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HEALTH TECHNOLOGY ASSESSMENT:

Disease modifying treatments for relapsing remitting multiple sclerosis, including rituximab

Title Disease-modifying treatments for relapsing remitting multiple sclerosis, including rituximab. A health technology assessment.

Norwegian title Sykdomsbegrensende legemidler for behandling av attakkpreget multippel sklerose, inkludert rituksimab. En metodevurdering.

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Executive summary

Title

Disease-modifying treatments for relapsing remitting multiple sclerosis (RRMS), including rituximab. A health technology assessment.

Objective

For disease-modifying treatments for RRMS

- To assess effectiveness, based on annual relapse rate, disability progression and new lesions detected by magnetic resonance imaging (MRI).
- To assess safety, based on risk of mortality, risk of serious adverse events, rate of treatment withdrawal due to adverse events, and risk of specific rare serious adverse events.
- To describe legal implications of off-label use of rituximab.

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YEAR: 2019

Key findings and conclusions

We have systematically collected and reviewed the evidence for clinical effectiveness and general safety issues for disease modifying treatments for relapsing remitting multiple sclerosis, synthesised evidence from randomised controlled trials and non-randomised registry-based studies using network meta-regression, and carefully interpreted the findings. We included rituximab in our analysis as it is used off-label for the treatment of patients with RRMS, even though it does not hold marketing authorisation for RRMS.

We included 35 randomised controlled trials and 11 non-randomised registry-based studies, with a total of almost 30 000 patients. We compared estimates of our predefined outcomes from meta-analysis of randomised controlled trials, of non-randomised registry-based studies, the network meta-regression, and other network meta-analytical models, and judged that the estimates are mutually consistent in most cases, and that where there is inconsistency, it could be explained.

Based on the available evidence and the meta-analysis used: alemtuzumab is most likely to be the best treatment with respect to annual relapse rate; ocrelizumab and alemtuzumab are equally likely to be the best treatments with respect to risk of disability progression. Further, we estimate that rituximab is likely to have the lowest risk of serious adverse events and treatment withdrawal due to adverse events. However, the evidence for rituximab is from one small randomised trial of short duration and one non-randomised study, making this finding uncertain.

Treatment rankings are based on available evidence and model assumptions, and in many cases confidence intervals for the highest-ranked treatments overlap, so rankings should not be interpreted as definitive.

There were very few deaths in the included studies (30 deaths out of a total of 22 060 patients). Although we performed a full network meta-analysis, we judged that the number of events was too small to support useful conclusions regarding mortality risk.

We compiled information of rare, and potentially life-threatening effects of disease modifying treatments from the included studies, but we have not searched other sources or databases that may be more suitable for such information. The risk of specific serious adverse events was not estimated due to the limited data available, but data were retrieved from all included studies. The events were generally uncommon in the included studies, which reported no statistically significant differences in rates of serious adverse events.

The effect estimates of annualised relapse rate and sustained disability progression were used in a health economic analyses that is reported in a separate publication.

Main results

Annualised relapse rate	Alemtuzumab, natalizumab and ocrelizumab were ranked as the best three treatments with respect to annualised relapse rate. We estimate probabilities of 93%, 88% and 85%, respectively, that these are the best of all treatments. We anticipate that a typical patient treated with alemtuzumab would experience 0.14 relapses per year (95% CI 0.10 to 0.20 relapses per year) compared to 0.53 relapses per year if they were treated with placebo (95% CI 0.44 to 0.64 relapses per year; annualised relapse rate ratio 0.27, 95% CI 0.19 to 0.40). However, the 95% CI for alemtuzumab overlaps with those for natalizumab (0.13 to 0.22 relapses per year), ocrelizumab (0.13 to 0.25 relapses per year), cladribine (0.17 to 0.30 relapses per year), fingolimod (0.19 to 0.29 relapses per year) and rituximab (0.12 to 0.44 relapses per year). It is therefore possible that these treatment options have similar efficacy with respect to this outcome. Based on the GRADE method for assessing certainty of evidence in network meta-analysis, we judged the certainty of evidence for alemtuzumab, ocrelizumab, and rituximab to be low due to reliance on evidence from non-randomised studies.

Risk of disability progression	Ocrelizumab and alemtuzumab were ranked joint best of the treatment options for this outcome, and natalizumab second best. We estimate probabilities of 77%, 77%, and 71%, respectively, that these are the best of all treatments. We anticipate that 86 per 1000 typical patients treated with ocrelizumab would experience disability progression over the duration of a typical trial (approximately 2 years) (95% CI 48 to 155 patients per 1000 patients), compared to 161 per 1000 patients treated with placebo (95% CI 116 to 225 patients per 1000; relative risk 0.53, 95% CI 0.27 to 1.05). We anticipate that 88 per 1000 typical patients treated with rituximab would experience disability progression over the duration of a typical trial (95% CI 33 to 236 patients per 1000). We found no statistically significant difference for any of the treatment comparisons. Ocrelizumab, alemtuzumab and IFN-beta-1a formed a subnetwork that is disconnected from the main network of evidence, so we were unable to assess the certainty of evidence for these treatments using the GRADE method. We assessed the certainty of evidence for natalizumab to be moderate, and for rituximab to be very low due to the contribution of NRS to the estimate.
Change in Expanded Disability Status Scale (EDSS) score	Natalizumab, alemtuzumab and rituximab were ranked as the best three treatment options for change in Expanded Disability Status Scale (EDSS) score. We estimate probabilities of 89%, 82%, and 76%, respectively, that these are the best of all treatments. We estimate that a typical patient treated with natalizumab would experience a change in EDSS of -0.26 steps (95% CI -0.43 to -0.10 steps) over the duration of a typical trial (approximately 2 years), compared to -0.25 steps (95% CI -0.85 to 0.35 steps) for rituximab, and 0.10 steps (95% CI 0.03 to 0.17 steps) for placebo. We did not assess certainty of evidence using the GRADE tool for this outcome. Rituximab was disconnected from the network and the evidence included one non-randomised study.
Risk of new Magnetic Resonance Imaging (MRI) lesions	Natalizumab, ocrelizumab and alemtuzumab were ranked as the best three treatments of interest for risk of new MRI. We estimate probabilities of 95%, 72%, and 71%, respectively, that these are the best of all treatments. We anticipate that 48 per 1000 typical patients treated with natalizumab would experience one or more new T1-weighted gadolinium (Gd)-enhancing lesions over the duration of a typical trial (approximately 2 years) (95% CI 25 to 91 patients per 1000), compared to 402 patients per 1000 patients treated with placebo (95% CI 314 to 515; relative risk 0.12, 95% CI 0.06 to 0.24). The results suggest that, over the duration of a typical trial, a typical patient treated with teriflunomide, glatiramer acetate or IFN-beta-1a might be expected to be at similar or higher risk of new lesions than a typical patient treated with placebo. We did not assess certainty of evidence using the GRADE tool for this outcome. Evidence for rituximab included one small RCT and one non-randomised study.

Mortality	We studied all-cause mortality. There were very few deaths in the included studies with a typical duration time of approximately 2 years (30 deaths out of a total of 22 060 patients). Mortality was generally uncommon in the included studies, which reported no statistically significant differences in mortality.
Risk of serious adverse events (SAE)	Rituximab, ocrelizumab and fingolimod were ranked as the best three treatment options for SAE. We estimate probabilities of 94%, 69%, and 65%, respectively, that these are the best of all treatments. We anticipate that 48 of 1000 typical patients treated with rituximab would experience one or more SAE over the duration of a typical trial (approximately 2 years) (95% CI 21 to 110 patients per 1000), compared to 120 per 1000 patients treated with placebo (95% CI 93 to 165 patients per 1000; relative risk 0.40, 95% CI 0.16 to 0.95). Rituximab was estimated to be superior to placebo, cladribine and teriflunomide. The confidence intervals for SAE overlapped across all the other treatments and it is therefore possible that these treatments have similar risk of SAE. Based on the GRADE method for assessing certainty of evidence in NMA, we judged the certainty of evidence for rituximab to be very low due to the reliance on evidence from NRS. We did not assess the certainty of the other treatments.
Risk of treatment withdrawal	Rituximab, natalizumab and alemtuzumab were ranked as the best three treatment options for risk of treatment withdrawal. We estimate probabilities of 92%, 80%, and 74%, respectively, that these are the best of all treatments. We anticipate that 10 of 1000 typical patients treated with rituximab would withdraw from treatment over the duration of a typical trial (approximately 2 years) (95% CI 2 to 43 patients per 1000), compared to 50 of 1000 patients treated with placebo (95% CI 35 to 70 patients per 1000; relative risk 0.19, 95% CI 0.04 to 0.89). Dimethyl fumarate was estimated to be inferior to placebo with respect to this outcome. Based on the GRADE method for assessing certainty of evidence in NMA, we judged the certainty of evidence for rituximab to be low due to the reliance on evidence from NRS. We did not assess the certainty of the other treatments.
Risk of specific serious adverse events	Specific serious adverse events were generally uncommon in the included studies, which reported no statistically significant differences in specific serious adverse events. None of the included studies reported any cases of progressive multifocal leukoencephalopathy (PML). This may be due to the studies being too small or having short duration.

Other aspects for the use of off-label medicine, rituximab

Juridiske aspekter

Rituksimab brukes off label i MS-behandling. Et lignende preparat, ocrelizumab, har markedsføringstillatelse, men er så langt ikke besluttet innført i norsk spesialisthelsetjeneste. Et overordnet spørsmål for det juridiske kapittelet blir om det er noen juridiske problemer eller utfordringer ved fortsatt bruk av rituksimab til MS-behandling når det finnes et lignende preparat for denne behandlingen med markedsføringstillatelse (ocrelizumab).

Ettersom rettskildene er få når det gjelder juridiske aspekter knyttet til off label-bruk av legemidler, har denne delen av metodevurderingen i stor grad måttet lene seg på alminnelige helserettslige prinsipper og generelle momenter og betraktninger vedrørende off label-bruk av legemidler.

Både i norsk rett og i EU-retten, gjøres det et skille mellom retten til å markedsføre legemidler og retten til å forskrive legemidler. Innvilget markedsføringstillatelse innebærer en rett til å selge/markedsføre et preparat i tråd med de vilkår som fremgår av tillatelsen, mens forskrivning av legemidler ligger innenfor legens frie forskrivningsrett. Ettersom legemidler med markedsføringstillatelse har vist at de tilfredsstiller krav til kvalitet, sikkerhet og effekt, for de tilstander som tillatelsen omfatter, vil dette legge føringer for forskrivningen av legemidler. Markedsføringstillatelsen er ikke bindende for forskriver og det er derfor ingen juridiske hindre, utover kravet til forsvarlighet, for om leger kan forskrive rituksimab for MS. Videre kjenner vi ikke til noen bestemmelse som positivt og eksklusivt avgrenser myndighetenes anbefalinger om bruk og forskrivning av legemidler, hvilket betyr at innføring av ocrelizumab i spesialisthelsetjenesten ikke er til hinder for at bruk av rituksimab ved behandling av MS kan anbefales.

EU-retten legger ikke føringer for off label-bruk av legemidler. Ulike stater innad i EU har derfor ulik regulering og praktisering av off label-bruk av legemidler. Men ser vi til Europa er det slik at prinsippet om pasientsikkerhet skal ha presedens over eksempelvis økonomiske hensyn. Det kan argumenteres for at et legemiddel med markedsføringstillatelse skal være foretrukket fremfor off label-preparater, nettopp fordi pasientsikkerheten er bedre ivaretatt gjennom kravene til markedsføringstillatelse. Disse hensynene vil imidlertid ikke i like stor grad gjøre seg gjeldende dersom det viser seg at dokumentasjonen for rituksimabs effekt og sikkerhet ved MS-behandling er tilstrekkelig overbevisende.

Off label-bruk faller inn under pasientskadeerstatningens virkeområde i Norge.

Summary of the assessment

Background

Multiple sclerosis (MS) is an immune-mediated inflammatory disease of the central nervous system (CNS) characterized by demyelination and axonal degeneration (1). It affects axons 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 in the CNS (1).

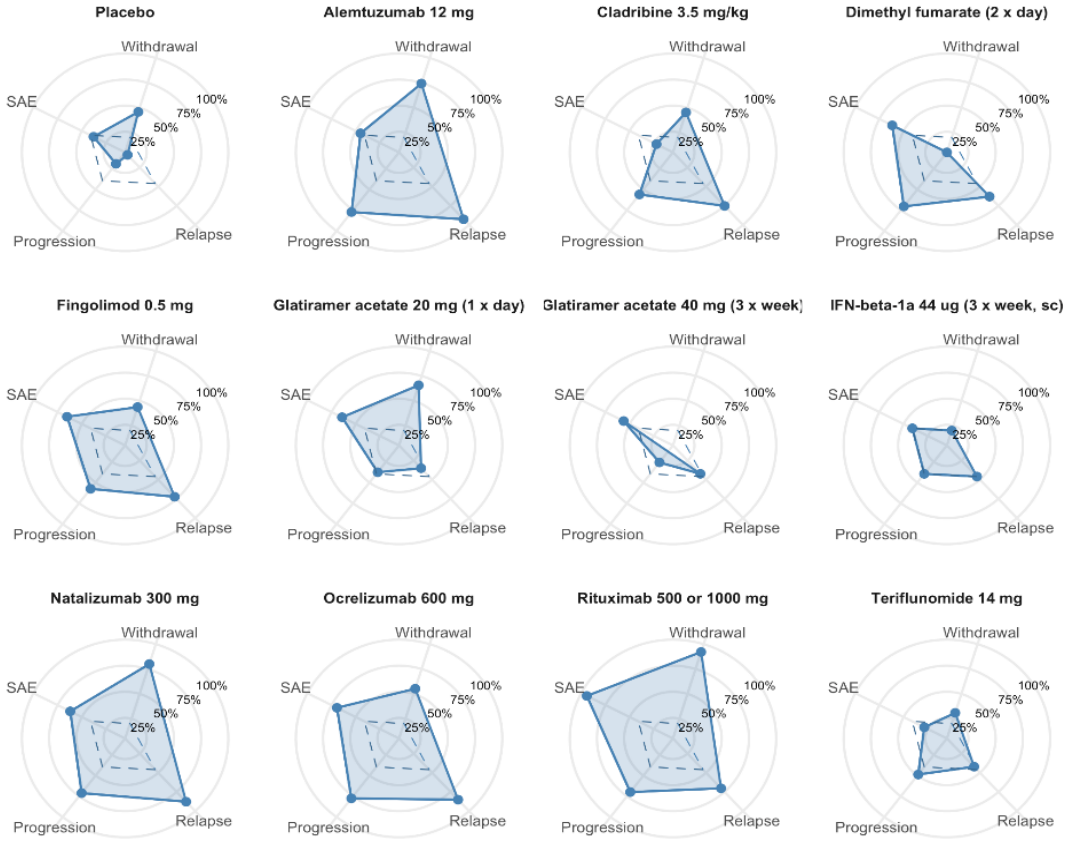
MS is classified into different categories according to course of disease (2). The relapsing-remitting course (RRMS) is the most common, characterised by relapses, followed by complete or partial remission, with stable neurological status until eventually new relapses. Repeated relapses increases the risk of developing a secondary progressive (SPMS) course. A progressive course is characterised by steadily increasing objectively documented neurological disability independent of relapses. Primary progressive multiple sclerosis, PPMS, (a progressive course from disease onset) and secondary progressive multiple sclerosis, SPMS (a progressive course following an initial relapsing-remitting course) are distinguished. Disease-modifying treatments (DMT) are the standard treatment for patients with RRMS.

