409 155	140,972,076	142,482,533	143,676,691	145,187,149
Fingolimod (Gilenya)	179,884,866	172,095,248	173,949,176	175,396,174	177,250,102
Glatiramer acetate (Copaxone)	49,276,655	47,406,610	47,916,734	48,315,953	48,826,077
Interferon beta-1a 30 mcg (Avonex)	33,691,593	32,727,302	30,916,393	31,174,127	31,502,362
Interferon beta-1a 22 mcg (Rebif)	13,167,637	12,733,796	11,927,325	12,026,598	12,153,335
Interferon beta-1a 44 mcg (Rebif)	60,609,419	59,065,448	56,138,239	56,606,768	57,202,424
Interferon beta-1b (Beta-feron)	6,899,458	6,588,894	6,022,076	6,071,961	6,136,109
Interferon beta-1b (Extavia)	12,465,793	11,852,383	10,737,660	10,826,455	10,940,936
Natalizumab (Tysabri)	149,923 462	147,436,954	149,016,551	150,265,611	151,,845,208
Peg-interferon beta-1a (Plegridy)	104,602	101,908	96,806	97,614	98,642
Teriflunomide (Aubagio)	69,119,685	66,483,177	67,198,605	67,758,440	68,473,868
Total	**789,509,563**	**740,848,115**	**701,807,807**	**707 598 265**	**715,104,659**

* Undiscounted costs, included VAT

Table 34. *Estimated costs* based on future practice*

Drugs	2016	2017	2018	2019	2020
Alemtuzumab (Lemtrada)	190,987,053	184,889,553	29,099,797	37,421,494	40,624,633
Dimethyl fumarate (Tecifidera)	109,173,395	107,318,114	100,124,293	92,549,822	85,020,717
Fingolimod (Gilenya)	130,374,387	119,931,479	116,374,524	117,342,587	118,582,892
Glatiramer acetate (Copaxone)	32,322,524	26,653,617	22,450,355	18,109,921	13,725,845
Interferon beta-1a 30 mcg (Avonex)	23,098,927	16,828,357	10,598,126	5,343,239	5,429,044
Interferon beta-1a 22 mcg (Rebif)	10,346,880	7,504,483	4,686,134	0	0
Interferon beta-1a 44 mcg (Rebif)	50,464,321	30,736,743	17,528,081	5,891,457	5,953,451
Interferon beta-1b (Beta-feron)	8,018,439	3,828,753	3,499,380	0	0
Interferon beta-1b (Extavia)	33,464,841	31,818,121	28,832,186	29,063,982	29,371,310
Natalizumab (Tysabri)	126,211,185	124,112,685	125,447,714	126,499,219	127,828,983
Peg-interferon beta-1a (Plegridy)	25,030,165	24,385,660	23,164,869	23,358,184	23,603,988
Teriflunomide (Aubagio)	77,266,215	74,318,964	80,484,336	81,154,855	82,011,729
Total	**816,758,333**	**752,326,530**	**562,289,795**	**536,734,760**	**532,152,591**

* Undiscounted costs, included VAT

Table 35. *The results of the budget impact; estimated costs based on future practice compared to estimated costs based on current practice*

Drugs	2016	2017	2018	2019	2020
Alemtuzumab (Lemtrada)	120,029,816	141,505,234	23,694,087	32,039,621	35,136,185
Dimethyl fumarate (Tecifidera)	-34,235,760	-33,653,961	-42,358,241	-51,126,869	-60,166,432
Fingolimod (Gilenya)	-49,510,480	-52,163,769	-57,574,651	-58,053,587	-58,667,210
Glatiramer acetate (Copaxone)	-16,954,131	-20,752,993	-25,466,378	-30,206,032	-35,100,232
Interferon beta-1a 30 mcg (Avonex)	-10,592,666	-15,898,945	-20,318,267	-25,830,888	-26,073,319
Interferon beta-1a 22 mcg (Rebif)	-2,820,756	-5,229,314	-7,241,192	-12,026,598	-12,153,335
Interferon beta-1a 44 mcg (Rebif)	-10,145,097	-28,328,706	-38,610,158	-50,715,312	-51,248,973
Interferon beta-1b (Betaferon)	1,118,981	-2,760,140	-2,522,696	-6,071,961	-6,136,109
Interferon beta-1b (Extavia)	20,999,048	19,965,738	18,094,526	18,237,527	18,430,374
Natalizumab (Tysabri)	-23,712,276	-23,324,269	-23,568,837	-23,766,392	-24,016,225
Peg-interferon beta-1a (Plegridy)	24,925,563	24,283,752	23,068,062	23,260,569	23,505,346
Teriflunomide (Aubagio)	8,146,530	7,835,788	13,285,731	13,396,415	13,537,861
Total	**27,248,771**	**11,478,415**	**-139,518,013**	**-170,863,506**	**-182,952,068**

The budgetary impact for the next 5 years is difficult to predict. The prediction depends on several factors, including any change in current clinical practice, the relative drug prices and the number of patients eligible for different treatment alternatives.

For budget impact analysis, we mainly assumed that alemtuzumab, the more effective and less costly treatment alternative, would capture higher market share in the future.

The results presented in Table 35 showed that in the first two years, there will be additional costs compared to costs estimated based on current practice. However, our results indicated that costs would decrease after the first two years and there is a potential for cost-savings. Overall, the potential cost-savings over a 5-year period were estimated to be NOK 454,606,000 compared to the costs estimated for current practice.

Discussion

In this HTA, we have systematically reviewed the literature on the clinical effect of disease modifying medicines used for multiple sclerosis. The evidence base comprised findings from 37 RCTs. Furthermore, we performed an economic evaluation to examine the cost-effectiveness of these disease-modifying medicines in a Norwegian setting.

Summary of key findings

Key findings of the clinical evaluation

All examined treatments were more effective than placebo against annual relapse. The strongest effect was seen for alemtuzumab 12 mg. Fingolimod oral 1.25 mg and dimethyl fumarate 240 mg two times a day were also associated with a reduction in annualised relapse rate.

For disability progression, there is high quality evidence showing that dimethyl fumarate 240 mg twice daily and fingolimod oral 0.5 mg are more effective than placebo. For withdrawal due to adverse events, the lower quality of the available evidence provides unclear conclusion. Results indicate that some treatments are associated with more withdrawal due to adverse events than placebo, such as interferon beta-1a 44 mcg, and all regimens of peg-interferon beta-1a mcg.

For change in disability status, serious adverse events and mortality, we did not access the quality of the available evidence. Therefore, one cannot conclude on how reliable results are for these outcomes. Our results indicate that interferon beta-1a 30 mcg is related to a negative progression in disability status scale. Finally, our results did not show that examined treatments increased mortality.

Key findings of economic evaluation

Our health economic analysis indicated that alemtuzumab was more effective and less costly than the other treatment alternatives dominating all other disease-modifying therapies.

A scenario analysis that excluded alemtuzumab (the dominant strategy) showed that natalizumab was the most effective (in terms of QALYs), and interferon beta-1a 22 mg was the least effective treatment. Fingolimod was the most expensive strategy and interferon beta-1b was the least expensive alternative. The results also showed that only three treatment alternatives (interferon beta-1b (Extavia), peg-interferon beta-1a and natalizumab) could be cost-effective depending on the willingness-to-pay (WTP) threshold. Interferon beta-1b was likely to be the cost-effective choice for a WTP per QALY below NOK 1,658,000. Peg-interferon was the cost-effective option for a WTP from NOK 1,658,450 to NOK 10,619,960, and natalizumab was the cost-effective alternative for a WTP above NOK 10,619,960. Assuming a WTP below NOK 1,000,000 per QALY, interferon beta-1b (Extavia) was approximately 40% likely to be the most cost-effective treatment, followed by peg-interferon beta-1a (approximately 30% likely).

The scenario analysis where all treatment alternatives were compared to "no treatment" indicated that alemtuzumab remained the dominant strategy. Interferon beta-1b had ICERs below NOK 500,000 per QALY. The ICER for peg-interferon compared to "no treatment" was NOK 731,730. Other treatment options had ICERs over NOK 1,000,000 per QALY. The treatment costs (included drug costs and monitoring costs associated with each treatment) had an impact on the ICERs.

The results of probabilistic analysis showed that there is some degree of uncertainty regarding the input parameters. More research on efficacy and epidemiologic input parameters would have the greatest impact on reducing decision uncertainty.

In addition to our probabilistic sensitivity analysis, we performed several scenario analyses to test the uncertainty around the model assumptions. The results showed that, while there were numerical changes to the ICERs, the cost-effectiveness results were robust to variations in the model assumptions and the conclusions of the analysis would not change.

Our bugdet impact analysis based on the results of our cost-effectiveness analysis, the drugs' adverse events profile, and current clinical practice showed that there is a substantial potential for cost saving.

Quality of the evidence

Quality of the evidence of the systematic review

We included a HTA of high quality. We updated the information with more recently published RCTs with generally low risk of bias.

We chose a conservative approach in grading the quality of the evidence. This implies that one can rely on the evidence we judged to be of high quality. We had evidence of

high quality only for annual relapse rates and disability progression. This implies that results on other outcomes are less reliable.

Quality of the economic evaluation

Our cost-effectiveness analysis showed that there is some degree of uncertainty around the estimates. This was mainly due to uncertainty in the efficacy data, followed by probabilities estimates.

Strengths and weaknesses

Strengths of the systematic review

We used an internationally recognised methodology to systematically search the evidence, extract the data, access bias of studies and the quality of evidence. While the focus of this report was MS treatments used in Norway, we included evidence for treatments that are both used in Norway and not to get a bigger network of evidence for medicines relevant to the Norwegian setting. Our network of evidence includes information on treatments that have been used for some years, and on emerging treatments.

Limitations of the systematic review

Many of the limitations of this report are related to the available evidence, and are not inherent to the methodology used in this report.

The available evidence differs by treatments according to how long these have been on the market, with newer treatments having a smaller amount of information.

Most MS medications are only approved for RRMS patients. The systematic review includes, therefore, only studies of RRMS patients. As RRMS patients represent the largest proportion of MS patients, the results of our report are relevant to the majority of MS patients in Norway. Furthermore, there is no reason to believe that the effect of these medications are different depending on if one treats after the first relapse (CIS scenario) or if the treatment is initiated after the second relapse (e.g. definite clinical MS including RRMS patients). Results related to newer medications carry more uncertainty. As MS diagnosis has changed through the years, studies conducted at a different time might differ in terms of the MS population included. Therefore, when comparing older with newer MS treatments, differences in results could partly be due to differences in patient population. Furthermore, follow-up time of newer medicines is usually shorter, and some serious adverse events might only occur after a longer use of the medicine. One should bear this in mind when interpreting results.

Through network meta-analysis, one can infer on the relationship between two treatments if those treatments were compared to a common comparator in RCTs. For such

an inference to be accurate, the contributing RCTs should be very similar regarding patient population and outcome definition, measurement and reporting. Treatment history among patients varied across the trials, being either unclear, treatment naive, treatment experienced or a mixture. However, different statistical analyses provided similar results, and results were consistent when considering direct evidence, indirect evidence or the evidence from the whole network.

The available evidence does not allow to investigate separately first and second line treatments. Most published studies did not examine first and second medications separately. Indeed, some studies have compared first and second line treatments. Furthermore, in some case, first-line treatments have been investigated in patients who had taken other medications before, hence considered as second line treatments. Finally, studies considered second-line treatments in a population that comprised patients who had not received any treatment before, and were therefore tested as first-line treatments. We, therefore, present results for all MS treatments together (independent of them being used as first or second line treatments). However, patients who use a first and a second treatment might differ, and discrepancies in treatments efficacy might be due to disparity in patients.

The clinical endpoints covered in the systematic review (clinical relapse and disability progression) are important clinical outcomes in MS. Magnetic resonance imaging (MRI) is a surrogate endpoint and, therefore, was not examined. However, a previous published HTA report described that the available evidence on MRI was of poorer quality compared to clinical relapse and disability progression (27). The population of studies examining MRI populations were usually smaller, and it is unclear how these populations were selected (27). Therefore, any conclusions on MS medicines use on that surrogate outcome would have a higher degree of uncertainty.

Some outcome definitions differed from one study to the other. For example, disability progression was measured as disability progression confirmed at 3 months, or confirmed at 6 months, or at two years, or as a change compared to baseline EDSS. Patients EDSS classification might also differ between studies.

The lengths of the included studies were relatively short with a maximum follow-up time of 3.5 years. Therefore, our results cannot conclude on the long-term effect of examined medicines. Observational follow-up studies, with a longer follow-up time have been published, and could be used to estimate the longer-term effect of MS medicines.

All these limitations would not only have an impact on the clinical effect results but could also influence the health economic evaluation results that incorporated some of the clinical effect results into the health economic model.

Strengths of the health economic model

We performed the economic evaluation of disease- modifying therapies based on a thorough systematic review of the literature, and estimates of treatment effect obtained through a network meta-analysis. We used a probabilistic Markov-model, considered the appropriate approach for simulating the natural history of multiple sclerosis. This model was previously used in a high quality HTA report. The model structure and all assumptions have been adapted to the Norwegian setting based on Norwegian clinical practice with close assistance of experts in this field.

Limitations of the health economic model

To model real life is very complex; hence, any simulation is a simplification. We have tried to find the most robust and best evidence available but limitations associated with the data, and the simplifications of our health economic model should be considered when interpreting the results.

Data from Norwegian MS-registry or Norwegian cohort studies should ideally be used in the model. However, we were not able to identify data sources that were compatible to the developed model. The transitional probabilities were therefore based on estimates reported in the published literature. Those were also used in previous health economic studies. Data on annual relapse rate were uncertain. Indeed, we were not able to identify any study that linked rates of annual relapse to different EDSS-scores by disease duration.

We found a Norwegian study from 1996 where EDSS distributions in the cohort patients were reported (92). 22.6% of the patients in this study had EDSS scores over 4.5 (6.4% of patients scored between 8 and 9.5). However, based on clinical experts' opinion, disease-modifying therapies are usually initiated in patients with an EDSS score less than 5, and most commonly for patients with an EDSS score between 1 and 3. Therefore, EDSS distributions used in our model were based on published literature of large cohort studies where over 91% of patients had EDSS scores less than 5.

The network meta-analyses were not performed separately for first and second line treatments. Therefore, we did not perform separate cost-effectiveness analyses for these two types of treatments. In addition, based on expert opinion, we did not include combination therapy in our model, as it is not relevant to Norwegian clinical practice at present.

There is lack of documentation regarding the long-term effect of the newer drugs. Further research could change current estimates and consequently the health economic results.

In our report, we assumed that 20% of patients might need three cycles of alemtuzumab during a 5-year period. However, it has been reported that this proportion might be higher (22 to 28% of patients), and that some patients may need four cycles (about 8 to 10% of patients), or five cycles (1.5%) of alemtuzumab. We performed a scenario analysis by varying the proportion of patients who need more than 2 cycles of alemtuzumab during a 5-year period. The results showed that alemtuzumab still was the dominant strategy.

We assumed fixed discontinuation rate across all treatment alternatives for the first two years. We performed scenario analyses to test different discontinuation rates. The results showed that discontinuation rate did not have a significant impact on the results.

We assumed that the average length of mild or moderate relapses was 45 days, and 90 days for severe relapses. The duration of the relapse might be shorter depending on the response to the treatment with corticosteroids. We conducted a scenario analysis where the average length of moderate and severe relapse were 21 days and 45 days. Although some changes in the results were observed, the conclusion remain the same.

The results of our systematic review showed no significant differences between the therapies for serious adverse events. However, the risk of developing progressive multifocal leukoencephalopathy (PML) associated with natalizumab, even if it is rare, was considered important, and, therefore, included in the model. We assumed that the costs and disutility related to other adverse events would not have a significant impact on the results. It should also be mentioned that recently PML has also been reported in some patients treated with other disease-modifying therapies, such as dimethyl fumurate and fingolimod.

The costs associated with inpatient treatment of PML were estimated based on prices from the Norwegian DRG system (DRG code 421). As the costs of inpatient treatment of PML might be underestimated, we performed a scenario analysis where the costs were 100% increased. As the risk of developing PML is low, the correction factor had no significant impact on the cost-effectiveness results.

We performed the health economic evaluation from a health care perspective. The health care perspective is relevant for prioritisation of interventions within a fixed budget if the aim of the decision maker is to maximize health.

Glatiramer acetate 20 mg was included in the base-case analysis. Based on the results from our systematic review regarding relative rates of annual relapse and relative risk of disability progression, and also the estimated 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 that all the other parameters are the same).

Due to the uncertain evidence regarding the potential added value of peroral drug administration and the probable effect of the different methods of administrating the medication on patients' utility, we did not include these parameters in the model.

The budget impact estimates were based on several factors that can vary such as disease prevalence and incidence, current clinical practice, drug and healthcare. The market share forecasts for the next five years in our analysis were estimated based on the results of our cost-effectiveness analysis and the drugs' adverse events. We also took under consideration the current practice where there is a trend in favour of oral medicines.

Consistency

Consistency of the systematic review with other publications

Our results are consistent with the results of the Canadian HTA report on drug therapies for RRMS (27), although we included more up to date evidence, and also evidence on more MS treatments. Our results are also consistent with a recently published Cochrane systematic review (93).

Consistency of the economic evaluation with other studies

While several cost-effectiveness studies have examined disease-modifying therapies for RRMS patients, to date, only the Canadian report (27) has compared almost all drugs in one analysis, as we have done in this report. However, it should be mentioned that peg-interferon beta-1a was not included in the Canadian report, and the pricing of alemtuzumab and teriflunomide was not available in Canada at the time the analyses were conducted. Therefore, they were not included in the Canadian base-case analysis.

The Canadian base-case analysis showed that glatiramer acetate was the most cost-effective treatment unless willingness to pay exceeded CAD 118,242 per QALY. Between CAD 118,242- CAD 425,655, interferon beta-1b was the most cost-effective treatment, between CAD 425,655- CAD 872,972 it was dimethyl fumarate, and above CAD 872,972, it was natalizumab. It is difficult to compare our results to the Canadian results, as we included more treatment strategies, and used different input data (efficacy, costs and quality of life data).

Conclusion and implications on practice

All examined treatments were more effective than placebo against annual relapse. The strongest effect was seen for alemtuzumab 12 mg. Fingolimod oral 0.5 mg and dimethyl fumarate 240 mg two times a day were also associated with a reduction in annualised relapse rate. For disability progression, direct evidence of high quality indicated that dimethyl fumarate 240 mg twice daily and fingolimod oral 0.5 mg were more effective than placebo. For withdrawal due to adverse events, the lower quality of the available evidence provides unclear conclusion. Results indicate that some treatments are associated with more withdrawal due to adverse events than placebo, such as interferon beta-1a 44 mcg, and all regimens of peg-interferon beta-1a mcg. These results should be considered bearing in mind that some of them are first line treatments while others are used as second line treatments, and may not be relevant to whole type of MS patients.

Our health economic analysis indicated that alemtuzumab dominated all other disease-modifying therapies, as it was more effective and less costly than the other treatment alternatives.

A scenario analysis that excluded alemtuzumab (the dominant strategy) showed that three treatment alternatives (interferon beta-1b (Extavia), peg-interferon beta-1a and natalizumab) could be cost-effective depending on the willingness-to-pay (WTP) threshold. Interferon beta-1b was likely to be the cost-effective choice for a WTP per QALY below NOK 1,658,000. Peg-interferon was the cost-effective option for a WTP from NOK 1,658,450 to NOK 10,619,960, and natalizumab was the cost-effective alternative for a WTP above NOK 10,619,960. Assuming a WTP below NOK 1,000,000 per QALY, interferon beta-1b (Extavia) was approximately 40% likely to be the most cost-effective treatment, followed by peg-interferon beta-1a (approximately 30% likely).

Our budget impact analysis showed that there is a substantial potential for cost saving.

Need for further research

The length of included RCTs is relatively short with a maximum of 3.5 years. We need longer studies to be able to conclude on the longh term efficacy and safety of MS medicines.

Study designs of published studies do not allow to investigate separately first and second line treatments, or to conclude on the sequential use of first and second line treatments. It is difficult to conclude which medicine is most effective when interested only in first or second line treatments. To address this, future studies should use appropriate study design that fits the type of the investigated treatment. For example, first line treatments should be examined as first-line (i.e. in treatment naïve patients), and second line treatments should be investigated as second-line treatments (that is in treatment experienced patients).

There is some degree of uncertainty regarding the health economic model input parameters. More research on efficacy and epidemiologic input parameters would have the greatest impact on reducing decision uncertainty.

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Appendix

Appendix 1: Literature search strategy

Search strategy - Drugs for multiple sclerosis

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), Economic Evaluations (NHS EED).
Centre for Reviews and Dissemination: DARE, HTA, NHS EED.
Web of Science, PubMed, SweMed+, SBU, Google scholar, PROSPERO.

Date: 2015.02.26.
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: 1613 records (277 SR + 729 RCT +607 Econ. Eval.) without duplicates
277 SR
729 RCT (644 + 85 in update search)
607 Economic evaluations

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 Present

Date: 2015.02.25

Codes: Embase: oemezd
MEDLINE: pmoz
SR

Results: 816 RCT + 69 (update search)

#	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 54	3363
56	limit 55 to yr="2013 -Current"	816
57	(eq5d or eq-5d or euroqol or euro qol or euroqol-eq-5d or eq-5d-euroqol or eq-5d-3L or eq-5d-5L).mp.	12866
58	(quality adjusted life or quality-adjust-life).mp.	26318

59	(qaly* or qald* or qale* or qtime* or qali*).mp.	15888
60	57 or 58 or 59	40089
61	25 and 60	249
62	limit 61 to yr="2013 -Current"	69
63	remove duplicates from 56	692
64	"Cost Benefit Analysis"/	128162
65	"Cost Effectiveness Analysis"/	165316
66	"Cost Minimization Analysis"/	44712
67	"Cost Utility Analysis"/	67265
68	(cost* adj2 (analys* or benefit* or effective* or minim* or utilit*)).tw.	246501
69	cba.tw.	19501
70	cea.tw.	41311
71	cua.tw.	1829
72	Economic Evaluation/	71524
73	Health economics/	34220
74	(health economic? or economic evaluation?).tw.	24738
75	Pharmacoeconomics/	8587
76	((pharmacoeconomic? or pharmac*) adj economic?).tw.	863
77	(15D or HRQoL or health-related quality of life instrument).mp.	23802
78	or/60,64-77	541256
79	25 and 78	799
80	Cost-Benefit Analysis/	128162
81	(cost* adj2 (analys* or benefit* or effective* or minim* or utilit*)).tw.	246501
82	cba.tw.	19501
83	cea.tw.	41311
84	cua.tw.	1829
85	Economics, Medical/	42830
86	(health economic? or economic evaluation?).tw.	24738
87	Economics, Pharmaceutical/	8587
88	(pharmac* adj economic?).tw.	863

89	pharmacoeconomic?.tw.	8935
90	Technology Assessment, Biomedical/	19671
91	technology assessment?.tw.	8787
92	(15D or HRQoL or health-related quality of life instrument).mp.	23802
93	or/60,80-92	489726
94	25 and 93	736
95	79 or 94	840
96	remove duplicates from 95	698
97	96 not 63	654
98	97 use oemezd	606
99	97 use pmoz	48
100	limit 56 to yr="2015 -Current"	69
101	remove duplicates from 100	62
102	101 use oemezd	7
103	101 use pmoz	55

Database: Cochrane Library
Date Run: 2015.02.26.
Results: 24 Cochrane Reviews (Reviews and Protocols),
20 Other Reviews,
37 Technology Assessments
41 Economic Evaluations
181 Clinical trials + 29 (update search)

ID	Search	Hits
#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)
Date: 2015.02.26.
Results: 84 DARE, HTA
46 NHS EED (Econ. eval.)

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
Date: 2015.02.26
Results: 10 Reviews
7 RCT + 11 (update search)
Search:
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)

Web of Science
Date: 2015.02.26
Results: 11 clinical trials
53 reviews

# 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
Date: 2015.02.20.
Results: 1
Search: multiple sclerosis

Database: SweMed+
Date: 2015.02.20.
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
Date: 2015.02.20.
Results: 0
Search: Multipel sckleros

Webpage: Google scholar
Date: 2015.02.20.
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

Appendix 2: Description of included studies

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 (28), included (incl.) in Khai et al. (27)

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. (29), in Khai et al. (27)

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. (30), in Khai et al. (27)

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 2012 (33), in Khai et al. (27)

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., (34), in Khai et al. (27)

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 2010 (37), in Khai et al. (27)

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, (38), in Khai et al. (27)

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 (39), included in Khai et al. (27)

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 (41), not included in Khai et al.(27)

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 (42), included in Khai et al. (27)

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 (43), included in Khai et al. (27)

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., (44), in Khai et al. (27)

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.(45), included in Khai et al. (27)

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. (46), included in Khai et al. (27)

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 (47), included in Khai et al. (27)

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 (35), not included in Khai et al. (27)

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., (48), included in Khai et al. (27)

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.(49), included in Khai et al. (27)

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.(50), included in Khai et al. (27)

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,(51), included in Khai et al. (27)

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 (52), included in Khai et al. (27)

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 (36), included in Khai et al. (27)

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 (53), not included in Khai et al. (27)

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 2014 (54), not included in Khai et al. (27)

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 (55), in Khai et al. (27)

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.,(94), included in Khai et al. (27)

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, (57), included in Khai et al. (27)

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(58), included in Khai et al. (27)

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 (60), in Khai et al. (27)

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. (31), not included in Khai et al. (27)

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 immunesuppressors 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., (61), not included in Khai et al. (27)

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 (32), not included in Khai et al. (27)

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.,(59), not in Khai et al. (27)

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 (62), included in Khai et al. (27)

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. (63, 64), included in Khai et al. (27)

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 (65), not included in Khai et al. (27)

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 (66), not included in Khai et al. (27)

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

Appendix 3: Excluded studies and reasons for 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)

	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.