NIPH conducted a Health Technology Assessment (HTA), including a network meta-analysis, on 11 different medicines for RRMS in 2016 (3). An updated report was commissioned in 2018, requesting that two new medicines with marketing authorisation for RRMS (cladribine and ocrelizumab), as well as rituximab (used off-label for the indication) were added to those included in the 2016 report. Rituximab holds marketing authorisation for several auto immune diseases, such as rheumatoid arthritis, B cell non-Hodgins's lymphomas and a few other types of cancer. Interferons were not included due to low priority use.

Results of safety and clinical effectiveness

Considering all combinations of dose, regimen and method of administration for the treatments of interest and of the controls or comparators reported in the literature, we conducted network meta-analyses of up to 29 different treatments for each outcome. We only present results for the treatments (i.e., combinations of active drug, dose, regimen, and method of administration) considered relevant for Norwegian clinical practice. In addition, we present results on one selected interferon (IFN) for reference purposes. We summarized the results above. In the chapter *Clinical effectiveness and safety*, we present effect estimates for each comparison as well as a ranking list of the included interventions.

Below we present the results as radar plots that show, for each treatment, probabilities that the treatment is superior with respect to the selected outcomes. Treatments with larger polygons are likely to be better than treatments with smaller polygons. Not all outcomes were available for all treatments.



SAE, Serious adverse events; Withdrawal, Treatment withdrawal; Progression, Sustained disability progression; Relapse, Annual relapse rate.

Method

We have performed a Health Technology Assessment in accordance with the handbook "Slik oppsummerer vi forskning", by Norwegian Institute of Public Health (4).

Literature

We performed several systematic searches, described in Methods (*pp 75*). We included both randomised controlled trials (RCT) and registry based non-randomised studies (NRS), 35 and 11 articles, respectively.

Inclusion criteria

Population	Men and women aged 18 and above diagnosed with multiple sclerosis who were treatment naïve or not. The eligible multiple sclerosis diagnoses were relapse-remitting multiple sclerosis (RRMS) at the start of the trial.
Interventions	All disease-modifying treatments approved by the National System for Managed Introduction of New Health Technologies within the Specialist Health Service, including ocrelizumab, except interferons and peg-interferon (due to low priority use). In addition, rituximab was included as an off-label medicine for the indication.
Comparators	All included interventions as well as interferons or placebo.
Outcome	• Annualised clinical relapse rate (ARR) • Risk of confirmed disability progression, defined as a sustained increase in patient's EDSS score (scale from 0.5 to 10). (Typically assessed as disability progression sustained over 12 or 24 weeks (12- or 24-CDP). We chose to estimate a single disability progression outcome, and used the longest confirmation time when a study reported more than one.) • Change in EDSS score • Risk of new lesions (detected using Magnetic Resonance Imaging (MRI)) • Risk of mortality • Risk of serious adverse events (SAE) • Risk of treatment withdrawal due to adverse events (AE) • Risk of selected serious adverse events (cancer, progressive multifocal leukoencephalopathy (PML), thyroid diseases, infections) Annualised relapse rate and confirmed disability progression were the clinical effect estimates used in the health economic evaluation.
Study design	Randomised controlled trials and non-randomised controlled trials (limited to include studies using national- or hospital-based registers, or chart reviews as data source).

Data analyses

We performed network meta-analyses to facilitate multiple treatment comparison via synthesis of all available evidence. We used the GRADE approach for network meta-analysis to assess the certainty of the effect estimates.

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Hovedbudskap

Multippel sklerose er en kronisk sykdom i sentralnervesystemet. Det finnes i dag ingen behandling som kan kurere MS, men det finnes flere legemidler som kan bremse utviklingen av sykdommen.

Vi har systematisk vurdert effekt og sikkerhet av flere av disse legemidlene. Vi har hentet data fra både randomiserte og ikke-randomiserte kontrollerte studier. Vi inkluderte rituksimab i analysene siden dette brukes for MS-behandling i Norge selv om det ikke har markedsføringstillatelse for denne sykdommen.

Vi inkluderte 35 randomiserte kontrollerte studier og 11 ikke-randomiserte kontrollerte studier basert på registerstudier. Vi sammenlignet resultatene for de forskjellige legemidlene ved å bruke nettverksmetaanalyser. I dette arbeidet inngikk det vurderinger og analyser av hvor like de inkluderte studiene er. Der de ikke var like, kunne det forklares.

Basert på tilgjengelige resultater fant vi at alemtuzumab er den beste behandlingen med hensyn på attakkrate, mens ocrelizumab og alemtuzumab sannsynligvis er like gode for å hindre sykdomsprogresjon. Rituksimab hadde lavest risiko for alvorlige bivirkninger og seponering på grunn av bivirkninger, men studiene som lå til grunn for disse resultatene var ikke-randomiserte studier, og tilliten til resultatene er derfor lav.

Rangeringen av behandlingene er basert på tilgjengelige resultat og statistiske modeller, og i mange tilfeller er konfidensintervallet overlappende for de behandlingene som rangeres høyest, hvilket betyr at rangeringene ikke er absolutte størrelser.

De inkluderte studiene rapporterte veldig få dødsfall og også få spesifikke alvorlige bivirkninger som progressive multifocal leukoencephalopathy (PML), kreft, sykdom i skjoldbruskkjertelen og leversykdom. Vi analyserte derfor ikke disse dataene, men telte kun opp antall tilfeller for hver behandling og sykdom.

Resultatene fra attakkrate og sykdomsprogresjon er brukt i en helseøkonomisk analyse og er publisert i en separat rapport.

Tittel
Sykdomsbegrensende legemidler for behandling av attakkpreget multippel sklerose, inkludert rituksimab. En metodevurdering av klinisk effekt og sikkerhet, og en vurdering av juridiske implikasjoner.

Publikasjonstype
Fullstendig metodevurdering som inkluderer klinisk effekt og sikkerhet, og vurdering av juridiske implikasjoner. (Helseøkonomisk analyse og vurdering av etiske implikasjoner er levert i separate dokument.)

Svarer ikke på alt
Vi gir ikke anbefalinger

Hvem står bak denne publikasjonen
Folkehelseinstituttet har gjennomført oppdraget etter forespørsel fra Bestillerforum, Nye metoder.

Når ble litteratursøket utført
Juni 2018

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Preface

This Health Technology Assessment (HTA) was commissioned by The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway (Nye Metoder). The Norwegian Institute of Public Health (NIPH) conducted an HTA, including a network meta-analysis, on 11 different medicines for relapsing remitting multiple sclerosis (RRMS) in 2016 (3). The present HTA was commissioned in 2018, requesting that two new medicines with marketing authorisation for RRMS (cladribine and ocrelizumab), as well as rituximab (used off-label for the indication) were added to those included in the 2016 report. Rituximab holds marketing authorisation for several auto immune diseases, such as rheumatoid arthritis, B cell non-Hodgins's lymphomas and a few other types of cancer.

The following commission was given 03.04.2018: *"Fullstendig metodevurdering gjennomføres ved Folkehelseinstituttet for legemidler, inkludert off label behandlingen rituksimab (Mabthera), til bruk ved multippel sklerose (MS)."* (**ID2018_004).** NIPH initiated the work 15.05.2018 (see progress log in *Appendix 1*).

This HTA includes assessment of safety and effectiveness (this report) and a health economy evaluation of RRMS medicines (separate report), as well as assessment of legal (this report) and ethical (separate document) implications for off-label use of rituximab.

In addition to the authors, the following have contributed to the work of the present report:

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Acknowledgements also go to Wolfgang Vierbauer who suggested the meta-analysis model we generally favoured, and Tim Spelman and co-authors for sharing data from Spelman et al (5).

We will emphasise that although the clinical experts and external reviewers have contributed with valuable input and comments, NIPH is solely responsible for the content of this report.

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Health problem and treatment

Overview of the disease

Multiple sclerosis (MS) (see *Appendix 2* for abbreviations) is an immune-mediated inflammatory disease of the central nervous system (CNS) characterized by demyelination and axonal degeneration (1). It affects axons 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 in the CNS (1).

Risk factors

To date, the most commonly reported risk factors for MS are exposure to Epstein Barr virus, smoking, low sunlight exposure and low vitamin D levels, and genetic predisposition (1;6).

Natural course

The disease usually presents around the age of 30, and prevalence rates peak at around 50 years (7). 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 both to differences in genes and environment.

The course of disease and development of clinical manifestations are characterised by relapses and gradual accumulation of disability. The 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 increments of 0.5 points from 1.0 (8).

Upon attacking the myelin cover of neurons in the brain and spinal cord, the immune system causes tissue damage (lesions) that can be detected by Magnetic Resonance Imaging (MRI). MRI is therefore used both when diagnosing MS, and in monitoring the disease and the treatment in patients with established MS. However, it is still uncertain whether there is a direct correlation between lesions detected by MRI and disability progression (9) although lesion number is a strong predictor for disability progression (10).

Effects of disease

Clinical manifestations of the disease depend on the distribution of affected areas in the CNS. Symptoms and signs reflect the involvement of motor, sensory, visual and autonomic systems (1) and tend to evolve over time. MS presents with different degrees of severity, from a mild form (with few and mild relapses without sequela or progression) to a more aggressive disease that can be highly disabling and impact on the quality of life of patients and their families (1;11).

Clinical management

Diagnosis

MS is classified in different categories according to the course of disease (2). The relapsing-remitting course (RRMS) is the most common, characterised by relapses, followed by fully or partial remission, with stable neurological status until eventually new relapses. Repeated relapses and increasing disability increase the risk of developing secondary progressive MS (SMPS). A progressive course is characterised by steadily increasing objectively documented neurological disability independent of relapses. Primary progressive multiple sclerosis, PPMS, (a progressive course from disease onset) and secondary progressive multiple sclerosis, SPMS (a progressive course following an initial relapsing-remitting course) are the other main categories.

Treatment – current and new

Swift and accurate MS diagnosis allows for early disease management. Disease-modifying treatments (DMT) are the standard treatments for patients with RRMS, used to treat both the underlying disease, relapses, and other MS-related symptoms. The various treatment options have different mechanisms of action, routes of administration, approved indications and other differences influencing their use. Presently, most medicines available only have marketing authorization for the treatment of RRMS. Ocrelizumab is the only pharmaceutical that also has marketing authorisation for PPMS. Due to safety issues, the medicines are classified as either active (dimethyl fumarate, teriflunomide, interferons, glatiramer acetate), or highly active treatments (natalizumab, fingolimod, and alemtuzumab) (12). Norwegian clinical practice guidelines (13) recommend customizing the treatment to individual patients based on the stage of disease or comorbidities. By doing so, there may be a trade-off between a possible disability progression using a less effective medicine with less side effects, and a more potent medicine with more side effects (14).

In this Health Technology Assessment, we evaluate the comparative effectiveness, safety, and cost-effectiveness (separate report) of the established medicines mentioned above, but exclude the interferons due to low priority use. In addition, two new medications are included, cladribine and ocrelizumab. We also include rituximab, a medicine with marketing authorisation for several autoimmune diseases, B cell non-Hodgins's lymphomas and a few types of cancer, and which is used off-label in MS-patients in several countries. This off-label use is controversial, and we will therefore address legal

perspectives in this report. See detailed description of medicines in the Method chapter (*pp 76*).

Treatment risks

Treatment of MS can have unintended consequences such as an increased risk for infections or of autoimmune disease.

One acknowledged risk of DMTs is progressive multifocal leukoencephalopathy (PML). PML is caused by infection of the brain with John Cunningham virus (JCV) that destroys the myelin sheaths of nerves in patients with decreased function of the immune system. When PML occurs in MS, approximately 25% of patients die within 6 months and the survivors have increased long-term disability (15). Natalizumab is recognized as an effective therapy for RRMS, but PML is associated with its use (16).

Alemtuzumab has been associated with thyroid disorders, and a phase III clinical trial showed a 5-year incidence of thyroid adverse events of up to 40.7% (summarised in a Belgian consensus group on diagnosis and management of thyroid disorders in alemtuzumab (17)).

Another condition recently linked to alemtuzumab is haemophagocytic lymphohistiocytosis (HLH), a highly aggressive and potentially fatal syndrome of excessive inflammation (18). Acquired forms of HLH are likely caused by having a predisposing condition, such as immunodeficiency or an autoimmune disease, and being subjected to a trigger, often a viral infection (18;19). The hyper inflammatory state of HLH is thought to be a result of dysregulation of the immune system, where there is a defect in the downregulation of activated immune cells (18;20). The immune cells continue to produce cytokines, which drive inflammation, causing further tissue and organ damage (18;20). If treated, there is about 50% chance of survival, whereas it will most likely be fatal if left untreated (21). Recently, there have been emerging reports of fatal or life-threatening cases of HLH (22), as well cardiovascular events (such as pulmonary haemorrhage (23), cardiac infarction, stroke, and cervicocephalic arterial dissection) and other immune-mediated conditions (such as hepatitis) (24;25). Because of this, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicine Agency (EMA) initiated a revision of alemtuzumab (Lemtrada), and healthcare professionals have been advised to temporarily restrict the use of alemtuzumab in new patients diagnosed with MS (24).

Other life-threatening risks of DMTs include autoimmune hepatitis and autoimmune blood disorders (14). Often, DMTs that are effective at slowing the progression of MS may also have higher risk for these unintended and life-threatening consequences (14).

Target population

Prevalence and incidence estimates for MS tend to be higher in the Northern countries, and incidence surveys show an increase in MS incidence in Norway in later years (26). Crude overall prevalence rate in Norway per 2014 was 203/100 000 (95% CI 199 to 207) with more than twice as many women as men affected (27). The gender bias has also been reported in other European countries (28) and other parts of the world. The

increase over time in MS incidence could be due, to some extent, to changes in diagnostic methods and criteria (7).

The estimated number of persons diagnosed with MS in Norway per 2013 was 10 628 (26), about 9 000 with RRMS (85%). Norwegian guidelines recommend initiating disease-modifying treatment in these patients immediately after diagnosis (13).

Study selection for assessment of clinical effectiveness and safety

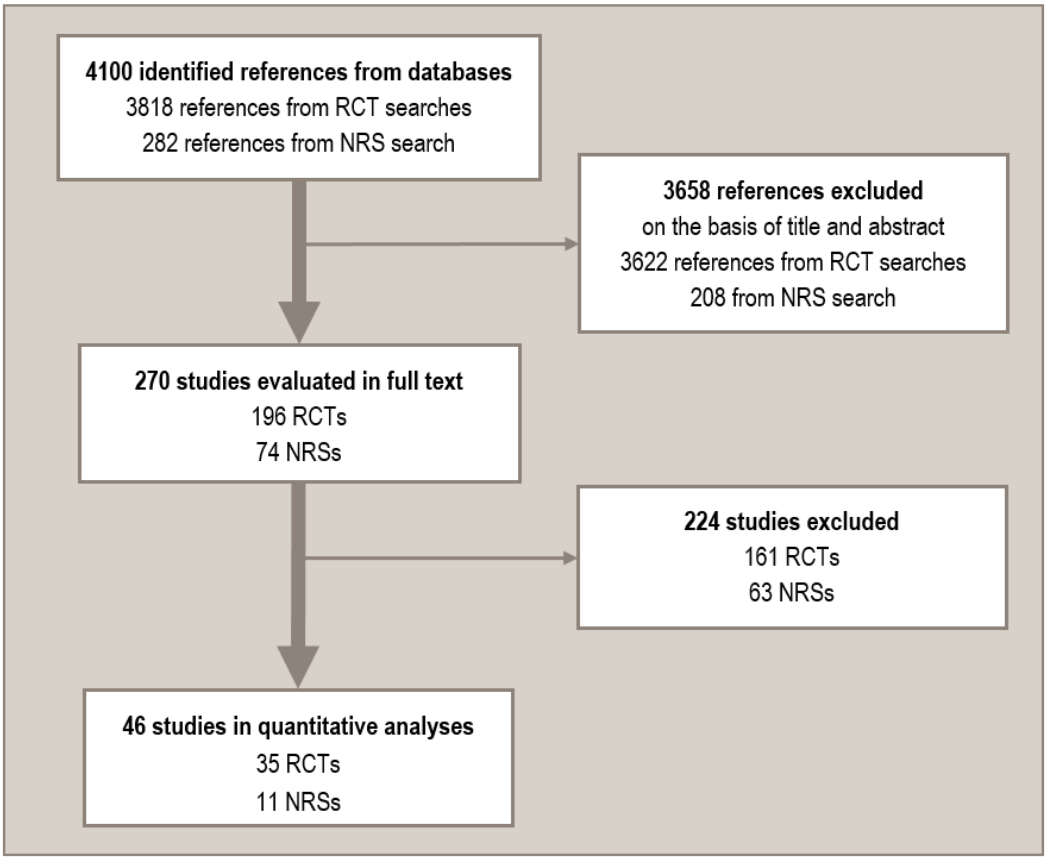
Objective

To search, identify and select literature for the analyses of clinical effectiveness and safety of disease-modifying treatments for patients with RRMS.

Literature search and selection of studies

We performed several searches according to the project plan (*Appendix 3*), described in Methods (*pp 75*). We included both randomised controlled trials (RCT) and registry studies (non-randomised studies, NRS) with comparator (35 and 11, respectively). See flow chart of article selection (*Figure 1*).

Figure 1. *Flow chart of article selection.*



RCT, randomised controlled trial; NRS, non-randomised study

Ongoing studies and ECTRIMS 2018 abstracts

We performed a search in trial registries for ongoing, terminated or unpublished studies and we did a manual search in the ECTRIMS (European Committee for Treatment and Research in Multiple Sclerosis) abstracts from 2018 in order to identify relevant studies.

We found 22 relevant ongoing clinical trials with more than 100 participants, and 32 abstracts from ECTRIMS 2018 fulfilling the inclusion criteria.

Description of included studies

The overall sample included 22 580 participants in 30 RCTs (35 articles) and data from 8 760 persons from 11 registry studies. Included studies are described in *Table 1*, and further details are found in *Appendix 4* (RCT) and *Appendix 5* (NRS). Detailed results of the risk of bias assessment of both RCTs and NRS are found in *Appendix 6*. For one of the studies we requested and received data from the study authors, which we used in our analysis (5) (*Appendix 7*). In *Appendix 8* we present excluded articles with reasons for exclusion.

Table 1. *Included RCTs and NRS for analyses of clinical effectiveness and safety*

ST	Study	Interventions and comparisons	End of study/ History*	RoB**
ALEMTUZUMAB (i.v.)				
R	**CAMMS223 (Coles 2008** (29)**);** NCT00050778; RCT; Phase 2	Alemtuzumab 12 mg, n=113 Alemtuzumab 24 mg, n=110 IFNβ-1a 44 ug (s.c.), n=111	3 years / Treatment-naive	+
R	**CARE MS II (Coles 2012** (30)**);** NCT00548405; RCT; Phase 3	Alemtuzumab 12 mg, n=436 Alemtuzumab 24 mg, n=173 IFNβ-1a 44 ug (s.c.), n=231	2 years / Treatment-experienced	+
R	**CARE-MS I (Cohen 2012** (31)**);** NCT00530348; RCT; Phase 3	Alemtuzumab 12 mg, n= 386 IFNβ-1a 44 ug (s.c.), n=195	2 years / treatment-naive	+
CLADRIBINE (oral)				
R	**CLARITY (Giovannoni 2010** (32)**, Cook 2011** (33)**, Comi 2013** (34)**);** NCT00213135; RCT; Phase 3	Cladribine 3,5 mg/kg, n=433 Cladribine 5,25 mg/kg, n=456 Placebo, n=437	8 years / Mixed	+
DIMETHYL FUMARATE, DF (oral)				
R	**DEFINE (Gold 2012** (35)**);** NCT00420212; RCT; Phase 2	Dimethyl fumarate 240 mg, n = 411 Placebo: n = 410	2 years / Mixed	+
R	**CONFIRM (Fox 2012** (36)**)** NCT00451451; RCT; Phase 3	Dimethyl fumarate 240 mg, n=359 Glatiramer acetate 20 mg, (s.c.), n=350 Placebo (oral), n=363	2 years / Mixed	+
N	**Ernst 2017** (37); Chart review; medical charts; Multicentre, USA	Dimethyl fumarate n=307 IFNβ-1a (s.c), n=143	2 years / Mixed	+
FINGOLIMOD (oral)				
R	**FREEDOMS (Kappos2010** (38)**);** NCT00289978; RCT; Phase 3	Fingolimod 0.5 mg, n = 425 Fingolimod 1.25 mg, n = 429 Placebo, n = 418	2 years / Mixed	+
R	**FREEDOMS II (Calabresi 2014** (39)**);** NCT00355134; RCT; Phase 3	Fingolimod 0.5 mg, n=358 Fingolimod 1.25 mg, n=370 Placebo, n=355	2 years / Mixed	+
R	**Saida 2012** (40)**;** NCT00537082); RCT; Phase 2	Fingolimod 0.5 mg, n=57 Fingolimod 1.25 mg, n=57 Placebo, n=57	0.5 years / Unclear	+

ST	Study	Interventions and comparisons	End of study/ History*	RoB**
R	**TRANSFORMS (Cohen 2010** (41)**);** NCT00340834; RCT; Phase 3	Fingolimod 0.5 mg, n=436 Fingolimod 1.25 mg, n=431 Interferon β-1a 30 ug (i.m.): n=435	1 year / Mixed	+
R	**GOLDEN (Comi 2017** (42)**);** NCT1333501; RCT; Pilot	Fingolimod 0.5 mg, n=106 Interferon β-1b 250 ug (s.c.), n=51	1.5 years / Mixed	−
GLATIRAMER ACETATE (s.c.)				
R	**BEYOND (O'Connor 2009** (43)**);** NCT00099502; RCT; Phase 3	Glatiramer acetate 20 mg, n=448 IFNβ-1b 250 ug, n=897 IFNβ-1b 500 ug, n=899	2-3,5 years / Treatment-naive	+
R	**CombiRx (Lublin 2013** (44)**, Lublin 2017** (45)**);** NCT00211887; RCT; Phase 3	Glatiramer acetate 20 mg **+** IFNβ-1a 30 ug (i.m.), n=499 Glatiramer acetate 20 mg **+** placebo (i.m.), n=259 Placebo (s.c.) **+** IFNβ-1a 30 ug (i.m.), n=250	3 years / Treatment-naïve	+
R	**GALA (Khan 2013** (46)**);** RCT; Phase 3	Glatiramer acetate 40 mg: n=943 Placebo, n=461	1 year / Mixed	+
R	**Calabrese 2012** (47)**, Rinaldi 2015** (48); RCT; Phase 4	Glatiramer acetate 20 mg, n = 55 IFNβ-1a 44 ug, n = 55 IFNβ-1a 30 ug (i.m.), n = 55 Reference population, n=50	2 years / Unclear	+
R	**Comi 2001** (49)**;** RCT; Double-blind	Glatiramer acetate 30 mg, n=119 Placebo, n=120	9 months / Unclear	+
R	**Johnson 1995** (50)**;** RCT; Phase 3	Glatiramer acetate 20 mg, n =125 Placebo, n=126	2 years / Treatment-naive	+
R	**REGARD (Mikol 2008** (51)**);** NCT00078338; RCT	Glatiramer acetate 20 mg, n=378 IFNβ-1a 44 ug, n=386	8 years / Treatment-naive	+
R	**GATE (Cohen 2015** (52)**);** NCT01489254; RCT; Phase 3	Glatiramer acetate generic 20 mg, n=355 Glatiramer acetate brand 20 mg, n=357 Placebo, n=84	9 months / No information	?
R	**Boiko 2018** (53)**;** RCT; Phase 3	Glatiramer acetate (BCD-063) 20 mg, n=61 Glatiramer acetate (Copaxone) 20 mg, n=61 Placebo, n=28	2 years / Unclear	?
N	**Kalincik 2015b** (54); ACTRN12605000455662; Observational study, MS-register; Multicentre (49 centres), 22 countries	Glatiramer acetate, n=482 IFNβ-1a (i.m.), n=832 IFNβ-1a (s.c.), n=1379 IFNβ-1b, n=633	3,7(2,2-6,3) years / Treatment-naïve	+
NATALIZUMAB (i.v.)				
R	**AFFIRM (Polman 2006** (55)**);** NCT000273; RCT; Phase 3	Natalizumab 300 mg, n=627 Placebo, n=315	Unclear	+
R	**Gobbi 2013** (56)**, Zecca 2014** (57)**;** NCT01144052); RCT; Pilot	Natalizumab 300 mg, n=10 IFNβ-1b 250 mg (s.c.), n=9	Treatment experienced	+
R	**Saida 2017** (58)**;** NTC01440101; RCT; Phase 2	Natalizumab 300 mg, n=47 Placebo, n=47	0.5 years	+
R	**RESTORE (Fox 2014** (59)**);** NCT01071083; RCT; Phase 4	Natalizumab 300 mg, n=45 IFNβ1a (i.m.), n=17. Glatiramer acetate (i.m.), n=17 Methylpresnisolone, n=54	0.5 years / Mixed	+
N	**Frisell 2016** (60); Observational study; MS-register; Sweden	Natalizumab, n=640 Fingolimod, n=876	1 year / Mixed	+
N	**Guger 2018** (61); Observational study; MS-register (AMSTR), Austria	Natalizumab, n=246 Fingolimod, n=332	24 months / Mixed	+
N	**Kalincik 2015a** (62) ACTRN12605000455662; Observational study, MS-register; Multicenter (66 centres), 26 countries	Natalizumab, n=407 Fingolimod, n=171	Natalizumab: 21 (12-34) months; Fingolimod: 14 (8-20) months / Treatment-experienced	+
N	**Koch-Henriksen 2017** (63); Observational study; MS-register; Denmark	Natalizumab: n=464 Fingolimod: n=464	≤3,75 years / Mixed	+
N	**Lanzillo 2017** (64); Observational study; MS-centre; Italy	Natalizumab, n=108 Fingolimod, n=71	24 months / Mixed	+