	CIS	Publication date	P	I	C	O	S	Exclusion/comments
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)

	CIS	Publication date	P	I	C	O	S	Exclusion/comments
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

	CIS	Publication date	P	I	C	O	S	Exclusion/comments
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

	CIS	Publication date	P	I	C	O	S	Exclusion/comments
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, Havrdova E, Jeffery D, 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

	CIS	Publication date	P	I	C	O	S	Exclusion/comments
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

	CIS	Publication date	P	I	C	O	S	Exclusion/comments
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

Appendix 4 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

3) 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

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

5) 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

6) 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

7) 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
8) 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

9) 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
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

11) 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

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

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=EUCTR2010-020315-36-BE

14) 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

15) 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

Appendix 5: GRADE evaluation of comparisons

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

Quality assessment							№ of patients		Effect		Quality	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectn ess	Impre-cision	Other con-sider-ations	Inter-feron beta-1a 22 mcg	Pla-cebo	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous [2]	seri-ous [3]	none	-/189	-/187	**RR 0.69** (0.57 to 0.83)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⨁⨁⨁◯ MODER-ATE [1 2 3]	
Disease Progression												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous [2]	very seri-ous [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	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous [2]	very seri-ous [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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectness	Impre-cision	Other con-sider-ations	Inter-feron beta-1a 30 mcg	Pla-cebo	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
3	ran-domis ed tri-als	not seri-ous	not seri-ous	not seri-ous [1]	not se-rious	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	ran-domis ed tri-als	not seri-ous	not seri-ous	not seri-ous [1]	seri-ous [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)	⊕⊕⊕○ MODER-ATE [1 2]	
Withdrawal due to adverse events												
3	ran-domis ed tri-als	not seri-ous	not seri-ous	not seri-ous [1]	very seri-ous [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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectn ess	Impre-cision	Other con-sider-ations	Inter-feron beta-1a 44 mcg	Pla-cebo	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
2	ran-domis ed tri-als	not seri-ous	not seri-ous	not seri-ous [1]	not se-rious	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	ran-domis ed tri-als	not seri-ous	not seri-ous [2]	not seri-ous [3]	very seri-ous [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	ran-domis ed tri-als	not seri-ous	not seri-ous [2]	not seri-ous [3]	very seri-ous [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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectness	Impre-cision	Other con-sidera-tions	Glati-ramer acetate 40 mg	Pla-cebo	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
1	ran-domised tri-als	not seri-ous	not seri-ous [1]	not seri-ous	not se-rious	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	ran-domised tri-als	not seri-ous	not seri-ous [1]	not seri-ous	very seri-ous [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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rect ness	Impre-cision	Other con-sider-ation s	Dimethyl fumarate 240 mg two times daily	Pla-cebo	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
2	ran-domis ed tri-als	not seri-ous	not seri-ous	not seri-ous	not se-rious	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	ran-domis ed tri-als	not seri-ous	not seri-ous	not seri-ous	not se-rious	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	ran-domis ed tri-als	not seri-ous	not seri-ous	not seri-ous	very seri-ous [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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rect ness	Im-preci-sion	Other con-sider-ation s	Dimethyl fumarate 240 mg three times daily	Pla-cebo	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
2	ran-domis ed tri-als	not seri-ous	not seri-ous	not seri-ous	not seri-ous	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	ran-domis ed tri-als	not seri-ous	not seri-ous	not seri-ous	not seri-ous	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	ran-domis ed tri-als	not seri-ous	not seri-ous	not seri-ous	very seri-ous [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	Im-portance
№ 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	Im-portance
№ 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	Im-portance
№ 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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectness	Impre-cision	Other con-sider-ations	Inter-feron beta-1b 250 mcg SC every other day	Pla-cebo	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
1	ran-domised tri-als	not seri-ous	not seri-ous [1]	not seri-ous [2]	seri-ous [3]	none	-/124	-/122	**RR 0.65** (0.51 to 0.83)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ MODER-ATE [1 2 3]	
Disease Progression												
1	ran-domised tri-als	not seri-ous	not seri-ous [1]	not seri-ous [2]	very seri-ous [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	ran-domised tri-als	not seri-ous	not seri-ous [1]	not seri-ous [2]	very seri-ous [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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectne ss	Impre-cision	Other con-sider-ations	Alemtu-zumab 24 mg IV q.d	Alemtu-zumab 12 mg IV q.d	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	seri-ous [2 3]	seri-ous [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	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	seri-ous [2 3]	very seri-ous [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	ran-domis ed tri-als	not seri-ous	not seri-ous	not se-rious [7]	very seri-ous [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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectness	Im-preci-sion	Other con-sider-ations	Inter-feron beta-1a 44 mcg	Alemtu-zumab 12 mg IV q.d	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
3	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not se-ri-ous [2,3]	not seri-ous	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	ran-domis ed tri-als	not seri-ous	not seri-ous	not se-ri-ous [2,3]	seri-ous [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)	⊕⊕⊕○ MODER-ATE [2,3,4]	
Withdrawal due to adverse events												
3	ran-domis ed tri-als	not seri-ous	not seri-ous	not se-ri-ous [2,3]	seri-ous [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)	⊕⊕⊕○ MODER-ATE [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	Im-portance
№ 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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectn ess	Impre-cision	Other con-sider-ations	Inter-feron beta-1a 44 mcg	Inter-feron beta-1a 22 mcg	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous [2]	seri-ous [3]	none	-/184	-/189	**RR 0.68** (0.56 to 0.83)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ MODER-ATE [1 2 3]	
Disease Progression												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous [2]	very seri-ous [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	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous [2]	very seri-ous [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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectn ess	Impre-cision	Other con-sider-ations	Inter-feron beta-1a 44 mcg	Inter-feron beta-1a 30 mcg	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
3	ran-domis ed tri-als	not seri-ous [1]	not seri-ous	not seri-ous [2]	not se-rious	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	ran-domis ed tri-als	not seri-ous	not seri-ous [3]	not seri-ous [4]	very seri-ous [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	ran-domis ed tri-als	not seri-ous	not seri-ous [3]	not seri-ous [4]	very seri-ous [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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectn ess	Impre-cision	Other con-sider-ations	Inter-feron beta-1a 60 mcg	Inter-feron beta-1a 30 mcg	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous [2]	seri-ous [3]	none	-/400	-/402	**RR 1.05** (0.88 to 1.25)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⨁⨁⨁◯ MODER-ATE [1 2 3]	
Disease Progression												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous [2]	very seri-ous [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	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous [2]	very seri-ous [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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectn ess	Impre-cision	Other con-sider-ations	Glati-ramer acetate 20 mg	Inter-feron beta-1a 30 mcg	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
2	ran-domis ed tri-als	not seri-ous [1]	not seri-ous	not seri-ous [2]	seri-ous [3]	none	-/314	-/305	**RR 0.79** (0.61 to 1.02)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⨁⨁⨁◯ MODER-ATE [1 2 3]	
Disease Progression												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [4]	not seri-ous [5]	very seri-ous [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	ran-domis ed tri-als	not seri-ous	not seri-ous [4]	not seri-ous [5]	very seri-ous [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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectn ess	Impre-cision	Other con-sider-ations	Fin-golimod oral 0.5 mg	Inter-feron beta-1a 30 mcg	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous	not se-rious	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	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous	very seri-ous [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	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous	very seri-ous [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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectn ess	Impre-cision	Other con-sider-ations	Fin-golimod oral 1.25 mg	Inter-feron beta-1a 30 mcg	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous	not se-rious	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	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous	very seri-ous [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	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous	very seri-ous [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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectn ess	Im-preci-sion	Other con-sider-ation s	Inter-feron beta-1b 250 mcg SC every other day	Inter-feron beta-1a 30 mcg	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
2	ran-domis ed tri-als	not seri-ous [1]	not seri-ous	not seri-ous [2]	seri-ous [3]	none	-/126	-/126	**RR 0.71** (0.53 to 0.91)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⨁⨁⨁◯ MODER-ATE [1 2 3]	
Disease Progression												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [4]	not seri-ous [5]	very seri-ous [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	ran-domis ed tri-als	not seri-ous	not seri-ous [4]	not seri-ous [5]	very seri-ous [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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectn ess	Impre-cision	Other con-sider-ations	Glati-ramer acetate 20 mg	Inter-feron beta-1a 44 mcg	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
2	ran-domis ed tri-als	not seri-ous [1]	not seri-ous	not seri-ous [2]	seri-ous [3]	none	-/433	-/441	**RR 1.02** (0.83 to 1.28)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⨁⨁⨁◯ MODER-ATE [1 2 3]	
Disease Progression												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [4]	not seri-ous [5]	very seri-ous [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	ran-domis ed tri-als	not seri-ous	not seri-ous [4]	not seri-ous [5]	very seri-ous [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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectn ess	Impre-cision	Other con-sider-ations	Teri-fluno-mide 7 mg oral	Inter-feron beta-1a 44 mcg SC t.i.w.	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous	seri-ous [2]	none	-/109	-/104	**RR 1.72** (1.24 to 2.44)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ MODER-ATE [1 2]	
Withdrawal due to adverse events												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous	very seri-ous [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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectn ess	Impre-cision	Other con-sider-ations	Teri-fluno-mide 14 mg oral	Inter-feron beta-1a 44 mcg SC t.i.w.	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous	very seri-ous [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	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous	very seri-ous [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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectn ess	Impre-cision	Other con-sider-ations	Inter-feron beta-1b 250 mcg SC every other day	Inter-feron beta-1a 44 mcg SC t.i.w.	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
1	ran-domis ed tri-als	seri-ous [1]	not seri-ous [2]	not seri-ous [3]	very seri-ous [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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectness	Impre-cision	Other con-sider-ations	Inter-feron beta-1b 250 mcg SC every other day	Glati-ramer acetate 20mg	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
2	ran-domis ed tri-als	not seri-ous	not seri-ous	not seri-ous [1]	seri-ous [2]	none	-/933	-/487	**RR 1.07** (0.90 to 1.27)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⨁⨁⨁◯ MODER-ATE [1 2]	
Disease Progression												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [3]	not seri-ous [1]	seri-ous [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)	⨁⨁⨁◯ MODER-ATE [1 2 3]	
Withdrawal due to adverse events												
2	ran-domis ed tri-als	not seri-ous	not seri-ous	not seri-ous [1]	very seri-ous [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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectness	Impre-cision	Other con-sider-ations	Inter-feron beta-1b 500 mcg SC every other day	Glati-ramer acetate 20mg	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous [2]	seri-ous [3]	none	-/899	-/448	**RR 0.95** (0.80 to 1.12)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⨁⨁⨁◯ MODER-ATE [1 2 3]	
Disease Progression												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous [2]	seri-ous [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)	⨁⨁⨁◯ MODER-ATE [1 2 3]	
Withdrawal due to adverse events												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous [2]	very seri-ous [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	Im-portance
№ 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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectn ess	Impre-cision	Other con-sider-ations	Teri-fluno-mide oral 14 mg	Teri-fluno-mide oral 7 mg	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
4	ran-domis ed tri-als	not seri-ous	not seri-ous	not seri-ous [1]	seri-ous [2]	none	-/935	-/912	**RR 0.86** (0.74 to 1.00)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ MODER-ATE [1 2]	
Disease Progression												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [3]	not seri-ous	very seri-ous [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	ran-domis ed tri-als	not seri-ous	not seri-ous	not seri-ous [1]	seri-ous [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)	⊕⊕⊕○ MODER-ATE [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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectn ess	Im-pre-cisio n	Other con-sider-ations	Fin-golimod oral 1.25 mg	Fingol-omid oral 0.5 mg	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
4	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous [2]	seri-ous [3]	none	-/1273	-/1269	**RR 0.98** (0.83 to 1.17)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⨁⨁⨁◯ MODER-ATE [1 2 3]	
Disease Progression												
3	ran-domis ed tri-als	not seri-ous	not seri-ous	not seri-ous	seri-ous [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)	⨁⨁⨁◯ MODER-ATE [3]	
Withdrawal due to adverse events												
4	ran-domis ed tri-als	not seri-ous	not seri-ous	not seri-ous [2]	seri-ous [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)	⨁⨁⨁◯ MODER-ATE [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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectn ess	Impre-cision	Other con-sider-ations	Peg-in-terferon beta-1a 125 mcg once every four weeks	Peg-in-terferon beta-1a 125 mcg once every two weeks	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous	seri-ous [2]	none	-/500	-/512	**RR 1.13** (0.84 to 1.52)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ MODER-ATE [1 2]	
Disease Progression												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous	very seri-ous [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	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous	very seri-ous [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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectness	Impre-cision	Other con-sider-ations	Inter-feron beta-1b 250 mcg SC every other day	Natali-zumab 300 mg intrave-nous every 4 weeks	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	seri-ous [2]	very seri-ous [3 4]	none	-/9	-/10	not esti-mabl e		⨁◯◯◯ 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	Im-portance
№ of stud-ies	Study de-sign	Risk of bias	Incon-sistency	Indi-rectn ess	Impre-cision	Other con-sider-ations	Inter-feron beta-1b 500 mcg SC every other day	Inter-feron beta-1b 250 mcg SC every other day	Rela-tive (95% CI)	Absolute (95% CI)		
Annualised relapse rate												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous [2]	seri-ous [3]	none	-/899	-/897	**RR 0.93** (0.80 to 1.10)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⨁⨁⨁◯ MODER-ATE [1 2 3]	
Disease Progression												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous [2]	seri-ous [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)	⨁⨁⨁◯ MODER-ATE [1 2 3]	
Withdrawal due to adverse events												
1	ran-domis ed tri-als	not seri-ous	not seri-ous [1]	not seri-ous [2]	very seri-ous [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).

Appendix 6: Full network meta-analysis results

A6.1: Annualised relapse rate

Treatment	Placebo	Alemtuzumab 12 mg IV q.d	Alemtuzumab 24 mg IV q.d	Interferon beta-1a 22 mcg SC t.i.w	Interferon beta-1a 30 mcg IM q.w	Interferon beta-1a 44 mcg SC t.i.w	Interferon beta-1a 60 mcg IM q.w	glatiramer acetate 20mg q.d	glatiramer acetate 40mg t.i.w	dimethyl fumarate 240 mg two times daily	dimethyl fumarate 240 mg three times daily	Teriflunomide oral 7 mg	Teriflunomide oral 14 mg	Fingolimod oral 0.5 mg	Fingolimod oral 1.25 mg	Peginterferon beta-1a 125 mcg once every 2 weeks	peginterferon beta-1a 125 mcg once every 4 weeks	Natalizumab	Interferon beta-1b 250 mcg SC every other day	Interferon beta-1b 500 mcg SC every other day
Placebo	1																			
Alemtuzumab 12 mg IV q.d	0.29 (0.23 to 0.35)	1																		
Alemtuzumab 24 mg IV q.d	0.16 (0.1 to 0.25)	0.55 (0.35 to 0.86)	1																	
Interferon beta-1a 22 mcg SC t.i.w	0.69 (0.57 to 0.83)	2.4 (1.9 to 3.12)	4.35 (2.71 to 7.13)	1																
Interferon beta-1a 30 mcg IM q.w	0.82 (0.73 to 0.91)	2.82 (2.33 to 3.59)	5.15 (3.24 to 8.29)	1.18 (0.97 to 1.46)	1															
Interferon beta-1a 44 mcg SC t.i.w	0.64 (0.56 to 0.72)	2.21 (1.9 to 2.64)	4.02 (2.6 to 6.34)	0.92 (0.76 to 1.11)	0.78 (0.68 to 0.89)	1														
Interferon beta-1a 60 mcg IM q.w	0.86 (0.7 to 1.06)	2.96 (2.31 to 4.02)	5.41 (3.3 to 8.99)	1.24 (0.96 to 1.63)	1.05 (0.88 to 1.25)	1.34 (1.09 to 1.7)	1													
glatiramer acetate 20mg q.d	0.65 (0.59 to 0.73)	2.25 (1.85 to 2.87)	4.1 (2.59 to 6.63)	0.94 (0.77 to 1.16)	0.8 (0.7 to 0.91)	1.02 (0.9 to 1.18)	0.76 (0.61 to 0.94)	1												
glatiramer acetate 40mg t.i.w	0.66 (0.52 to 0.82)	2.27 (1.7 to 3.14)	4.14 (2.47 to 6.95)	0.95 (0.72 to 1.27)	0.8 (0.62 to 1.02)	1.03 (0.8 to 1.33)	0.77 (0.56 to 1.03)	1.01 (0.78 to 1.28)	1											
dimethyl fumarate 240 mg two times daily	0.5 (0.42 to 0.6)	1.73 (1.35 to 2.31)	3.15 (1.92 to 5.23)	0.72 (0.56 to 0.93)	0.61 (0.49 to 0.75)	0.78 (0.63 to 0.97)	0.58 (0.44 to 0.76)	0.77 (0.63 to 0.93)	0.76 (0.57 to 1.01)	1										
dimethyl fumarate 240 mg three times daily	0.5 (0.42 to 0.6)	1.73 (1.35 to 2.33)	3.16 (1.93 to 5.28)	0.72 (0.57 to 0.94)	0.62 (0.5 to 0.75)	0.79 (0.64 to 0.98)	0.58 (0.45 to 0.76)	0.77 (0.64 to 0.93)	0.77 (0.58 to 1.02)	1.01 (0.82 to 1.23)	1									
Teriflunomide oral 7 mg	0.77 (0.68 to 0.9)	2.68 (2.13 to 3.53)	4.89 (3.03 to 7.93)	1.12 (0.9 to 1.42)	0.95 (0.8 to 1.13)	1.21 (1.02 to 1.47)	0.9 (0.71 to 1.16)	1.19 (1. to 1.42)	1.18 (0.91 to 1.55)	1.55 (1.24 to 1.96)	1.54 (1.23 to 1.94)	1								
Teriflunomide oral 14 mg	0.67 (0.58 to 0.77)	2.3 (1.83 to 3.03)	4.19 (2.6 to 6.9)	0.96 (0.77 to 1.22)	0.82 (0.68 to 0.98)	1.04 (0.87 to 1.27)	0.78 (0.6 to 0.99)	1.02 (0.85 to 1.22)	1.02 (0.78 to 1.33)	1.33 (1.06 to 1.68)	1.33 (1.05 to 1.67)	0.86 (0.74 to 1.)	1							
Fingolimod oral 0.5 mg	0.46 (0.39 to 0.54)	1.6 (1.25 to 2.09)	2.91 (1.79 to 4.79)	0.67 (0.53 to 0.85)	0.57 (0.47 to 0.67)	0.72 (0.6 to 0.88)	0.54 (0.42 to 0.68)	0.71 (0.59 to 0.85)	0.7 (0.54 to 0.92)	0.92 (0.73 to 1.17)	0.92 (0.73 to 1.16)	0.6 (0.48 to 0.73)	0.69 (0.56 to 0.85)	1						
Fingolimod oral 1.25 mg	0.45 (0.39 to 0.53)	1.57 (1.23 to 2.06)	2.86 (1.76 to 4.66)	0.65 (0.52 to 0.83)	0.55 (0.47 to 0.66)	0.71 (0.58 to 0.87)	0.53 (0.41 to 0.67)	0.69 (0.57 to 0.83)	0.69 (0.53 to 0.9)	0.9 (0.71 to 1.15)	0.9 (0.71 to 1.14)	0.59 (0.47 to 0.71)	0.68 (0.55 to 0.84)	0.98 (0.83 to 1.17)	1					
Peginterferon beta-1a 125 mcg once every 2 weeks	0.65 (0.49 to 0.85)	2.23 (1.6 to 3.19)	4.07 (2.33 to 7.07)	0.93 (0.67 to 1.29)	0.79 (0.58 to 1.06)	1.01 (0.74 to 1.36)	0.75 (0.53 to 1.05)	0.99 (0.73 to 1.32)	0.98 (0.69 to 1.41)	1.29 (0.93 to 1.8)	1.29 (0.92 to 1.77)	0.83 (0.6 to 1.13)	0.97 (0.7 to 1.32)	1.4 (1.02 to 1.92)	1.43 (1.03 to 1.95)	1				
peginterferon beta-1a 125 mcg once every 4 weeks	0.73 (0.56 to 0.95)	2.52 (1.83 to 3.59)	4.59 (2.68 to 7.94)	1.06 (0.76 to 1.46)	0.89 (0.66 to 1.2)	1.14 (0.85 to 1.54)	0.85 (0.6 to 1.19)	1.12 (0.83 to 1.5)	1.11 (0.78 to 1.58)	1.46 (1.06 to 2.01)	1.45 (1.05 to 1.99)	0.94 (0.69 to 1.27)	1.1 (0.8 to 1.49)	1.58 (1.16 to 2.16)	1.61 (1.18 to 2.2)	1.13 (0.84 to 1.52)	1			
Natalizumab	0.3 (0.24 to 0.36)	1.03 (0.79 to 1.37)	1.88 (1.14 to 3.09)	0.43 (0.33 to 0.56)	0.36 (0.29 to 0.45)	0.47 (0.37 to 0.59)	0.35 (0.26 to 0.46)	0.46 (0.36 to 0.57)	0.45 (0.34 to 0.61)	0.59 (0.45 to 0.77)	0.59 (0.45 to 0.77)	0.39 (0.3 to 0.49)	0.45 (0.35 to 0.56)	0.65 (0.5 to 0.83)	0.66 (0.51 to 0.84)	0.46 (0.33 to 0.25)	0.41 (0.29 to 0.57)	1		
Interferon beta-1b 250 mcg SC every other day	0.66 (0.57 to 0.76)	2.28 (1.84 to 2.94)	4.15 (2.6 to 6.71)	0.95 (0.77 to 1.19)	0.81 (0.69 to 0.93)	1.03 (0.88 to 1.22)	0.77 (0.61 to 0.96)	1.01 (0.88 to 1.16)	1.01 (0.78 to 1.3)	1.32 (1.06 to 1.65)	1.32 (1.06 to 1.63)	0.86 (0.69 to 1.03)	0.99 (0.81 to 1.2)	1.44 (1.17 to 1.75)	1.46 (1.19 to 1.78)	1.02 (0.75 to 0.83)	0.91 (0.66 to 1.22)	2.22 (1.76 to 2.81)	1	
Interferon beta-1b 500 mcg SC every other day	0.62 (0.51 to 0.74)	2.13 (1.67 to 2.84)	3.87 (2.39 to 6.41)	0.89 (0.69 to 1.15)	0.76 (0.62 to 0.91)	0.96 (0.79 to 1.19)	0.72 (0.55 to 0.93)	0.95 (0.8 to 1.12)	0.94 (0.7 to 1.26)	1.24 (0.96 to 1.59)	1.23 (0.96 to 1.57)	0.8 (0.62 to 1.)	0.93 (0.73 to 1.17)	1.34 (1.06 to 1.69)	1.37 (1.07 to 1.72)	0.96 (0.69 to 0.91)	0.85 (0.61 to 1.17)	2.07 (1.6 to 2.73)	0.93 (0.8 to 1.1)	1