ST	Study	Interventions and comparisons	End of study/ History*	RoB**
N	**Prosperini 2017** (65); Observational study; MS-centre; Italy	Natalizumab, n=150 Fingolimod, n=150 IFNβ/glatiarmer acetate, n=150	24 months / Mixed	+
OCRELIZUMAB (i.v.)				
R	**OPERA I and II (Hauser 2017** (66)**);** NCT01247324m NCT01412333; RCT; Phase 3	**OPERA I:** Ocrelizumab 600 mg, n=410 IFNβ-1a 44 ug (s.c.), n= 411 **OPERA II:** Ocrelizumab 300 mg, n=417 IFNβ-1a 44 ug (s.c.), n=418	8 years / Mixed	+
R	**Kappos 2011** (67)**;** NCT00676715; RCT; Phase 2	Ocrelizumab 600 mg, n=56 Ocrelizumab 2000 mg, n=55 Placebo, n=54	0.5 (1) year) / Mixed	−
RITUXIMAB (i.v.)				
R	**Hauser 2008** (68)**;** NCT00097188; RCT; Phase 2	Rituximab 1000 mg, n=69 Placebo, n=35	48 weeks / Mixed	−
N	**STOPMS (Alping 2016** (69)**);** Observational study; MS-register; Multicentre (3 centres), Sweden	Rituximab, n=114 Fingolimod, n=142	Rituximab: 1,24 years; Fingolimod**:** 1,82 years / Treatment-experienced	+
N	**Spelman 2018** (5); Observational study; MS-register; Sweden	Rituximab, n=461	2 years / Treatment-experienced	+
N	**Granqvist 2018** (70); Observational study; MS-register; Multicentre (3 centres), Sweden	Rituximab, n=120 Natalizumab, n=50 Dimethyl fumarate, n= 86 Fingolimod, n=17 IFNβ + glatiramer acetate, n=215	Treatment-naïve Follow-up: ≥ 7 months to ≤ 4,33 years	+
TERIFLUNOMIDE (oral)				
R	**TEMSO (O'Connor 2011** (71)**);** NCT00134563; RCT; Phase 3	Teriflunomide 7 mg, n=365 Teriflunomide 14 mg, n=358 Placebo, n=363	Mixed	+
R	**TENERE (Vermersch 2014** (72)**);** NCT00883337; RCT; Phase 3	Teriflunomide 7 mg, n=109 Teriflunomide 14 mg, n=111 IFNβ-1a 44 ug (s.c.), n=104	Up to 48 weeks/ Mixed	+
R	**TOWER (Confavreux 2014** (73)**);** NCT00751881; RCT; Phase 3	Teriflunomide 7 mg, n=408 Teriflunomide 14 mg, n=372 Placebo, n=389	Up to 48 weeks/ Mixed	+

ST, study type; R, randomised controlled trials (RCT); N, non-randomised study; S.c., subcutaneous; i.v., intravenous; RoB, Risk of Bias

* "History" refers to the treatment history.

** Overall risk of Bias assessment result (+, low risk of bias; −, high risk of bias; ?, unclear risk of bias);

Ongoing studies

We found 22 ongoing RCTs in the trial registries representing a total of 57 236 planned or recruited participants. The largest ongoing study is an 8-year observational cohort study on the safety of natalizumab (n=34 600), planned to finish by 2023. Ocrelizumab is the main medicine in six studies with a total of 4 386 participants, while three studies include rituximab (n=4 800) in comparison with multiple other treatments. The full list of relevant ongoing clinical trials is in *Appendix 9*.

Abstracts from ECTRIMS 2018

The 32 relevant abstracts included a total of 463 738 participants. The studies with the higher representation both focused on safety outcomes, and were on dimethyl fumarate (n=241 031) and natalizumab (n=180 656). We did not check for overlapping abstracts with the included studies for quantitative analyses. The full list of relevant abstracts from the ECTRIMS is found in *Appendix 10*.

Clinical effectiveness and safety

Objectives

To assess effectiveness of disease-modifying treatments for RRMS, based on annual relapse rate, disability progression and new lesions detected by magnetic resonance imaging (MRI).

To assess safety of disease-modifying treatments for RRMS, based on risk of mortality, risk of serious adverse events, rate of treatment withdrawal due to adverse events, and risk of specific rare serious adverse events.

How we present the findings

All combinations of dose, regimen and method of administration of the included active drugs, as well as the comparators placebo and untreated, were modelled as distinct treatments (analyses included evidence on up to 29 treatments). However, we only present results for treatments considered relevant for Norwegian clinical practice (i.e. dosages in accordance with the Norwegian Pharmaceutical Product Compendium (Felleskatalogen)). In addition, we present results on placebo and one selected interferon (IFN) for reference purposes. The following table defines treatment names and their abbreviations used in this chapter. Dosages, regimens, and administration methods are excluded from the treatment name if they did not vary within drug name across the included studies.

Treatments with notations shown in this chapter See *Table 10* for complete posology.	**Short name used in this chapter**
• Alemtuzumab, 12 mg, i.v.	Alemtuzumab
• Cladribine, 3.5 mg/kg	Cladribine
• Dimethyl fumarate, 240 mg x 2/day	Dimethyl fumarate
• Fingolimod, 0.5 mg x 1/day	Fingolimod
• Glatiramer acetate, 20 mg, 1 x day, s.c.	GA 20 mg
• Glatiramer acetate, 40 mg, 3 x week, s.c.	GA 40 mg
• IFN-beta-1a, 44 ug, 3 x week, s.c.	IFN-beta-1a
• Natalizumab, 300 mg, i.v.	Natalizumab
• Ocrelizumab, 600 mg, i.v.	Ocrelizumab
• Rituximab, 500 or 1000 mg, i.v.	Rituximab
• Teriflunomide, 14 mg x 1/day	Teriflunomide

We included one RCT that studied a 1000 mg dose of rituximab (68). The one included NRS of rituximab did not clearly report on dose, and our understanding is that some patients may have received the 1000 mg dose, while others may have received 500 mg. Based on advice from our clinical experts, we chose to consider rituximab as a single

treatment in the network meta-analyses. However, this difference is a potential source of heterogeneity in our results.

For each outcome, we present:

- A table summarising the findings comprising relative and absolute anticipated treatment effect estimates, and estimated ranks and P-scores for the treatments of interest (74). A P-score quantifies the extent of certainty that a particular treatment is better than all other competing treatments. A P-score of 0.90 for treatment A, for example, can be roughly interpreted as follows: based on the available evidence and the assumed model, the probability that treatment A is better than all other treatments is 90%. We state results using this interpretation of the P-score. If treatment A has a P-score of 0.90 and treatment B has a P-score of 0.50, there is reasonably good evidence that treatment A is better than treatment B, but some uncertainty remains, and it remains possible that treatment B is better than treatment A. In simple terms, treatments with larger P-scores are probably better than treatments with smaller P-scores. The P-score is a frequentist equivalent to the Bayesian SUCRA value that is also used in network meta-analysis.
- A forest plot with point estimates (dots) and 95% confidence intervals (black lines) for the mean absolute anticipated effect estimates, and 95% prediction intervals (blue bands), for the treatments of interest. In the forest plots, a confidence interval quantifies the uncertainty on the estimate of mean absolute anticipated effect (more precisely in the context of the random effects models used, a confidence interval quantifies the uncertainty on the mean of the distribution of absolute effects). In the forest plots, a prediction interval quantifies the range of values that comparable future studies would likely report (which, due to the play of chance and other factors, may differ from the point estimate).
- A forest plot showing the network meta-analysis model fitted to the extracted data. These plots show the means and 95% CIs extracted from the included studies (RCT data are shown in blue; NRS data are shown is red), and the fitted model as point estimates of absolute anticipated treatment effect (black dots) and 95% confidence intervals on the point estimates (black lines), and 95% prediction intervals (black vertical lines). Model fits are adjusted for RCT rather than NRS evidence.
- A matrix plot that shows relative treatment effect estimates for each pair of the treatments of interest. Treatment comparisons with confidence intervals excluding no treatment effect are color-coded to indicate the treatment which is favoured. However, a confidence interval that includes no effect should not be interpreted to mean that there is no treatment effect, but that we lack sufficient evidence to estimate the effect more precisely.

For each treatment of interest, we also present a radar plot of P-scores for the following outcomes to facilitate treatment comparison across multiple effectiveness and safety

outcomes in a single figure: annualised relapse rate, risk of disability progression, risk of serious adverse event, and risk of study withdrawal due to adverse event.

In appendices for each outcome, we additionally show:

- The network of evidence
- The complete ranking list of all treatments included in the network meta-analyses (NMA)
- Selected transitivity assessments
- Inconsistency assessment, i.e. estimates with 95% confidence intervals from network meta-analyses that assume there is no difference between RCT and NRS evidence (naïve), and which exclude NRS evidence, and the network meta-regression (i.e. the model that accounts for possible differences between RCT and NRS evidence)
- Detailed information about the GRADE assessment

Network meta-analysis, NMA

Conventional meta-analysis synthesises evidence from studies that each compare a single pair of treatments (e.g. a treatment of interest versus placebo). NMA is a generalisation of conventional meta-analysis to the case where there are multiple treatments, and therefore multiple pairs of treatments that may be compared. In the common case, each study included in an NMA directly compares some but not all treatments, and the studies form a network of evidence (i.e., each trial studies at least one treatment that is also studied by at least one other trial). See Methods (*p 81*) for more details about network meta-analysis. Where we observe inconsistency between the various forms of evidence, we comment on possible sources of intransitivity.

Certainty of evidence

We evaluated the certainty of the estimates of annual relapse rate and risk of disability progression using the GRADE-NMA approach (75;76).

We used GRADE to assess the certainty of all *direct estimates* in the meta-analytical network (not shown). Further, we show the details of the assessment of the estimates of the *network meta-analysis estimate* of the included treatments compared to placebo (shown under the appendices for the given outcome). The final GRADE-classification is presented in the summary of findings tables. We did not rate the certainty of evidence for all treatments for the other outcomes. To provide certainty of evidence statements for rituximab (given it is a treatment of particular interest in this report), we GRADEd this treatment if it was ranked among the three best treatments for the other outcomes we report.

Annualised relapse rate

We included data from 38 studies of which 31 were RCTs. The analyses included 27 treatments, including placebo and untreated, 99 study arms, 28 856 patients and 60 448 patient years of follow-up (*Figure 2*).

Annualised relapse rate (ARR) was modelled on the log rate scale and is presented as ARRs with 95% confidence intervals (CI) and 95% prediction intervals (*Figure 3*). Data extracted from the included studies and the fitted network meta-regression model are shown in *Figure 4*. We judged that network estimates are consistent with pairwise meta-analysis estimates based on direct RCT evidence (where placebo or IFN-beta-1a are used as the comparator). Relative treatment effect estimates are reported as annualised relapse rate ratios (ARRRs; *Figure 5*).

The summary of findings table (*Table 2*) presents effect estimates ranked by P-score and includes the certainty of evidence assessment. Details of the NMA as well as a complete ranking list of all 27 interventions used in the analyses are presented in *Appendix 11.*

Alemtuzumab, natalizumab and ocrelizumab were ranked as the best three treatments with respect to this outcome. We estimate probabilities of 93%, 88% and 85%, respectively, that these are the best of all treatments. We anticipate that a typical patient treated with alemtuzumab would experience 0.14 relapses per year (95% CI 0.10 to 0.20 relapses per year) compared to 0.53 relapses per year if they were treated with placebo (95% CI 0.44 to 0.64 relapses per year; annualised relapse rate ratio 0.27, 95% CI 0.19 to 0.40). However, the 95% CI for alemtuzumab overlaps with those for natalizumab (0.13 to 0.22 relapses per year), ocrelizumab (0.13 to 0.25 relapses per year), cladribine (0.17 to 0.30 relapses per year), fingolimod (0.19 to 0.29 relapses per year) and rituximab (0.12 to 0.44 relapses per year). It is therefore possible that these treatment options have similar efficacy with respect to this outcome.

Based on the GRADE method for assessing certainty of evidence in NMA, we judged the certainty of evidence for alemtuzumab, ocrelizumab, and rituximab to be low due to reliance on evidence from NRS.