A6.2: Disability progression

Treatment	Placebo	Alemtuzumab 12 mg IV q.d	Alemtuzumab 24 mg IV q.d	Interferon beta-1a 22 mcg SC t.i.w	Interferon beta-1a 30 mcg IM q.w	Interferon beta-1a 44 mcg SC t.i.w	Interferon beta-1a 60 mcg IM q.w	glatiramer acetate 20mg q.d	dimethyl fumarate 240 mg two times daily	dimethyl fumarate 240 mg three times daily	Teriflunomide oral 7 mg	Teriflunomide oral 14 mg	Fingolimod oral 0.5 mg	Fingolimod oral 1.25 mg	Peginterferon beta-1a 125 mcg once every 2 weeks	peginterferon beta-1a 125 mcg once every 4 weeks	Natalizumab	Interferon beta-1b 250 mcg SC every other day	**Interferon beta-1b 500 mcg SC every other day**
Placebo	1																		
Alemtuzumab 12 mg IV q.d	0.4 (0.27 to 0.6)	1																	
Alemtuzumab 24 mg IV q.d	0.36 (0.16 to 0.74)	0.91 (0.42 to 1.8)	1																
Interferon beta-1a 22 mcg SC t.i.w	0.84 (0.61 to 1.19)	2.12 (1.34 to 3.34)	2.33 (1.09 to 5.26)	1															
Interferon beta-1a 30 mcg IM q.w	0.8 (0.65 to 0.99)	2.01 (1.32 to 3.01)	2.21 (1.05 to 4.94)	0.95 (0.65 to 1.38)	1														
Interferon beta-1a 44 mcg SC t.i.w	0.77 (0.6 to 1.01)	1.95 (1.45 to 2.59)	2.15 (1.1 to 4.55)	0.92 (0.65 to 1.3)	0.97 (0.73 to 1.3)	1													
Interferon beta-1a 60 mcg IM q.w	0.79 (0.54 to 1.19)	2. (1.17 to 3.37)	2.22 (0.96 to 5.17)	0.94 (0.57 to 1.56)	0.99 (0.71 to 1.39)	1.03 (0.66 to 1.58)	1												
glatiramer acetate 20mg q.d	0.78 (0.63 to 0.96)	1.97 (1.28 to 2.92)	2.17 (1.04 to 4.9)	0.93 (0.63 to 1.35)	0.98 (0.76 to 1.23)	1.01 (0.75 to 1.33)	0.99 (0.64 to 1.47)	1											
dimethyl fumarate 240 mg two times daily	0.65 (0.49 to 0.85)	1.63 (1.01 to 2.57)	1.82 (0.81 to 4.18)	0.77 (0.5 to 1.17)	0.81 (0.58 to 1.13)	0.84 (0.58 to 1.2)	0.82 (0.51 to 1.29)	0.83 (0.61 to 1.15)	1										
dimethyl fumarate 240 mg three times daily	0.68 (0.52 to 0.89)	1.73 (1.06 to 2.69)	1.9 (0.88 to 4.31)	0.81 (0.52 to 1.22)	0.86 (0.62 to 1.17)	0.89 (0.61 to 1.26)	0.86 (0.54 to 1.36)	0.88 (0.64 to 1.18)	1.06 (0.78 to 1.42)	1									
Teriflunomide oral 7 mg	0.8 (0.55 to 1.13)	2. (1.15 to 3.35)	2.2 (0.99 to 5.4)	0.94 (0.57 to 1.52)	0.99 (0.65 to 1.48)	1.03 (0.65 to 1.58)	1.01 (0.58 to 1.69)	1.01 (0.67 to 1.53)	1.23 (0.78 to 1.91)	1.16 (0.74 to 1.81)	1								
Teriflunomide oral 14 mg	0.73 (0.51 to 1.05)	1.85 (1.06 to 3.11)	2.03 (0.91 to 4.89)	0.87 (0.52 to 1.41)	0.93 (0.6 to 1.38)	0.95 (0.6 to 1.46)	0.92 (0.54 to 1.57)	0.94 (0.62 to 1.43)	1.13 (0.72 to 1.76)	1.07 (0.68 to 1.69)	0.92 (0.64 to 1.35)	1							
Fingolimod oral 0.5 mg	0.71 (0.55 to 0.9)	1.78 (1.11 to 2.77)	1.96 (0.92 to 4.55)	0.83 (0.54 to 1.26)	0.89 (0.65 to 1.16)	0.91 (0.64 to 1.3)	0.89 (0.57 to 1.37)	0.9 (0.66 to 1.23)	1.09 (0.75 to 1.57)	1.03 (0.72 to 1.48)	0.89 (0.58 to 1.37)	0.97 (0.62 to 1.5)	1						
Fingolimod oral 1.25 mg	0.71 (0.56 to 0.9)	1.8 (1.12 to 2.78)	1.96 (0.93 to 4.49)	0.85 (0.55 to 1.26)	0.89 (0.66 to 1.18)	0.92 (0.65 to 1.3)	0.9 (0.57 to 1.38)	0.91 (0.67 to 1.25)	1.1 (0.77 to 1.59)	1.04 (0.73 to 1.49)	0.9 (0.59 to 1.38)	0.97 (0.63 to 1.5)	1.01 (0.78 to 1.32)	1					
Peginterferon beta-1a 125 mcg once every 2 weeks	0.61 (0.36 to 0.98)	1.53 (0.8 to 2.87)	1.68 (0.69 to 4.18)	0.72 (0.39 to 1.28)	0.76 (0.43 to 1.27)	0.78 (0.44 to 1.36)	0.77 (0.4 to 1.4)	0.78 (0.45 to 1.31)	0.94 (0.53 to 1.62)	0.89 (0.5 to 1.55)	0.77 (0.41 to 1.4)	0.83 (0.44 to 1.49)	0.86 (0.49 to 1.49)	0.86 (0.49 to 1.47)	1				
peginterferon beta-1a 125 mcg once every 4 weeks	0.62 (0.38 to 1.01)	1.56 (0.84 to 2.86)	1.74 (0.71 to 4.23)	0.73 (0.4 to 1.33)	0.78 (0.46 to 1.33)	0.8 (0.46 to 1.38)	0.79 (0.41 to 1.44)	0.8 (0.47 to 1.37)	0.96 (0.55 to 1.66)	0.91 (0.52 to 1.57)	0.79 (0.43 to 1.43)	0.85 (0.46 to 1.55)	0.88 (0.51 to 1.54)	0.87 (0.51 to 1.53)	1.02 (0.61 to 1.74)	1			
Natalizumab	0.59 (0.42 to 0.84)	1.49 (0.86 to 2.5)	1.65 (0.73 to 3.9)	0.7 (0.43 to 1.13)	0.74 (0.49 to 1.11)	0.76 (0.49 to 1.18)	0.75 (0.44 to 1.25)	0.75 (0.5 to 1.15)	0.91 (0.59 to 1.42)	0.86 (0.56 to 1.34)	0.74 (0.45 to 1.23)	0.8 (0.49 to 1.34)	0.84 (0.55 to 1.28)	0.83 (0.55 to 1.27)	0.97 (0.53 to 1.81)	0.94 (0.53 to 1.73)	1		
Interferon beta-1b 250 mcg SC every other day	0.72 (0.54 to 0.92)	1.8 (1.1 to 2.77)	1.97 (0.92 to 4.52)	0.85 (0.54 to 1.26)	0.9 (0.65 to 1.17)	0.93 (0.64 to 1.28)	0.9 (0.56 to 1.36)	0.92 (0.69 to 1.16)	1.1 (0.75 to 1.58)	1.05 (0.72 to 1.48)	0.9 (0.57 to 1.38)	0.98 (0.61 to 1.51)	1.02 (0.7 to 1.42)	1.01 (0.69 to 1.41)	1.17 (0.66 to 2.07)	1.16 (0.63 to 0.74)	1.22 (0.76 to 1.84)	1	
Interferon beta-1b 500 mcg SC every other day	0.79 (0.56 to 1.1)	1.99 (1.18 to 3.2)	2.18 (1. to 5.02)	0.94 (0.58 to 1.47)	0.99 (0.68 to 1.39)	1.02 (0.68 to 1.49)	1. (0.6 to 1.59)	1.01 (0.74 to 1.36)	1.22 (0.8 to 1.84)	1.15 (0.77 to 1.73)	1. (0.6 to 1.61)	1.08 (0.65 to 1.76)	1.12 (0.74 to 1.68)	1.11 (0.73 to 1.66)	1.3 (0.71 to 2.38)	1.27 (0.68 to 1.19)	1.34 (0.81 to 2.16)	1.1 (0.84 to 1.51)	1

A6.3: Withdrawal due to adverse events

Treatment	Placebo	Alemtuzumab 12 mg IV q.d	Alemtuzumab 24 mg IV q.d	Interferon beta-1a 22 mcg SC t.i.w	Interferon beta-1a 30 mcg IM q.w	Interferon beta-1a 44 mcg SC t.i.w	Interferon beta-1a 60 mcg IM q.w	glatiramer acetate 20mg q.d	glatiramer acetate 40mg t.i.w	dimethyl fumarate 240 mg two times daily	dimethyl fumarate 240 mg three times daily	Teriflunomide oral 7 mg	Teriflunomide oral 14 mg	Fingolimod oral 0.5 mg	Fingolimod oral 1.25 mg	Peginterferon beta-1a 125 mcg once every 2 weeks	peginterferon beta-1a 125 mcg once every 4 weeks	Natalizumab	Interferon beta-1b 250 mcg SC every other day	**Interferon beta-1b 500 mcg SC every other day**
Placebo	1																			
Alemtuzumab 12 mg IV q.d	0.61 (0.25 to 1.47)	1																		
Alemtuzumab 24 mg IV q.d	0.54 (0.17 to 1.54)	0.88 (0.3 to 2.31)	1																	
Interferon beta-1a 22 mcg SC t.i.w	1.68 (0.5 to 5.98)	2.78 (0.7 to 11.12)	3.16 (0.7 to 15.17)	1																
Interferon beta-1a 30 mcg IM q.w	1.33 (0.85 to 2.17)	2.18 (0.89 to 5.5)	2.46 (0.85 to 8.1)	0.8 (0.22 to 2.82)	1															
Interferon beta-1a 44 mcg SC t.i.w	2.2 (1.29 to 3.97)	3.6 (1.88 to 7.33)	4.08 (1.69 to 11.42)	1.31 (0.4 to 4.36)	1.65 (0.91 to 3.08)	1														
Interferon beta-1a 60 mcg IM q.w	1.9 (0.79 to 4.81)	3.1 (0.96 to 10.5)	3.5 (0.95 to 14.59)	1.14 (0.25 to 4.94)	1.43 (0.66 to 3.11)	0.86 (0.32 to 2.29)	1													
glatiramer acetate 20mg q.d	1.17 (0.74 to 1.94)	1.91 (0.79 to 4.89)	2.16 (0.76 to 7.2)	0.7 (0.19 to 2.48)	0.88 (0.51 to 1.55)	0.53 (0.29 to 0.96)	0.62 (0.24 to 1.63)	1												
glatiramer acetate 40mg t.i.w	2.5 (0.86 to 8.29)	4.08 (1.02 to 18.4)	4.7 (1.05 to 24.1)	1.47 (0.29 to 8.02)	1.87 (0.58 to 6.69)	1.13 (0.33 to 4.18)	1.32 (0.32 to 5.79)	2.13 (0.65 to 7.5)	1											
dimethyl fumarate 240 mg two times daily	1.24 (0.74 to 2.13)	2.02 (0.75 to 5.59)	2.29 (0.74 to 8.12)	0.74 (0.19 to 2.73)	0.94 (0.47 to 1.82)	0.56 (0.27 to 1.15)	0.66 (0.23 to 1.81)	1.07 (0.56 to 1.92)	0.5 (0.14 to 1.64)	1										
dimethyl fumarate 240 mg three times daily	1.25 (0.74 to 2.13)	2.03 (0.76 to 5.6)	2.32 (0.74 to 8.16)	0.75 (0.19 to 2.74)	0.94 (0.47 to 1.83)	0.57 (0.27 to 1.17)	0.66 (0.23 to 1.81)	1.07 (0.56 to 1.93)	0.5 (0.14 to 1.65)	1.01 (0.58 to 1.73)	1									
Teriflunomide oral 7 mg	1.37 (0.82 to 2.21)	2.24 (0.87 to 5.55)	2.53 (0.85 to 8.25)	0.82 (0.22 to 2.84)	1.03 (0.52 to 1.91)	0.62 (0.31 to 1.12)	0.72 (0.25 to 1.9)	1.17 (0.57 to 2.16)	0.55 (0.15 to 1.74)	1.1 (0.52 to 2.19)	1.1 (0.52 to 2.19)	1								
Teriflunomide oral 14 mg	1.53 (0.96 to 2.54)	2.51 (1.02 to 6.37)	2.85 (0.98 to 9.45)	0.9 (0.25 to 3.25)	1.15 (0.61 to 2.19)	0.69 (0.37 to 1.28)	0.81 (0.29 to 2.2)	1.31 (0.68 to 2.48)	0.62 (0.17 to 1.99)	1.23 (0.62 to 2.54)	1.23 (0.61 to 2.53)	1.12 (0.73 to 1.85)	1							
Fingolimod oral 0.5 mg	1.54 (0.98 to 2.52)	2.52 (0.96 to 6.8)	2.85 (0.93 to 9.82)	0.91 (0.24 to 3.35)	1.16 (0.65 to 2.04)	0.7 (0.34 to 1.4)	0.81 (0.31 to 2.1)	1.31 (0.68 to 2.48)	0.62 (0.17 to 1.99)	1.24 (0.62 to 2.52)	1.24 (0.62 to 2.5)	1.12 (0.59 to 2.29)	1.01 (0.52 to 1.96)	1						
Fingolimod oral 1.25 mg	2.21 (1.42 to 3.58)	3.62 (1.38 to 9.71)	4.09 (1.34 to 14.02)	1.31 (0.35 to 4.8)	1.66 (0.94 to 2.91)	1. (0.49 to 1.99)	1.16 (0.45 to 3.02)	1.88 (0.99 to 3.53)	0.89 (0.25 to 2.84)	1.78 (0.89 to 3.61)	1.77 (0.89 to 3.6)	1.6 (0.86 to 3.27)	1.45 (0.74 to 2.79)	1.43 (0.94 to 2.21)	1					
Peginterferon beta-1a 125 mcg once every 2 weeks	3.57 (1.27 to 11.14)	5.78 (1.51 to 24.42)	6.67 (1.5 to 33.69)	2.12 (0.41 to 11.18)	2.67 (0.85 to 9.09)	1.62 (0.49 to 5.69)	1.88 (0.47 to 7.82)	3.04 (0.95 to 10.19)	1.43 (0.29 to 6.88)	2.87 (0.9 to 9.95)	2.85 (0.9 to 9.93)	2.59 (0.84 to 9.15)	2.31 (0.73 to 8.02)	2.3 (0.73 to 7.85)	1.61 (0.51 to 5.43)	1				
peginterferon beta-1a 125 mcg once every 4 weeks	3.47 (1.25 to 10.9)	5.75 (1.48 to 24.35)	6.48 (1.48 to 33.07)	2.07 (0.4 to 10.92)	2.61 (0.83 to 8.91)	1.58 (0.48 to 5.61)	1.83 (0.46 to 7.75)	2.96 (0.94 to 10.)	1.4 (0.29 to 6.78)	2.8 (0.87 to 9.8)	2.78 (0.88 to 9.76)	2.54 (0.83 to 8.99)	2.28 (0.72 to 7.88)	2.27 (0.72 to 7.71)	1.59 (0.5 to 5.33)	0.98 (0.41 to 2.37)	1			
Natalizumab	1.22 (0.5 to 2.74)	1.98 (0.56 to 6.49)	2.26 (0.56 to 8.94)	0.72 (0.15 to 3.06)	0.91 (0.32 to 2.31)	0.55 (0.18 to 1.44)	0.65 (0.17 to 2.1)	1.04 (0.36 to 2.6)	0.48 (0.11 to 1.84)	0.98 (0.34 to 2.52)	0.98 (0.33 to 2.53)	0.89 (0.32 to 2.3)	0.79 (0.28 to 2.)	0.79 (0.28 to 1.98)	0.55 (0.19 to 1.36)	0.34 (0.08 to 1.54)	0.34 (0.08 to 1.28)	1		
Interferon beta-1b 250 mcg SC every other day	0.84 (0.4 to 1.87)	1.36 (0.46 to 4.29)	1.56 (0.46 to 6.11)	0.49 (0.12 to 2.07)	0.63 (0.28 to 1.44)	0.38 (0.16 to 0.93)	0.44 (0.15 to 1.37)	0.72 (0.35 to 1.49)	0.33 (0.09 to 1.28)	0.68 (0.29 to 1.67)	0.67 (0.29 to 1.67)	0.61 (0.26 to 1.57)	0.55 (0.23 to 1.34)	0.54 (0.23 to 1.32)	0.38 (0.16 to 0.92)	0.23 (0.06 to 5.98)	0.24 (0.06 to 0.9)	0.7 (0.23 to 2.37)	1	
Interferon beta-1b 500 mcg SC every other day	1.37 (0.52 to 3.92)	2.25 (0.63 to 8.47)	2.55 (0.64 to 11.48)	0.8 (0.17 to 3.91)	1.03 (0.37 to 2.99)	0.62 (0.21 to 1.9)	0.72 (0.2 to 2.71)	1.16 (0.46 to 3.05)	0.54 (0.12 to 2.46)	1.1 (0.38 to 3.38)	1.09 (0.38 to 3.39)	1. (0.34 to 3.22)	0.89 (0.3 to 2.74)	0.89 (0.3 to 2.73)	0.62 (0.21 to 1.9)	0.38 (0.09 to 2.17)	0.39 (0.09 to 1.75)	1.13 (0.32 to 4.63)	.63 (0.66 to 4.11	1