Figure 2. *Study design and sample sizes for annualised relapse rate*

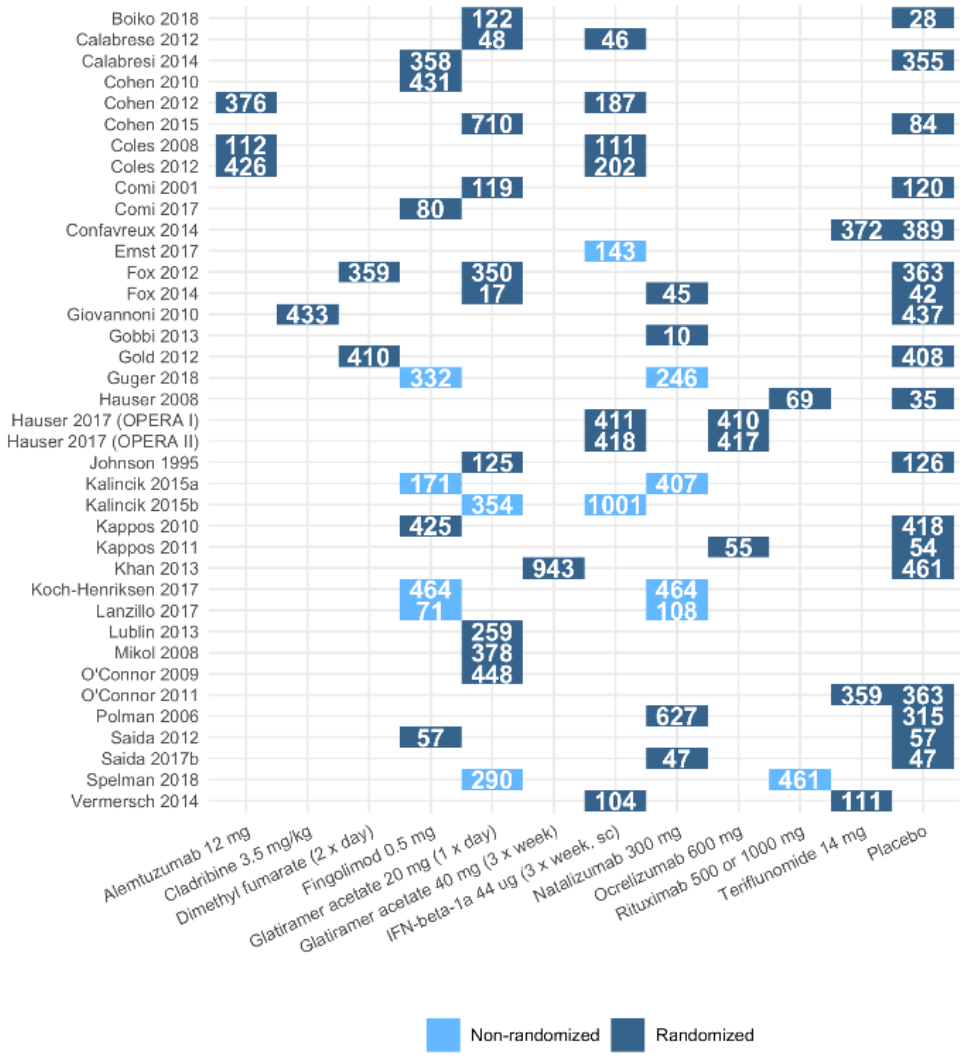


***Figure 3**. Network meta-regression estimates of annualised relapse rate*

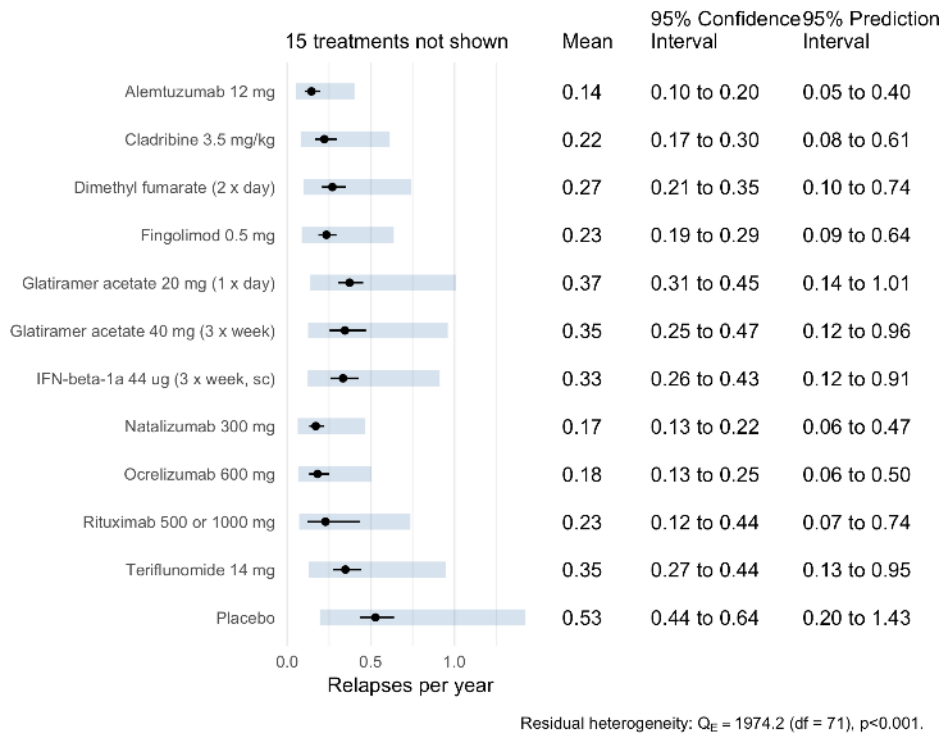


***Figure 4.** Network meta-regression of annual relapse rate with results from each included study*

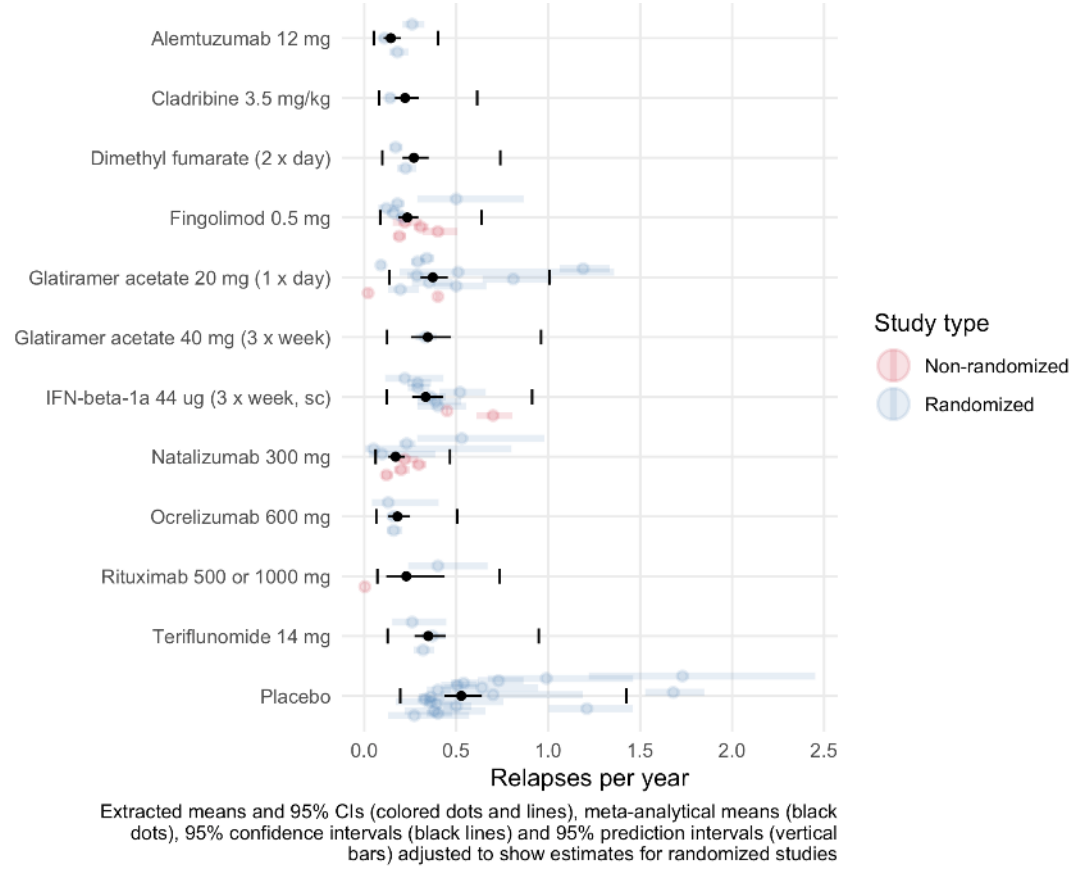


Figure 5. *Effect estimates of annualised relapse rate ratios (95% confidence intervals in parentheses).*

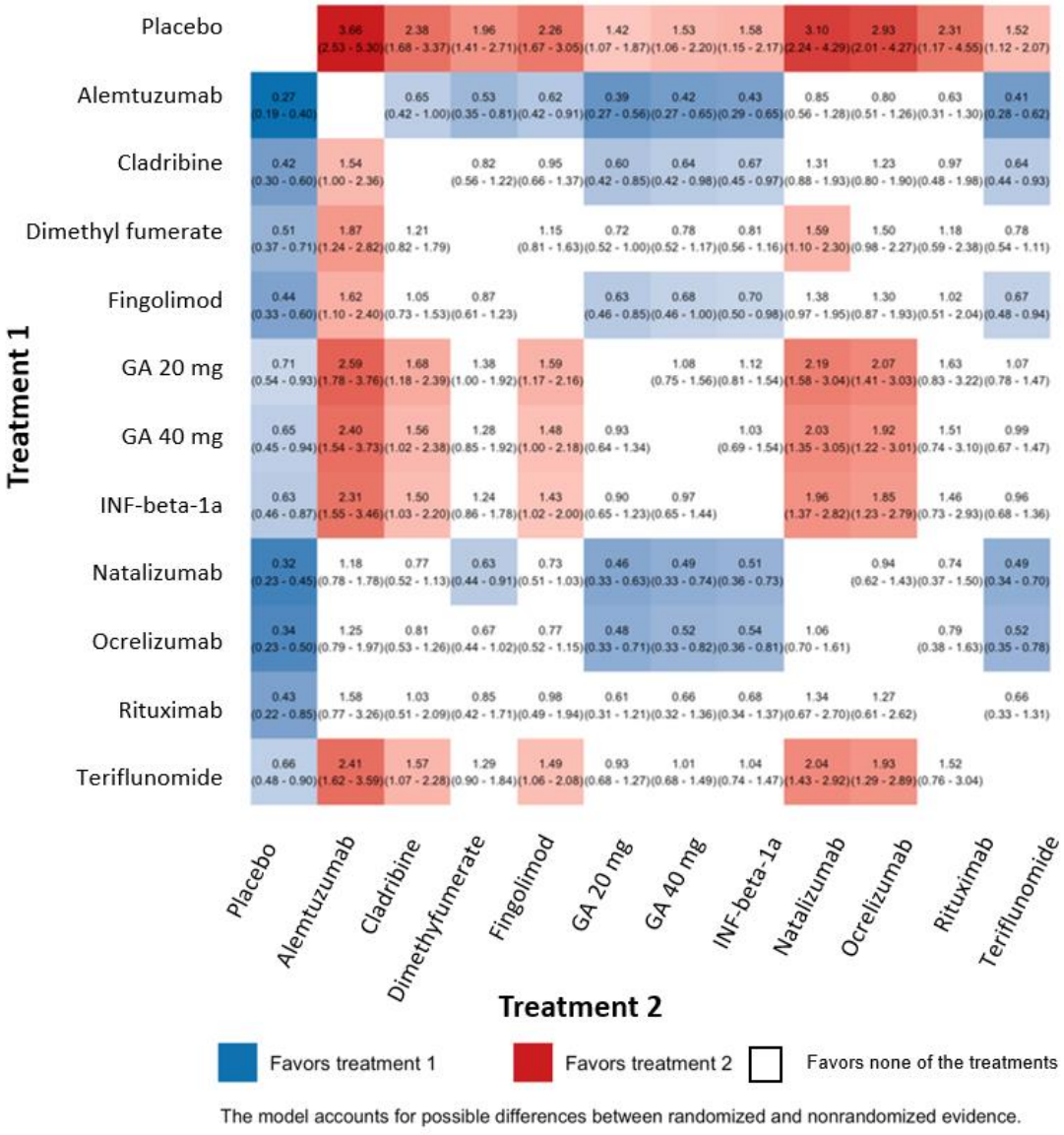


Table 2. *Summary of findings for annualised relapse rate (treatments are ordered by rank)*

Treatment* *Study type, participants, person years*	**Annualised relapse rate ratio** (95% CI)**	**Anticipated annualised relapse rate (95% CI)**			**Certainty of evidence**	**Rank**** **(P-score)**
		With placebo	**With treatment**	**Difference*** (95% CI)**		
Alemtuzumab *3 RCT n=914; PY=1940*	**0.27** (0.19 to 0.40)	0.53 relapses/year	0.14 relapses/year	-0.38 relapses/year (-0.42 to -0.33)	⊕⊕◯◯ LOW[1]	**2** (0.93)
Natalizumab *4 RCT; 4 NRS n=1 945; PY=4 162*	**0.32** (0.23 to 0.45)	0.53 relapses/year	0.17 relapses/year	-0.36 relapses/year (-0.40 to -0.31)	⊕⊕⊕⊕ HIGH	**3** (0.88)
Ocrelizumab *3 RCT N=882; PY=1 552*	**0.34** (0.23 to 0.50)	0.53 relapses/year	0.18 relapses/year	-0.35 relapses/year (-0.40 to -0.28)	⊕⊕◯◯ LOW[1]	**4** (0.85)
Cladribine *1 RCT n=433; PY=799*	**0.42** (0.30 to 0.60)	0.53 relapses/year	0.22 relapses/year	-0.31 relapses/year (-0.36 to -0.23)	⊕⊕⊕⊕ HIGH	**6** (0.75)
Fingolimod *5 RCT; 4 NRS n=2 389; PY=4 863*	**0.44** (0.33 to 0.60)	0.53 relapses/year	0.23 relapses/year	-0.29 relapses/year (-0.34 to -0.23)	⊕⊕⊕◯ MODERATE[2]	**8** (0.72)
Rituximab *1 RCT; 1 NRS n=530; PY=988*	**0.43** (0.22 to 0.85)	0.53 relapses/year	0.23 relapses/year	-0.30 relapses/year (-0.41 to -0.09)	⊕⊕◯◯ LOW[1]	**9** (0.70)
Dimethyl fumarate *2 RCT n=769; PY=1 538*	**0.51** (0.37 to 0.71)	0.53 relapses/year	0.27 relapses/year	-0.26 relapses/year (-0.32 to -0.18)	⊕⊕⊕⊕ HIGH	**11** (0.63)
IFN-beta-1a *7 RCT; 2 NRS n= 2623; PY=6 819*	**0.63** (0.46 to 0.87)	0.53 relapses/year	0.33 relapses/year	-0.19 relapses/year (-0.27 to -0.10)	⊕◯◯◯ VERY LOW[1,3]	**13** (0.46)
GA 40 mg *1 RCT n=943; PY=943*	**0.65** (0.45 to 0.94)	0.53 relapses/year	0.35 relapses/year	-0.18 relapses/year (-0.27 to -0.06)	NA	**14** (0.42)
Teriflunomide *3 RCT n=842; PY=1 192*	**0.66** (0.48 to 0.90)	0.53 relapses/year	0.35 relapses/year	-0.18 relapses/year (-0.25 to -0.09)	⊕⊕⊕◯ MODERATE[3]	**15** (0.42)
GA 20 mg *10 RCT; 2 NRS n=3 220; PY=6 721*	**0.71** (0.54 to 0.93)	0.53 relapses/year	0.37 relapses/year	-0.15 relapses/year (-0.22 to -0.07)	⊕⊕⊕◯ MODERATE[3]	**18** (0.35)

RCT, randomised controlled trial; NRS, non-randomised studies; n, total number of patients; PY, person years; CI, Confidence Intervals; GA, glatiramer acetate; NA, not assessed

* See doses for the treatments at the beginning of the chapter

** Relative effect is annualised relapse rate ratio; CIs account for uncertainty on the effect of treatment and placebo

*** CIs on anticipated differences do not account for uncertainty on the effect of placebo

**** Ranked from best (rank 1) to worst by P-score. 15 treatments are not shown and the ranking is therefore not continuous. All treatments are shown in the appendix.

[1]NRS contributes to the dominant loop-evidence; [2]Inconsistency in dominant direct estimate contributing; [3]Imprecision in the network estimate

Risk of confirmed disability progression (CDP)

We included data from 26 studies of which 19 were RCTs. The studies included 24 treatments, 64 study arms, 22 470 patients and 47 485 patient years of follow-up (*Figure 6*).

There is greater variation in the definition of CDP than for relapse. Studies typically confirm progression after 12 or 24 weeks (12- and 24-CDP). Evidence from a network meta-analysis of disease-modifying drugs for relapsing-remitting multiple sclerosis by McCool et al. (77) that analysed 12- and 24-CDP as separate outcomes showed that the two definitions lead to statistically similar meta-analytical estimates of relative treatment effect. The OPERA I and II trials (66) assessed both 12- and 24-CDP, and reported hazard ratios that are identical to two decimal places. The literature appears to acknowledge that the two definitions attempt to measure the same underlying concept, but it is debated which definition best measures that concept (78). We chose to model a single disability progression outcome, and preferentially used the longest confirmation time when more than one was available.

Risk of confirmed disability progression (CDP) was modelled on the log risk scale and is presented as the number of patients, per 1000, who would be expected to experience disability progression over the duration of a typical trial (approximately 2 years; *Figure 7*). Results from each included study are shown in *Figure 8*. For all treatments, the network meta-regression estimates were consistent with pairwise meta-analysis estimates based on direct RCT evidence (i.e., the 95% confidence intervals overlapped). Relative treatment effect estimates are reported as risk ratios (RRs; *Figure 9*).

The summary of findings table (*Table 3*) presents the effect estimates in ranked order (selected treatments compared to placebo), including the certainty assessments. Details of the analyses as well as a complete ranking list of all interventions used in the analyses are presented in *Appendix 12*.

Ocrelizumab and alemtuzumab were ranked joint best of the treatment options for this outcome, and natalizumab second best. We estimate probabilities of 77%, 77%, and 71%, respectively, that these are the best of all treatments. We anticipate that 86 per 1000 typical patients treated with ocrelizumab would experience disability progression over the duration of a typical trial (95% CI 48 to 155 patients per 1000 patients), compared to 161 per 1000 patients treated with placebo (95% CI 116 to 225 patients per 1000; relative risk 0.53, 95% CI 0.27 to 1.05). We anticipate that 88 per 1000 typical patients treated with rituximab would experience disability progression over the duration of a typical trial (95% CI 33 to 236 patients per 1000). We found no statistically significant difference for any of the treatment comparisons.

Ocrelizumab, alemtuzumab and IFN-beta-1a formed a subnetwork that is disconnected from the main network of evidence, so we were unable to assess the certainty of evidence for these treatments using the GRADE approach. We assessed the certainty of evidence for natalizumab to be moderate, and for rituximab to be very low due to the contribution of NRS to the estimate.

Figure 6. *Study design and sample sizes for disability progression*

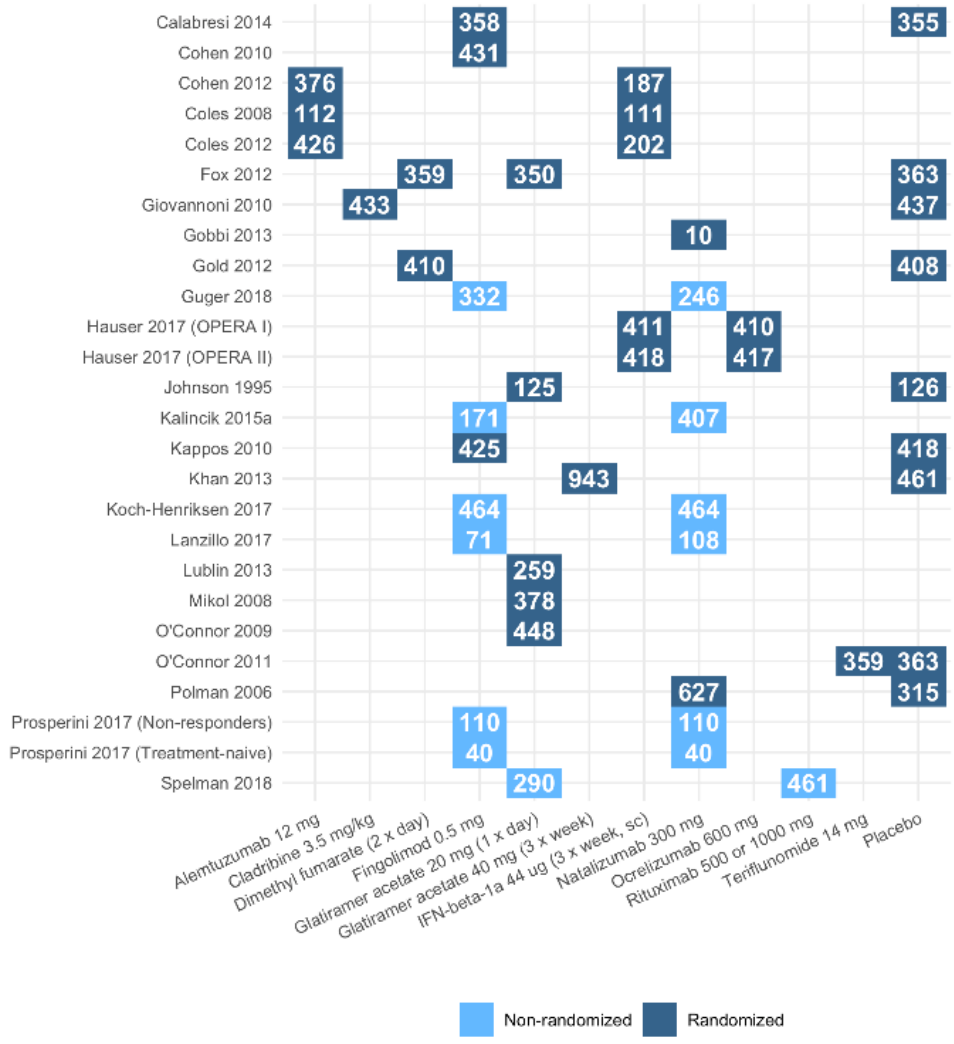
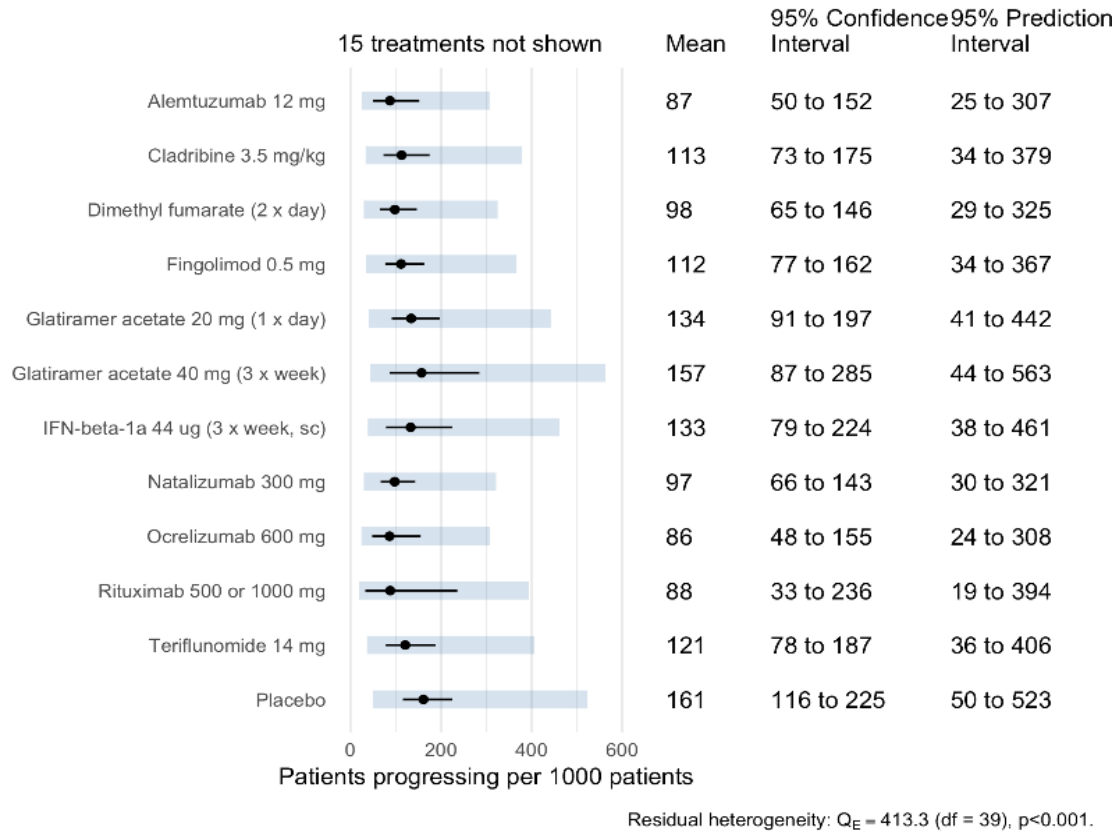
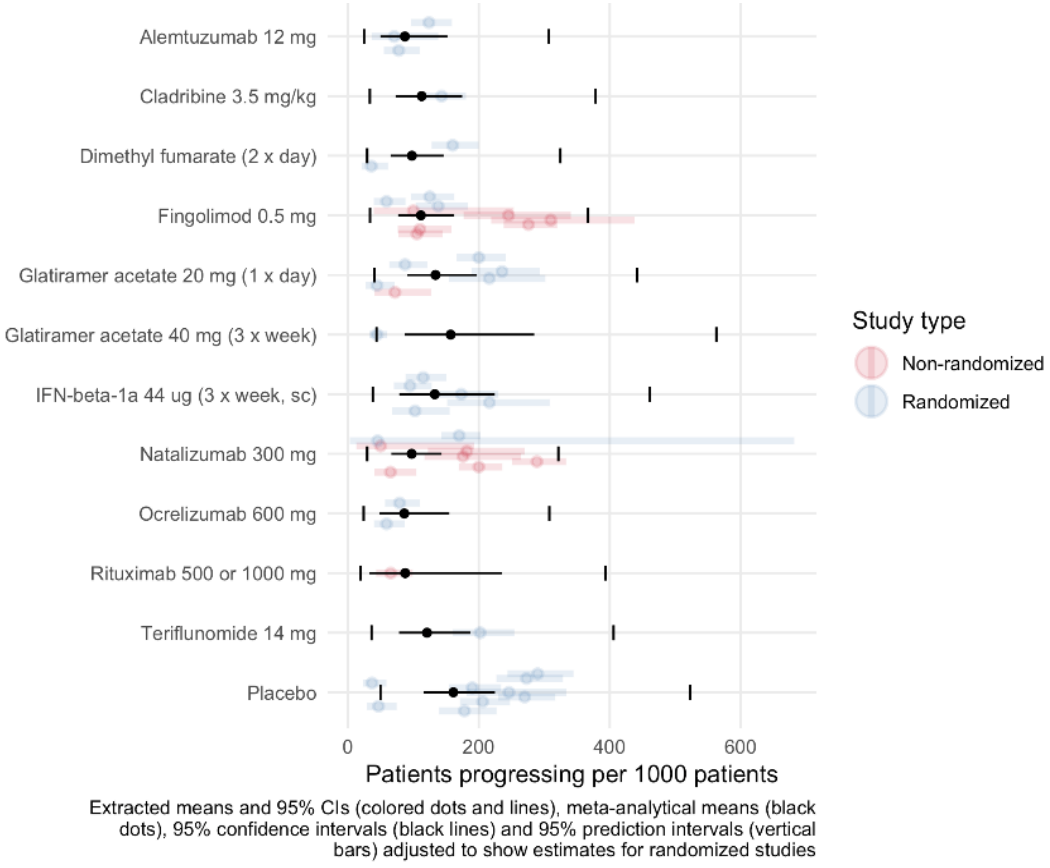


***Figure 7**. Network meta-regression estimates of risk of disability progression per 1000 patients*



Residual heterogeneity: $Q_E = 413.3$ (df = 39), p<0.001.