A6.4: Change in Expanded Disability Status Scale

Treatment	Placebo	Alemtuzumab 12 mg IV q.d	Alemtuzumab 24 mg IV q.d	Interferon beta-1a 22 mcg SC t.i.w	Interferon beta-1a 30 mcg IM q.w	Interferon beta-1a 44 mcg SC t.i.w	Interferon beta-1a 60 mcg IM q.w	glatiramer acetate 20mg q.d	Teriflunomide oral 7 mg	Teriflunomide oral 14 mg	Fingolimod oral 0.5 mg	Fingolimod oral 1.25 mg	Interferon beta-1b 250 mcg SC every other day
Placebo	1												
Alemtuzumab 12 mg IV q.d	-0.6 (-1.02 to -0.24)	1											
Alemtuzumab 24 mg IV q.d	-0.91 (-1.48 to -0.4)	-0.31 (-0.76 to 0.15)	1										
Interferon beta-1a 22 mcg SC t.i.w	-0.27 (-0.71 to 0.15)	0.33 (-0.15 to 0.85)	0.64 (0.03 to 1.28)	1									
Interferon beta-1a 30 mcg IM q.w	-0.22 (-0.48 to 0.02)	0.38 (0.04 to 0.77)	0.69 (0.18 to 1.24)	0.05 (-0.4 to 0.51)	1								
Interferon beta-1a 44 mcg SC t.i.w	-0.28 (-0.58 to -0.02)	0.32 (0.07 to 0.6)	0.63 (0.18 to 1.1)	-0.01 (-0.44 to 0.41)	-0.06 (-0.32 to 0.18)	1							
Interferon beta-1a 60 mcg IM q.w	-0.25 (-0.76 to 0.24)	0.35 (-0.19 to 0.95)	0.66 (0. to 1.36)	0.02 (-0.6 to 0.65)	-0.03 (-0.47 to 0.41)	0.03 (-0.46 to 0.54)	1						
glatiramer acetate 20mg q.d	-0.13 (-0.4 to 0.11)	0.47 (0.08 to 0.9)	0.78 (0.24 to 1.35)	0.14 (-0.33 to 0.61)	0.09 (-0.2 to 0.38)	0.15 (-0.15 to 0.47)	0.12 (-0.41 to 0.64	1					
Teriflunomide oral 7 mg	-0.05 (-0.47 to 0.36)	0.55 (0.01 to 1.15)	0.86 (0.21 to 1.57)	0.22 (-0.36 to 0.83)	0.17 (-0.3 to 0.66)	0.23 (-0.25 to 0.75)	0.19 (-0.44 to 0.86	0.08 (-0.4 to 0.58)	1				
Teriflunomide oral 14 mg	-0.14 (-0.56 to 0.27)	0.46 (-0.08 to 1.06)	0.77 (0.12 to 1.48)	0.13 (-0.46 to 0.74)	0.08 (-0.39 to 0.57)	0.14 (-0.34 to 0.66)	0.11 (-0.53 to 0.77	-0.01 (-0.48 to 0.49)	-0.09 (-0.5 to 0.33)	1			
Fingolimod oral 0.5 mg	-0.16 (-0.41 to 0.1)	0.44 (0.04 to 0.91)	0.76 (0.21 to 1.36)	0.12 (-0.36 to 0.61)	0.06 (-0.22 to 0.36)	0.12 (-0.2 to 0.48)	0.09 (-0.42 to 0.63	-0.03 (-0.35 to 0.33)	-0.1 (-0.59 to 0.38)	-0.02 (-0.5 to 0.47)	1		
Fingolimod oral 1.25 mg	-0.22 (-0.47 to 0.04)	0.38 (-0.02 to 0.85)	0.69 (0.14 to 1.3)	0.06 (-0.42 to 0.55)	0. (-0.28 to 0.3)	0.06 (-0.26 to 0.42)	0.03 (-0.48 to 0.56	-0.09 (-0.42 to 0.26)	-0.17 (-0.65 to 0.32)	-0.08 (-0.56 to 0.41)	-0.06 (-0.3 to 0.18)	1	
Interferon beta-1b 250 mcg SC every other day	-0.58 (-0.94 to -0.22)	0.02 (-0.37 to 0.47)	0.33 (-0.21 to 0.92)	-0.31 (-0.81 to 0.21)	-0.36 (-0.64 to -0.06)	-0.3 (-0.61 to 0.04)	-0.33 (-0.84 to 0.2)	-0.45 (-0.83 to -0.05	-0.53 (-1.08 to 0.02)	-0.44 (-0.99 to 0.11)	-0.42 (-0.82 to -0.02	-0.36 (-0.76 to 0.04)	1

A6.5: Serious adverse events

Treatment	Placebo	Alemtuzumab 12 mg IV q.d	Alemtuzumab 24 mg IV q.d	Interferon beta-1a 30 mcg IM q.w	Interferon beta-1a 44 mcg SC t.i.w	glatiramer acetate 20mg q.d	glatiramer acetate 40mg t.i.w	dimethyl fumarate 240 mg two times daily	dimethyl fumarate 240 mg three times daily	Teriflunomide oral 7 mg	Teriflunomide oral 14 mg	Fingolimod oral 0.5 mg	Fingolimod oral 1.25 mg	Peginterferon beta-1a 125 mcg once every 2 weeks	peginterferon beta-1a 125 mcg once every 4 weeks	Natalizumab	Interferon beta-1b 250 mcg SC every other day	**Interferon beta-1b 500 mcg SC every other day**
Placebo	1																	
Alemtuzumab 12 mg IV q.d	0.67 (0.37 to 1.28)	1																
Alemtuzumab 24 mg IV q.d	0.79 (0.42 to 1.53)	1.18 (0.79 to 1.71)	1															
Interferon beta-1a 30 mcg IM q.w	0.77 (0.54 to 1.13)	1.14 (0.61 to 2.07)	0.97 (0.51 to 1.83)	1														
Interferon beta-1a 44 mcg SC t.i.w	0.86 (0.52 to 1.46)	1.28 (0.91 to 1.75)	1.09 (0.74 to 1.59)	1.12 (0.67 to 1.86)	1													
glatiramer acetate 20mg q.d	0.78 (0.54 to 1.14)	1.16 (0.62 to 2.08)	0.99 (0.52 to 1.83)	1.01 (0.67 to 1.53)	0.91 (0.55 to 1.49)	1												
glatiramer acetate 40mg t.i.w	0.99 (0.49 to 2.04)	1.47 (0.57 to 3.72)	1.25 (0.48 to 3.23)	1.28 (0.58 to 2.87)	1.15 (0.48 to 2.75)	1.27 (0.57 to 2.83)	1											
dimethyl fumarate 240 mg two times daily	0.81 (0.56 to 1.19)	1.21 (0.59 to 2.36)	1.03 (0.49 to 2.07)	1.05 (0.63 to 1.72)	0.94 (0.51 to 1.71)	1.04 (0.65 to 1.63)	0.82 (0.36 to 1.81)	1										
dimethyl fumarate 240 mg three times daily	0.72 (0.49 to 1.07)	1.08 (0.52 to 2.1)	0.92 (0.44 to 1.84)	0.94 (0.56 to 1.54)	0.84 (0.45 to 1.53)	0.93 (0.58 to 1.46)	0.73 (0.33 to 1.62)	0.89 (0.6 to 1.33)	1									
Teriflunomide oral 7 mg	1.03 (0.71 to 1.51)	1.54 (0.77 to 2.92)	1.31 (0.64 to 2.58)	1.34 (0.8 to 2.2)	1.2 (0.67 to 2.12)	1.33 (0.79 to 2.19)	1.05 (0.46 to 2.31)	1.28 (0.75 to 2.16)	1.43 (0.84 to 2.44)	1								
Teriflunomide oral 14 mg	1.07 (0.73 to 1.54)	1.58 (0.78 to 3.01)	1.35 (0.66 to 2.65)	1.38 (0.82 to 2.26)	1.24 (0.68 to 2.18)	1.37 (0.81 to 2.24)	1.08 (0.48 to 2.36)	1.32 (0.77 to 2.21)	1.48 (0.86 to 2.49)	1.03 (0.71 to 1.48)	1							
Fingolimod oral 0.5 mg	0.96 (0.68 to 1.39)	1.43 (0.71 to 2.77)	1.22 (0.59 to 2.44)	1.25 (0.8 to 1.95)	1.12 (0.61 to 2.01)	1.24 (0.76 to 2.01)	0.97 (0.44 to 2.14)	1.19 (0.71 to 1.99)	1.33 (0.8 to 2.25)	0.93 (0.56 to 1.56)	0.9 (0.55 to 1.52)	1						
Fingolimod oral 1.25 mg	1.22 (0.87 to 1.77)	1.81 (0.91 to 3.53)	1.54 (0.76 to 3.11)	1.58 (1.03 to 2.47)	1.41 (0.79 to 2.56)	1.56 (0.97 to 2.55)	1.23 (0.56 to 2.74)	1.5 (0.92 to 2.55)	1.68 (1.03 to 2.88)	1.18 (0.72 to 1.99)	1.14 (0.7 to 1.95)	1.26 (0.91 to 1.8)	1					
Peginterferon beta-1a 125 mcg once every 2 weeks	1.67 (0.94 to 2.94)	2.48 (1.04 to 5.55)	2.11 (0.88 to 4.9)	2.16 (1.08 to 4.21)	1.93 (0.88 to 4.1)	2.14 (1.06 to 4.16)	1.69 (0.68 to 4.13)	2.06 (1.03 to 4.07)	2.31 (1.16 to 4.57)	1.62 (0.81 to 3.16)	1.56 (0.79 to 3.1)	1.73 (0.87 to 3.34)	1.37 (0.69 to 2.62)	1				
peginterferon beta-1a 125 mcg once every 4 weeks	1.55 (0.88 to 2.74)	2.31 (0.97 to 5.19)	1.96 (0.81 to 4.57)	2.02 (1. to 3.95)	1.8 (0.82 to 3.85)	2. (0.99 to 3.89)	1.57 (0.63 to 3.84)	1.92 (0.95 to 3.8)	2.15 (1.07 to 4.25)	1.5 (0.75 to 2.96)	1.45 (0.74 to 2.9)	1.61 (0.81 to 3.12)	1.28 (0.64 to 2.43)	0.93 (0.54 to 1.61)	1			
Natalizumab	0.81 (0.49 to 1.39)	1.21 (0.53 to 2.62)	1.03 (0.45 to 2.31)	1.06 (0.56 to 1.99)	0.95 (0.46 to 1.93)	1.04 (0.56 to 1.95)	0.82 (0.34 to 1.97)	1.01 (0.53 to 1.92)	1.13 (0.6 to 2.15)	0.79 (0.42 to 1.5)	0.76 (0.41 to 1.47)	0.85 (0.46 to 1.59)	0.67 (0.36 to 1.23)	0.49 (0.23 to 1.07)	0.52 (0.25 to 1.15)	1		
Interferon beta-1b 250 mcg SC every other day	0.66 (0.35 to 1.26)	0.99 (0.43 to 2.18)	0.84 (0.36 to 1.9)	0.86 (0.43 to 1.68)	0.77 (0.36 to 1.61)	0.85 (0.49 to 1.45)	0.67 (0.25 to 1.72)	0.82 (0.4 to 1.64)	0.92 (0.45 to 1.86)	0.64 (0.31 to 1.33)	0.62 (0.3 to 1.31)	0.69 (0.33 to 1.41)	0.55 (0.26 to 1.09)	0.4 (0.17 to 0.94)	0.43 (0.18 to 1.02)	0.82 (0.36 to 1.78)	1	
Interferon beta-1b 500 mcg SC every other day	0.93 (0.49 to 1.8)	1.38 (0.6 to 3.05)	1.18 (0.5 to 2.67)	1.21 (0.61 to 2.36)	1.08 (0.51 to 2.25)	1.19 (0.69 to 2.06)	0.94 (0.36 to 2.43)	1.15 (0.57 to 2.33)	1.29 (0.64 to 2.63)	0.9 (0.43 to 1.9)	0.87 (0.42 to 1.85)	0.97 (0.46 to 2.)	0.77 (0.36 to 1.55)	0.56 (0.24 to 1.34)	0.6 (0.25 to 1.44)	1.14 (0.5 to 1.53)	1.4 (0.83 to 2.4)	1