***Figure 8.** Network meta-regression estimates of risk of disability progression with results of each included study*



Extracted means and 95% CIs (colored dots and lines), meta-analytical means (black dots), 95% confidence intervals (black lines) and 95% prediction intervals (vertical bars) adjusted to show estimates for randomized studies

Figure 9. *Effect estimates of relative risk of disability progression (95% confidence intervals in parentheses)*

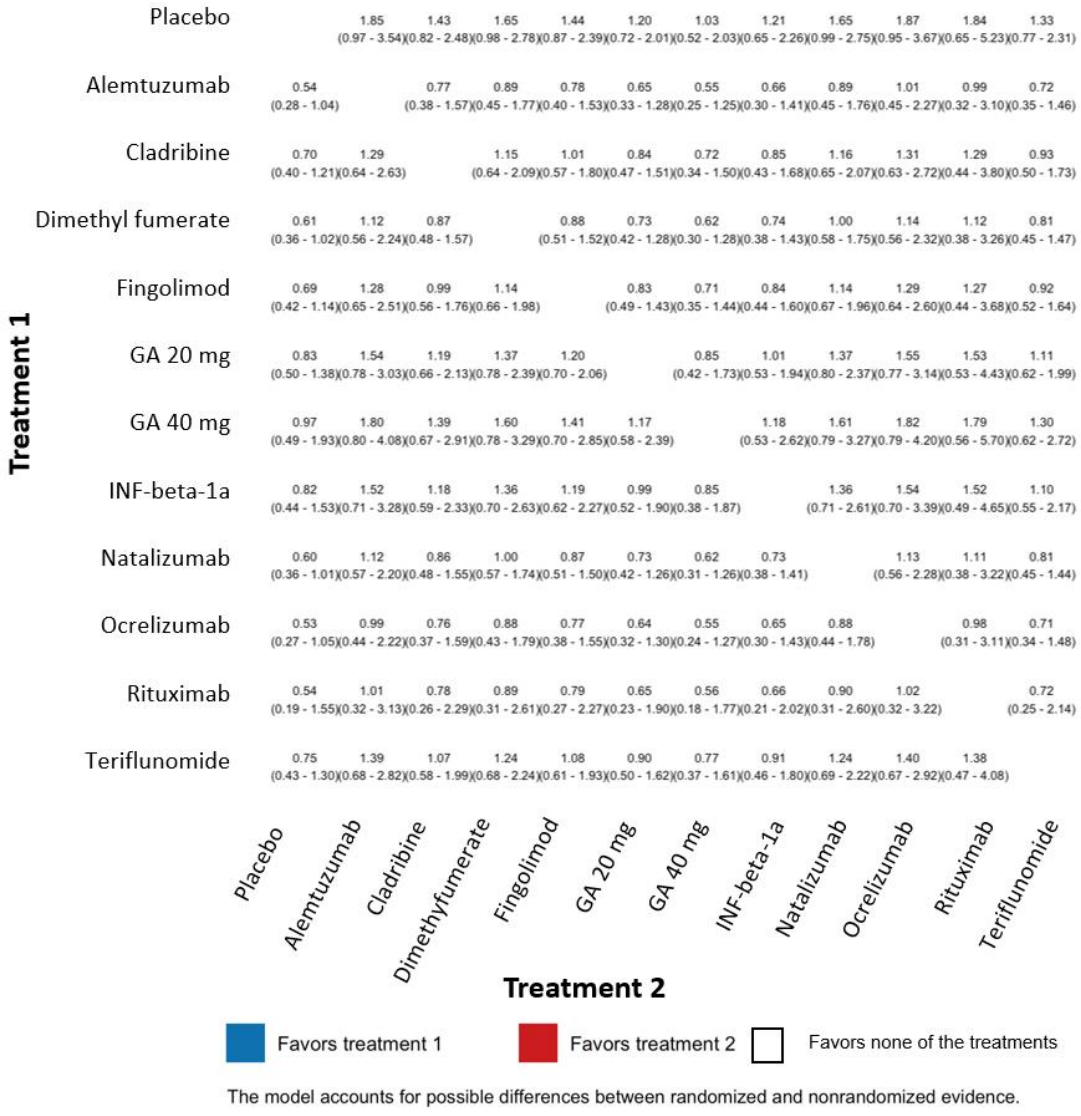


Table 3. *Summary of findings for risk of disability progression*

Treatment* *Study type, participants, person years*	**Relative risk** (95% CI)**	**Anticipated risk of disease progression over the duration of a typical trial (patients per 1000 patients)**			**Certainty of evidence**	**Rank**** (P-score)**
		With placebo	**With treatment**	**Difference*** (95% CI)**		
Ocrelizumab *2 RCT n=827; PY=1 527*	**0.53** (0.27 to 1.05)	161 per 1000	86 per 1000	-75 per 1000 (-113 to -6)	Disconnected from the network	**2** (0.77)
Alemtuzumab *3 RCT n=914; PY=1 940*	**0.54** (0.28 to 1.04)	161 per 1000	87 per 1000	-74 per 1000 (-111 to -9)	Disconnected from the network	**3** (0.77)
Natalizumab *2 RCT; 6 NRS n=2 012; PY=4 419*	**0.60** (0.36 to 1.01)	161 per 1000	97 per 1000	-64 per 1000 (-95 to -18)	⊕⊕⊕◯ MODERATE[1]	**4** (0.71)
Dimethyl fumarate *2 RCT n=769; PY=1 538*	**0.61** (0.36 to 1.02)	161 per 1000	98 per 1000	-63 per 1000 (-96 to -15)	⊕⊕⊕◯ MODERATE[1]	**5** (0.70)
Rituximab *1 NRS n=461; PY=922*	**0.54** (0.19 to 1.55)	161 per 1000	88 per 1000	-74 per 1000 (-129 to 75)	⊕◯◯◯ VERY LOW[1,2]	**6** (0.70)
Fingolimod *3 RCT; 6 NRS n=2 402; PY=5 014*	**0.69** (0.42 to 1.14)	161 per 1000	112 per 1000	-50 per 1000 (-85 to 1)	⊕⊕⊕◯ MODERATE[1]	**9** (0.58)
Cladribine *1 RCT n=433; PY=799*	**0.70** (0.40 to 1.21)	161 per 1000	113 per 1000	-48 per 1000 (-88 to 13)	⊕⊕⊕◯ MODERATE[1]	**10** (0.56)
Teriflunomide *1 RCT n=359; PY=746*	**0.75** (0.43 to 1.30)	161 per 1000	121 per 1000	-40 per 1000 (-83 to 26)	⊕⊕◯◯ LOW[1,2]	**13** (0.49)
IFN-beta-1a *5 RCT n=1 329; PY=2 642*	**0.82** (0.44 to 1.53)	161 per 1000	133 per 1000	-28 per 1000 (-83 to 63)	Disconnected from the network	**17** (0.40)
GA 20 mg *5 RCT n=1 850; PY=4 573*	**0.83** (0.50 to 1.38)	161 per 1000	134 per 1000	-27 per 1000 (-70 to 36)	⊕⊕⊕◯ MODERATE[1]	**19** (0.38)
GA 40 mg *1 RCT n=943; PY=943*	**0.97** (0.49 to 1.93)	161 per 1000	157 per 1000	-4 per 1000 (-75 to 124)	Not assessed	**22** (0.26)

RCT, randomised controlled trial; NRS, non-randomised controlled trial; n, total number of patients; PY, person years; CI, Confidence Intervals; GA, glatiramer acetate

* See doses for the treatments at the beginning of the chapter

** Relative risk of disease progression compared to placebo; CIs account for uncertainty on the effect of treatment and placebo

*** CIs on anticipated differences do not account for uncertainty on the effect of placebo

**** Ranked from best (rank 1) to worst by computed P-score. 15 treatments are not shown and the ranking is therefore not continuous. All treatments are shown in the appendix.

[1]Imprecision in the network estimate; [2]High risk of bias in study

Change in EDSS score

We included data from 17 studies of which 14 were RCTs. The studies included 27 treatments, 40 study arms, 10 639 patients and 16 166 patient years (*Figure 10*). The included studies for ocrelizumab or dimethyl fumarate did not report change in EDSS.

While EDSS is an ordinal scale ranging from 0.5 to 10, we modelled change in EDSS as a continuous variable as is typical in the literature. We judged that this outcome was measured in a reasonably consistent way for the purpose of evidence synthesis.

Estimates of "absolute" anticipated treatment effect for each of the treatments of interest are presented as change in EDSS over the duration of a typical trial (approximately 2 years; *Figure 11*), and results from each included study are shown in *Figure 12*. For all treatments, the network meta-regression estimates were consistent with pairwise meta-analysis estimates based on direct RCT evidence (i.e., the 95% confidence intervals overlapped). Estimates of relative treatment effect (i.e., comparisons of pairs of treatments) are presented as differences in change in EDSS (*Figure 13*); in a treatment versus placebo comparison, for example, a difference less than zero favours the treatment, while a difference greater than zero favours placebo.

The summary of findings table (*Table 4*) presents the effect estimates in ranked order (selected treatments compared to placebo). Details of the analyses as well as a complete ranking list of all interventions used in the analyses, are presented in *Appendix 13*.

Natalizumab, alemtuzumab and rituximab were ranked as the best three treatment options for this outcome. We estimate probabilities of 89%, 82%, and 76%, respectively, that these are the best of all treatments. We estimate that a typical patient treated with natalizumab would experience a change in EDSS of -0.26 steps (95% CI -0.43 to -0.10 steps) over the duration of a typical trial, compared to -0.25 steps (95% CI -0.85 to 0.35 steps) for rituximab, and 0.10 steps (95% CI 0.03 to 0.17 steps) for placebo.

A change in EDSS of less than 0.5 steps may not be clinically important relative to the EDSS scores of typical patients enrolled into the included studies, we are reluctant to use these data to support superiority to any of the treatments.

We did not assess certainty of evidence using the GRADE tool for this outcome. Rituximab was disconnected from the network and the evidence included one non-randomised study.

Figure 10. *Study design and sample sizes for change in disability (EDSS score)*

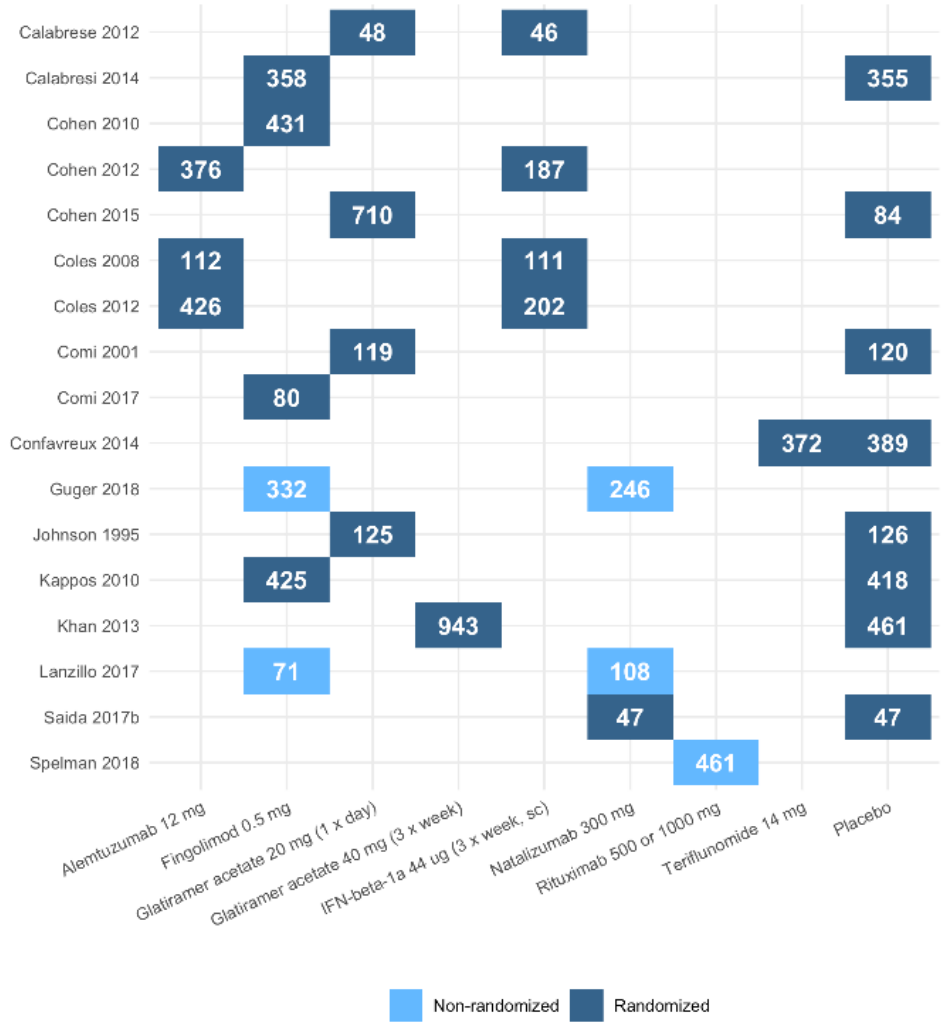


Figure 11. *Network meta-regression estimates of change in disability score*

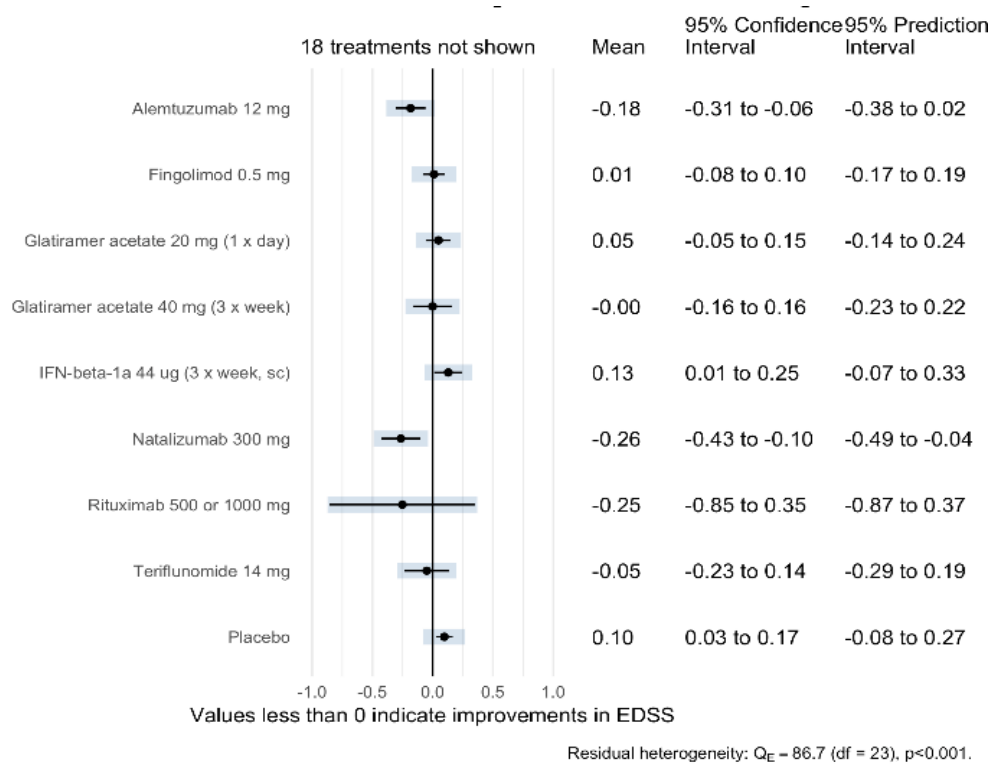


Figure 12. *Network meta-regression estimates of change in disability score with results from each included study*