A6.6: Mortality

Treatment	Placebo	Alemtuzumab 12 mg IV q.d	Alemtuzumab 24 mg IV q.d	Interferon beta-1a 22 mcg SC t.i.w	Interferon beta-1a 30 mcg IM q.w	Interferon beta-1a 44 mcg SC t.i.w	Interferon beta-1a 60 mcg IM q.w	glatiramer acetate 20mg q.d	glatiramer acetate 40mg t.i.w	dimethyl fumarate 240 mg two times daily	dimethyl fumarate 240 mg three times daily	Teriflunomide oral 7 mg	Teriflunomide oral 14 mg	Fingolimod oral 0.5 mg	Fingolimod oral 1.25 mg	Peginterferon beta-1a 125 mcg once every 2 weeks	peginterferon beta-1a 125 mcg once every 4 weeks	Natalizumab	Interferon beta-1b 250 mcg SC every other day	**Interferon beta-1b 500 mcg SC every other day**
Placebo	1																			
Alemtuzumab 12 mg IV q.d	2.81 (0.08 to 168.2)	1																		
Alemtuzumab 24 mg IV q.d	2.08 (0.04 to 125.5)	0.73 (0.06 to 5.88)	1																	
Interferon beta-1a 22 mcg SC t.i.w	1.6 (0.07 to 34.77)	0.55 (0.01 to 24.67)	0.78 (0.01 to 51.33)	1																
Interferon beta-1a 30 mcg IM q.w	2.1 (0.26 to 24.45)	0.82 (0.01 to 40.09)	1.09 (0.01 to 84.65)	1.4 (0.04 to 55.3)	1															
Interferon beta-1a 44 mcg SC t.i.w	0.97 (0.06 to 17.15)	0.35 (0.02 to 2.55)	0.46 (0.02 to 6.62)	0.62 (0.02 to 14.92)	0.43 (0.01 to 12.35)	1														
Interferon beta-1a 60 mcg IM q.w	2.28 (0.03 to 222.1)	0.88 (0. to 177.5)	1.15 (0. to 358.5)	1.51 (0.01 to 308.9)	1.01 (0.02 to 55.64)	2.48 (0.01 to 420.6)	1													
glatiramer acetate 20mg q.d	0.9 (0.11 to 7.85)	0.33 (0.01 to 10.23)	0.44 (0.01 to 19.73)	0.55 (0.02 to 22.44)	0.42 (0.03 to 4.39)	0.97 (0.06 to 14.14)	0.41 (0. to 42.93)	1												
glatiramer acetate 40mg t.i.w	0.08 (0. to 3.54)	0.02 (0. to 4.79)	0.04 (0. to 8.96)	0.05 (0. to 7.02)	0.04 (0. to 2.97)	0.08 (0. to 9.45)	0.03 (0. to 14.21)	0.09 (0. to 7.16)	1											
dimethyl fumarate 240 mg two times daily	0.52 (0.04 to 5.34)	0.18 (0. to 10.34)	0.24 (0. to 19.9)	0.32 (0.01 to 14.89)	0.24 (0.01 to 4.56)	0.51 (0.02 to 16.38)	0.22 (0. to 29.21)	0.57 (0.03 to 7.89)	6.69 (0.06 to 7441.)	1										
dimethyl fumarate 240 mg three times daily	0.89 (0.09 to 8.41)	0.3 (0. to 16.87)	0.42 (0. to 32.89)	0.53 (0.01 to 25.59)	0.42 (0.02 to 7.26)	0.9 (0.03 to 26.01)	0.4 (0. to 46.87)	0.98 (0.08 to 11.73)	1.07 (0.13 to 11810	1.69 (0.18 to 18.19)	1									
Teriflunomide oral 7 mg	2.59 (0.12 to 82.51)	0.93 (0. to 126.9)	1.36 (0. to 242.8)	1.66 (0.02 to 167.7)	1.16 (0.03 to 67.28)	2.73 (0.04 to 238.5)	.08 (0.01 to 383.4	2.88 (0.07 to 196.5)	6.05 (0.27 to 53180	5.18 (0.12 to 307.1)	3.08 (0.07 to 174.6)	1								
Teriflunomide oral 14 mg	0.94 (0.02 to 37.74)	0.33 (0. to 56.46)	0.48 (0. to 98.06)	0.58 (0. to 88.85)	0.45 (0. to 34.11)	0.99 (0.01 to 105.1)	0.42 (0. to 157.2)	1.05 (0.01 to 71.67)	2.64 (0.05 to 19540	1.88 (0.02 to 147.7)	1.1 (0.01 to 79.34)	0.39 (0.01 to 7.5)	1							
Fingolimod oral 0.5 mg	0.1 (0. to 2.57)	0.03 (0. to 4.24)	0.04 (0. to 8.67)	0.05 (0. to 5.39)	0.04 (0. to 2.2)	0.08 (0. to 8.4)	0.04 (0. to 12.77)	0.1 (0. to 5.12)	1.03 (0. to 1842.)	0.17 (0. to 12.01)	0.1 (0. to 6.16)	0.03 (0. to 3.64)	0.09 (0. to 18.86)	1						
Fingolimod oral 1.25 mg	0.52 (0.02 to 6.76)	0.17 (0. to 13.59)	0.24 (0. to 24.79)	0.31 (0. to 17.09)	0.24 (0.01 to 6.36)	0.5 (0.01 to 23.87)	0.22 (0. to 40.74)	0.57 (0.01 to 15.09)	6.57 (0.05 to 8530.)	0.98 (0.02 to 36.2)	0.59 (0.01 to 17.31)	0.19 (0. to 9.23)	0.5 (0. to 63.23)	5.46 (0.12 to 4103.)	1					
Peginterferon beta-1a 125 mcg once every 2 weeks	0.41 (0.01 to 8.87)	0.13 (0. to 12.73)	0.18 (0. to 25.17)	0.25 (0. to 19.58)	0.17 (0. to 8.06)	0.41 (0. to 22.98)	0.17 (0. to 38.09)	0.43 (0.01 to 19.38)	5.11 (0.02 to 7408.)	0.79 (0.01 to 44.58)	0.44 (0.01 to 21.56)	0.15 (0. to 11.05)	0.42 (0. to 71.51)	4.72 (0.02 to 4890.)	0.79 (0.01 to 65.78)	1				
peginterferon beta-1a 125 mcg once every 4 weeks	0.4 (0.01 to 10.22)	0.13 (0. to 14.86)	0.18 (0. to 26.14)	0.24 (0. to 19.82)	0.17 (0. to 8.86)	0.39 (0. to 24.78)	0.16 (0. to 42.68)	0.42 (0. to 20.5)	4.75 (0.02 to 7254.)	0.78 (0.01 to 43.94)	0.45 (0. to 21.3)	0.14 (0. to 10.48)	0.4 (0. to 69.74)	4.66 (0.03 to 5197.)	0.74 (0.01 to 66.19)	1. (0.02 to 44.74)	1			
Natalizumab	4.34 (0.16 to 2761.)	1.73 (0.01 to 2475.)	2.19 (0.01 to 4596.)	3.03 (0.04 to 3566.)	2.21 (0.03 to 2092.)	5.17 (0.06 to 4779.)	.53 (0.01 to 3792.	5.25 (0.1 to 4005.)	.25 (0.34 to 20170	9.32 (0.14 to 8262.)	5.45 (0.09 to 4151.)	1.88 (0.02 to 1428.)	5.75 (0.03 to 5626.)	.43 (0.48 to 340300	0.91 (0.14 to 10330.	2.92 (0.12 to 125.5	3.91 (0.12 to 23380	1		
Interferon beta-1b 250 mcg SC every other day	0.07 (0. to 6.65)	0.02 (0. to 4.5)	0.03 (0. to 7.49)	0.04 (0. to 8.89)	0.03 (0. to 3.51)	0.08 (0. to 8.68)	0.03 (0. to 16.62)	0.08 (0. to 3.74)	0.93 (0. to 1388.)	0.14 (0. to 17.77)	0.08 (0. to 9.03)	0.02 (0. to 6.09)	0.07 (0. to 25.39)	0.8 (0. to 1492.)	0.14 (0. to 31.76)	0.18 (0. to 34.77)	0.17 (0. to 154.9)	0.01 (0. to 4.83)	1	
Interferon beta-1b 500 mcg SC every other day	0.08 (0. to 5.9)	0.02 (0. to 4.32)	0.04 (0. to 8.01)	0.05 (0. to 8.57)	0.03 (0. to 3.12)	0.08 (0. to 7.76)	0.03 (0. to 13.35)	0.09 (0. to 3.55)	0.95 (0. to 2803.)	0.15 (0. to 17.67)	0.09 (0. to 8.48)	0.03 (0. to 5.52)	0.08 (0. to 31.17)	0.87 (0. to 1764.)	0.15 (0. to 31.31)	0.19 (0. to 24.45)	0.19 (0. to 128.)	0.01 (0. to 4.47)	1.08 (0. to 863.8)	1

Appendix 7: Results for direct pairwise meta-analyses

A7.1 Annual relapse for multiple sclerosis treatments compared to placebo

Interventions	RR (95% CI)
Natalizumab	0.31 (0.26 to 0.36)
Fingolimod oral 1.25 mg	0.44 (0.38 to 0.51)
Fingolimod oral 0.5 mg	0.45 (0.41 to 0.56)
Dimethyl fumarate 240 mg two times daily	0.51 (0.44 to 0.60)
Dimethyl fumarate 240 mg three times daily	0.51 (0.44 to 0.60)
Interferon beta-1a 44 mcg SC t.i.w.	0.67 (0.58 to 0.77)
Peg-interferon beta-1a 125 mcg once every 2 weeks	0.64 (0.50 to 0.82)
Glatiramer acetate 20mg q.d.	0.71 (0.62 to 0.80)
Glatiramer acetate 40mg t.i.w.	0.66 (0.55 to 0.78)
Interferon beta-1b 250 mcg SC every other day	0.65 (0.54 to 0.79)
Teriflunomide oral 14 mg	0.66 (0.58 to 0.75)
Interferon beta-1a 22 mcg SC t.i.w.	0.71 (0.62 to 0.82)
Peg-interferon beta-1a 125 mcg once every 4 weeks	0.73 (0.57 to 0.92)
Teriflunomide oral 7 mg	0.73 (0.65 to 0.82)
Interferon beta-1a 30 mcg IM q.w.	0.79 (0.69 to 0.89)

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,

A7.2: Disability progression for multiple sclerosis treatments compared to placebo

Interventions	RR (95% CI)
Natalizumab	0.59 (0.46, 0.75)
Peg-interferon beta-1a 125 mcg once every 2 weeks	0.61 (0.39, 0.93)
Peg-interferon beta-1a 125 mcg once every 4 weeks	0.62 (0.40, 0.95)
Dimethyl fumarate 240 mg two times daily	0.66 (0.52, 0.84)
Dimethyl fumarate 240 mg three times daily	0.70 (0.57, 0.86)
Fingolimod oral 0.5 mg	0.75 (0.60, 0.92)
Fingolimod oral 1.25 mg	0.70 (0.57, 0.87)
Interferon beta-1b 250 mcg SC every other day	0.77 (0.56, 1.04)
Teriflunomide oral 14 mg	0.74 (0.57, 0.96)
Interferon beta-1a 44 mcg SC t.i.w	0.71 (0.54, 0.95)
Glatiramer acetate 20mg q.d	0.92 (0.70, 1.20)
Teriflunomide oral 7 mg	0.79 (0.61, 1.03)
Interferon beta-1a 30 mcg IM q.w	0.69 (0.52, 0.91)
Interferon beta-1a 22 mcg SC t.i.w	0.82 (0.63, 1.07)

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,

A7.3: Withdrawal due to adverse events for multiple sclerosis treatments compared to placebo

Interventions	RR (95% CI)
Interferon beta-1b 250 mcg SC every other day	0.10 (0.01, 0.76)
Glatiramer acetate 20mg q.d	1.20 (0.59, 2.43)
Dimethyl fumarate 240 mg two times daily	1.21 (0.93, 1.57)
Dimethyl fumarate 240 mg three times daily	1.18 (0.91, 1.53)
Interferon beta-1a 30 mcg IM q.w	1.55 (0.91, 2.65)
Teriflunomide oral 7 mg	1.54 (0.81, 2.94)
Teriflunomide oral 14 mg	1.70 (1.25, 2.33)
Fingolimod oral 0.5 mg	1.41 (0.89, 2.24)
Interferon beta-1a 22 mcg SC t.i.w	2.97 (0.61, 14.52)
Glatiramer acetate 40mg t.i.w	2.36 (0.99, 5.65)
Interferon beta-1a 44 mcg SC t.i.w	4.57 (1.00, 20.88)
Fingolimod oral 1.25 mg	1.87 (1.43, 2.45)
Peg-interferon beta-1a 125 mcg once every 4 weeks	3.43 (1.49, 7.88)
Peg-interferon beta-1a 125 mcg once every 2 weeks	3.49 (1.52, 7.99)

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,

Appendix 8 Monitorings costs

8.1: Monitoring costs associated with each of the treatments (1. year)

Drug	NAB-analyses	Infusion costs	Eye examina-tions	Startup costs	Medical consulta-tions	MRI	Blood tests (outpatient visits)	Travel costs	Total
Alemtuzumab (Lemtrada)	0	9777 (5/year)	0	0	7350 (4/year)	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 ace-tate (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)

8.2: Monitoring costs associated with each of the treatments (2. year)

Drug	NAB-analyses	Infusion costs	Eye examina-tions	Startup costs	Medical consulta-tions	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)

8.3: Monitoring costs associated with each of the treatments (beyond 2. year)

Drug	NAB-analyses	Infusion costs	Eye examina-tions	Startup costs	Medical consulta-tions	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)

Appendix 9 Scenario analyses

9.1: The results of sensitivity analysis regarding stopping rule at EDSS=7 (discounted)*

Drugs	Total costs (NOK)	Effects (QALYs)	Versus Interferon beta-1b 250 mg (Extavia)			Sequential ICER (NOK/QALY)
			Incremental cost (NOK)	Incremental effect (QALYs)	ICER (NOK/QALY)	
Interferon beta-1b (Extavia)	6,026,196	7.45				
Peg-interferon beta-1a (Plegridy)	6,290,635	7.64	264,439	0.19	1,424,765	1,424,765
Natalizumab (Tysabri)	6,956,053	7.71	92,857	0.26	3,549,122	8,710,280
Dominated therapies						
Interferon beta-1b (Betaferon)	6,083,022	7.45	56,826	-	Dominated by interferon beta-1b (Extavia)	Dominated by interferon beta-1b (Extavia)
Glatiramer acetate (Copaxone)	6,252,584	7.35	226,388	-0.10	Dominated	Dominated by interferon beta-1b (Extavia) and interferon beta-1b (Betaferon)
Teriflunomide (Aubagio)	6,332,238	7.42	306,042	-0.03	Dominated	Dominated by interferon beta-1b (Extavia), interferon beta-1b (Betaferon) and peg-interferon beta-1a
Interferon beta-1a 22 mcg (Rebif)	6,500,898	7.24	474,702	-0.21	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)	6,542,166	7.3	515,970	-0.15	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)	6,572,277	7.36	546,081	-0.09	Dominated	Dominated by interferon beta-1b (Extavia), interferon beta-1b (Betaferon), peg-interferon beta-1a, glatiramer acetate and teriflunomide
Dimethyl fumarate (Tecifidera)	6,692,516	7.58	666,319	0.13	4,953,711	Dominated by peg-interferon beta-1a
Fingolimod (Gilenya)	7,034,538	7.47	1,008,342	0.03	40,301,928	Dominated by peg-interferon beta-1a, dimethyl fumarate and natalizumab

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

* Alemtuzumab still was more effective (QALYS: 8.22) and less costly (Costs: 4,828,145) relative to other treatments (dominant strategy).

9.2: The results of sensitivity analysis using a 30-year time horizon of analysis (discounted) *

Drugs	Total costs (NOK)	Effects (QALYs)	Versus Interferon beta-1b 250 mg (Extavia)			Sequential ICER (NOK/QALY)
			Incremental cost (NOK)	Incremental effect (QALYs)	ICER (NOK/QALY)	
Interferon beta-1b (Extavia)	8,026,896	8.29				
Peg-interferon beta-1a (Plegridy)	8,276,892	8.55	249,995	0.26	960,134	960,134
Natalizumab (Tysabri)	9,033,436	8.64	1,006,540	0.36	2,818796	7,823,148
Dominated therapies						
Interferon beta-1b (Beta-feron)	8,090,003	8.29	255,409	-	Dominated by interferon beta-1b (Extavia)	Dominated by interferon beta-1b (Exta-via)
Glatiramer ace-tate (Copaxone)	8,282,305	8.17	331,284	-0.11	Dominated	Dominated by interferon beta-1b (Exta-via), interferon beta-1b (Beta-feron) and peg-interferon beta-1a
Teriflunomide (Aubagio)	8,358,180	8.26	565,095	-0.02	Dominated	Dominated by interferon beta-1b (Exta-via), interferon beta-1b (Beta-feron) and peg-interferon beta-1a
Interferon beta-1a 22 mcg (Rebif)	8,591,992	8.02	576,680	-0.327	Dominated	Dominated by interferon beta-1b (Exta-via), interferon

						beta-1b (Betaferon), peg-interferon beta-1a, glatiramer acetate and teriflunomide
Interferon beta-1a 30 mg (Avonex)	8,603,576	8.12	611,852	-0.16	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)	8,638,748	8.19	717,167	-0.10	Dominated	Dominated by interferon beta-1b (Extavia), interferon beta-1b (Betaferon), peg-interferon beta-1a, glatiramer acetate and teriflunomide
Dimethyl fumarate (Tecifidera)	8,744,063	8.48	255,409	0.19	3,690,151	Dominated peg-interferon beta-1a
Fingolimod (Gilenya)	9162,932	8.32	1,136,036	0.03	37,196,628	Dominated by peg-interferon beta-1a, dimethyl fumarate and natalizumab

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

* Alemtuzumab still was more effective (QALYS: 9.24) and less costly (Costs: 6,541,067) relative to other treatments (dominant strategy).

9.3: The results of sensitivity analysis regarding "no EDSS improvement" (discounted) *

Drugs	Total costs (NOK)	Effects (QALYs)	Versus Interferon beta-1b 250 mg (Extavia)			Sequential ICER (NOK/QALY)
			Incremental cost (NOK)	Incremental effect (QALYs)	ICER (NOK/QALY)	
Interferon beta-1b (Extavia)	6,902,178	6.57				
Peg-interferon beta-1a (Plegridy)	7,109,166	6.73	206,988	0.16	1,309,477	1,309,477
Natalizumab (Tysabri)	7,706,752	6.78	804,573	0.20	3,935,743	12,890,581
Dominated therapies						
Interferon beta-1b (Betaferon)	6,951,138	6.57	48,960	-	Dominated by interferon beta-1b (Extavia)	Dominated by interferon beta-1b (Extavia)
Glatiramer acetate (Copaxone)	7,104,889	6.49	202,710	-0.08	Dominated	Dominated by interferon beta-1b (Extavia), interferon beta-1b (Betaferon) and peg-interferon beta-1a
Teriflunomide (Aubagio)	7,176,103	6.54	273,925	-0.03	Dominated	Dominated by interferon beta-1b (Extavia), interferon beta-1b (Betaferon) and peg-interferon beta-1a
Interferon beta-1a 22 mcg (Rebif)	7,329,592	6.4	427,413	-0.17	Dominated	Dominated by interferon beta-1b (Extavia), interferon

						beta-1b (Betaferon), peg-interferon beta-1a, glatiramer acetate and teriflunomide
Interferon beta-1a 30 mg (Avonex)	7,362,604	6.45	460,425	-0.12	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)	7,380,177	6,5	477,998	-0.07	Dominated	Dominated by interferon beta-1b (Extavia), interferon beta-1b (Betaferon), peg-interferon beta-1a, glatiramer acetate and teriflunomide
Dimethyl fumarate (Tecifidera)	7,470,947	6.68	568,769	0.11	5,111,539	Dominated peg-interferon beta-1a
Fingolimod (Gilenya)	7,768,104	6.60	865,925	0.03	28,491,096	Dominated by peg-interferon beta-1a, dimethyl fumarate and natalizumab

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

* Alemtuzumab still was more effective (QALYS: 7.18) and less costly (Costs: 5,820,891) relative to other treatments (dominant strategy).

9.4: The results of sensitivity analysis regarding utility values (discounted) *

Drugs	Total costs (NOK)	Effects (QALYs)	Versus Interferon beta-1b 250 mg (Extavia)			Sequential ICER (NOK/QALY)
			Incremental cost (NOK)	Incremental effect (QALYs)	ICER (NOK/QALY)	
Interferon beta-1b (Extavia)	6,035,711	7.88				
Peg-interferon beta-1a (Plegridy)	6,324,629	8.02	288,918	0.15	1,967,737	1,967,737
Natalizumab (Tysabri)	7,000,849	8.08	965,138	0.21	4,649,607	11,131,827
Dominated therapies						
Interferon beta-1b (Betaferon)	6,094,252	7.88	58,541	-	Dominated by interferon beta-1b (Extavia)	Dominated by interferon beta-1b (Extavia)
Glatiramer acetate (Copaxone)	6,259,628	7.79	223,917	-0.08	Dominated	Dominated by interferon beta-1b (Extavia), interferon beta-1b (Betaferon) and peg-interferon beta-1a
Teriflunomide (Aubagio)	6,353,620	7.84	317,909	-0.03	Dominated	Dominated by interferon beta-1b (Extavia), interferon beta-1b (Betaferon) and peg-interferon beta-1a
Interferon beta-1a 22 mcg (Rebif)	6,511,148	7.69	475,437	-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 mg (Avonex)	6,556,702	7.74	520,991	-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)	6,586,671	7.79	550,959	-0.08	Dominated	Dominated by interferon beta-1b (Extavia), interferon beta-1b (Betaferon), peg-interferon beta-1a, glatiramer acetate and teriflunomide
Dimethyl fumarate (Tecifidera)	6,715,056	7.99	679,345	0.11	6,182,526	Dominated peg-interferon beta-1a
Fingolimod (Gilenya)	7,059,978	7.89	1,024,267	0.01	78,665,232	Dominated by peg-interferon beta-1a, dimethyl fumarate and natalizumab

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

* Alemtuzumab still was more effective (QALYS: 8.46) and less costly (Costs: 4,985,254) relative to other treatments (dominant strategy).

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