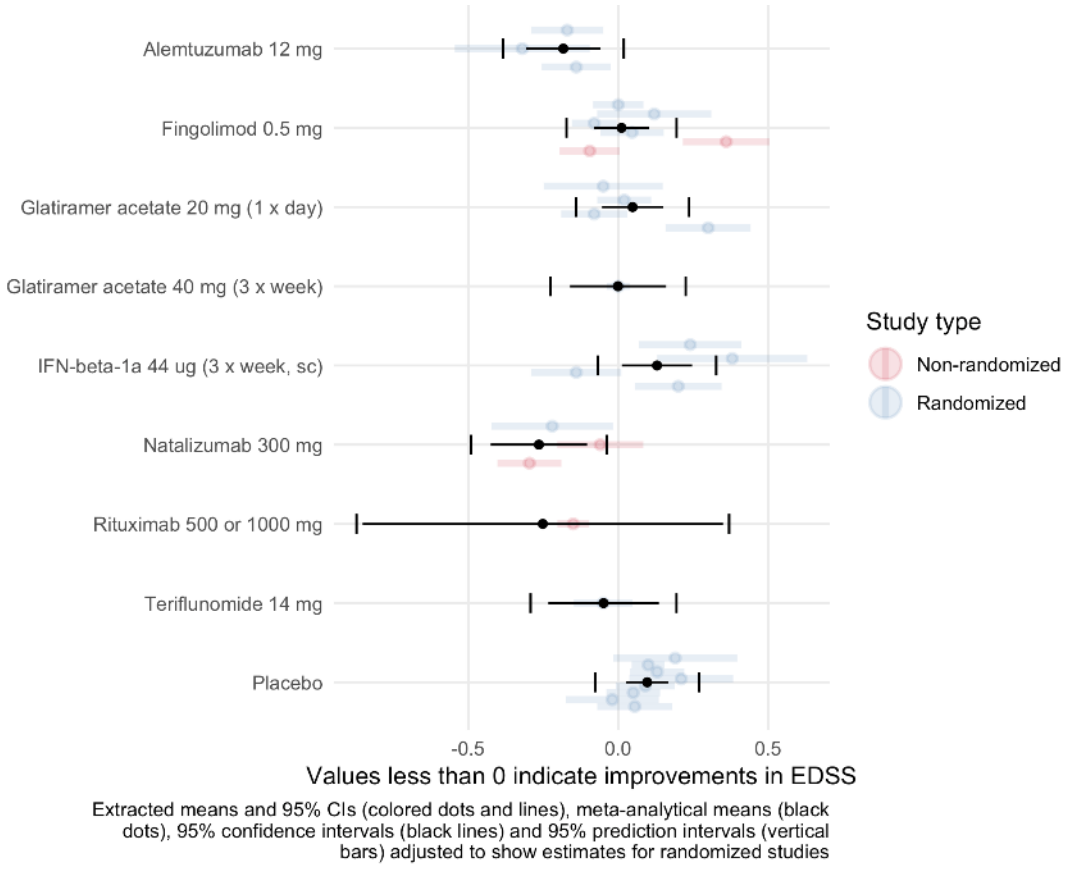


Figure 13. *Estimates of change in disability (EDSS score) ratios (95% confidence intervals in parentheses)*

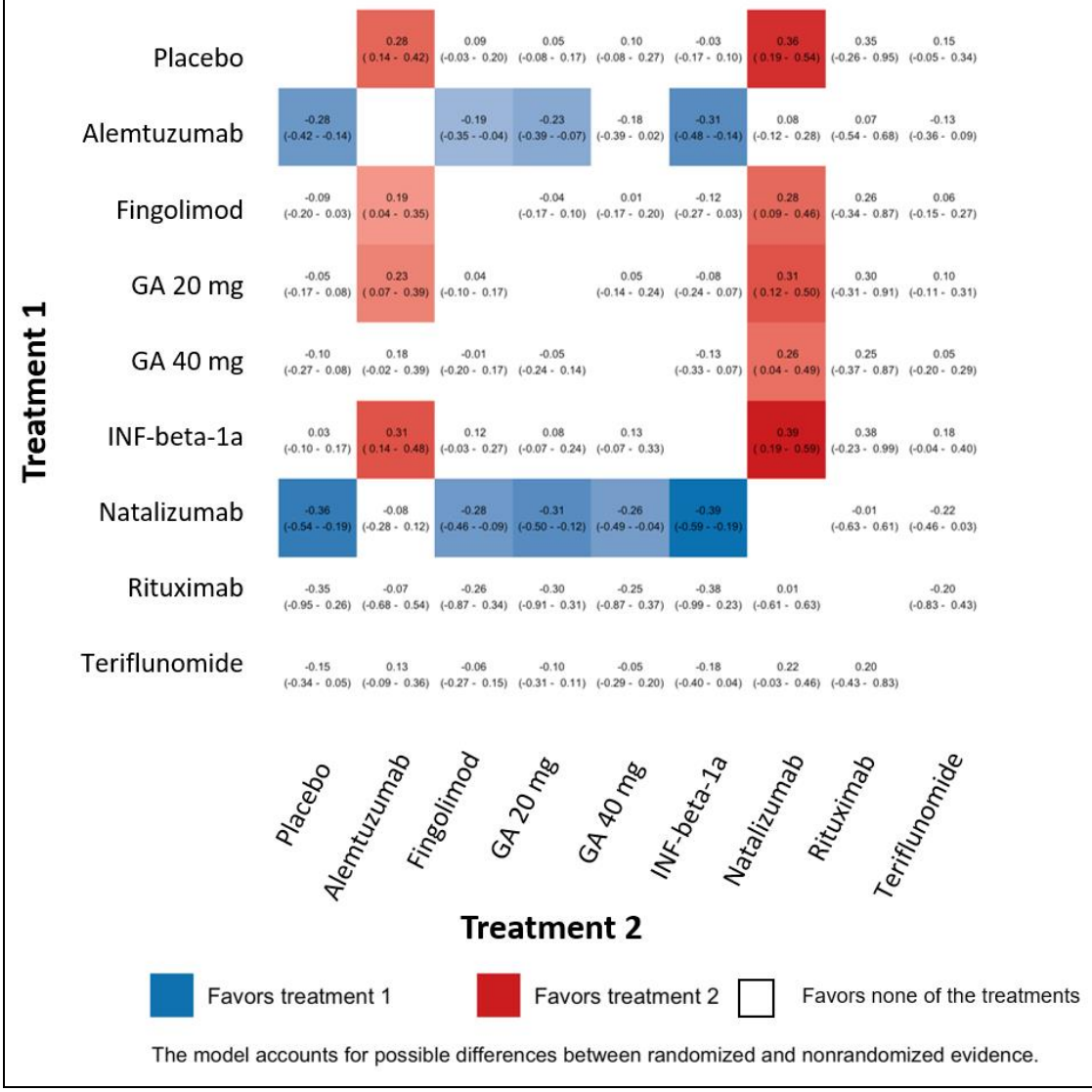


Table 4. *Summary of findings for change in disability (EDSS score) from baseline*

Treatment* *Study type, participants, person years*	**Relative effect** (95% CI)**	**Anticipated change in EDSS score over the duration of a typical trial**			**Rank**** (P-score)
		With placebo	**With treatment**	**Difference*** (95% CI)**	
Natalizumab *1 RCT; 2 NRS n=401; PY=730*	**-0.36** (-0.54 to -0.19)	0.10 steps	-0.26 steps	-0.36 steps (-0.52 to -0.20)	**2** (0.89)
Alemtuzumab *3 RCT n=914; PY=1 940*	**-0.28** (-0.42 to -0.14)	0.10 steps	-0.18 steps	-0.28 steps (-0.40 to -0.16)	**3** (0.82)
Rituximab *1 NRS n=461; PY=922*	**-0.35** (-0.95 to 0.26)	0.10 steps	-0.25 steps	-0.35 steps (-0.95 to 0.25)	**4** (0.76)
Teriflunomide *1 RCT n=372; PY343*	**-0.15** (-0.34 to 0.05)	0.10 steps	-0.05 steps	-0.15 steps (-0.33 to 0.04)	**6** (0.62)
GA 40 mg *1 RCT n=943; PY=743*	**-0.10** (-0.27 to 0.08)	0.10 steps	-0.00 steps	-0.10 steps (-0.26 to 0.06)	**7** (0.52)
Fingolimod *4 RCT; 2 NRS n=1 697; PY=2 923*	**-0.09** (-0.20 to 0.03)	0.10 steps	0.01 steps	-0.09 steps (-0.18 to 0.01)	**8** (0.51)
GA 20 mg *4 RCT n=1002; PY=968*	**-0.05** (-0.17 to 0.08)	0.10 steps	0.05 steps	-0.05 steps (-0.15 to 0.05)	**11** (0.41)
IFN-beta-1a *4 RCT n=546; PY=1 203*	**0.03** (-0.10 to 0.17)	0.10 steps	0.13 steps	0.03 steps (-0.08 to 0.15)	**13** (0.23)

RCT, randomised controlled trial; NRS, non-randomised study; n, total number of patient; PY, person years; CI, Confidence Intervals; GA, glatiramer acetate

* See doses for the treatments at the beginning of the chapter

** Difference in change in EDSS score compared to placebo; CIs account for uncertainty on the effect of treatment and placebo

*** CIs on anticipated differences do not account for uncertainty on the effect of placebo

**** Ranked from best (rank 1) to worst by P-score. 18 treatments are not shown and the ranking is therefore not continuous. All treatments are shown in the appendix.

Risk of new MRI lesions

We included data from 21 studies of which 18 were RCTs. The analyses included 17 treatments, including the placebo group, 54 study arms, 13 962 patients and 25 102 patient years (*Figure 14*).

We estimated the risk of experiencing one or more lesions detected using T1-weighted gadolinium (Gd)-enhanced MRI over the duration of a typical trial (approximately 2 years).

This outcome was modelled on the log risk scale and is presented as the number of patients, per 1000, who would be expected to develop one or more new lesions over the duration of a typical trial (approximately 2 years; *Figure 15*), with estimates for each included study in *Figure 16*. For all treatments, the network meta-regression estimates were consistent with pairwise meta-analysis estimates based on direct RCT evidence (i.e., the 95% confidence intervals overlapped). Relative treatment effect estimates are reported as risk ratios (RRs; *Figure 17*).

The summary of findings table (*Table 5*) presents effect estimates in ranked order (selected treatments compared to placebo). Details of the analyses as well as a complete ranking list of all interventions used in the analyses are presented in *Appendix 14*.

Natalizumab, ocrelizumab and alemtuzumab were ranked as the best three treatments of interest with respect to this outcome. We estimate probabilities of 95%, 72%, and 71%, respectively, that these are the best of all treatments. We anticipate that 48 per 1000 typical patients treated with natalizumab would experience one or more new Gd-enhancing lesions over the duration of a typical trial (95% CI 25 to 91 patients per 1000), compared to 402 patients per 1000 patients treated with placebo (95% CI 314 to 515; relative risk 0.12, 95% CI 0.06 to 0.24).

The results suggest that, over the duration of a typical trial, a typical patient treated with teriflunomide, glatiramer acetate or IFN-beta-1a would be expected to be at similar or higher risk of new lesions than a typical patient treated with placebo (see *Figure 17* for relative effect estimates).

We did not assess certainty of evidence using the GRADE tool for this outcome. Evidence for rituximab included one small RCT and one NRS.

Figure 14. *Study design and sample sizes for risk of ≥1 new T1-weighted Gd-enhancing lesions*

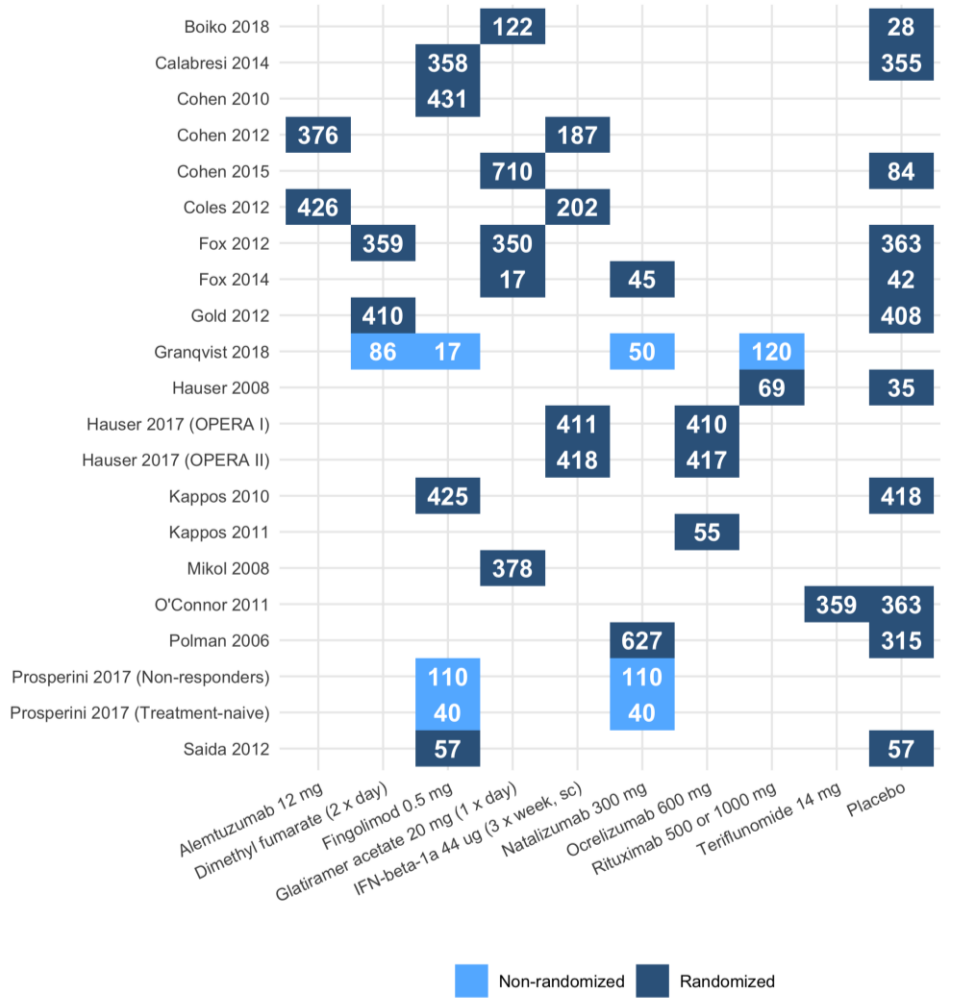
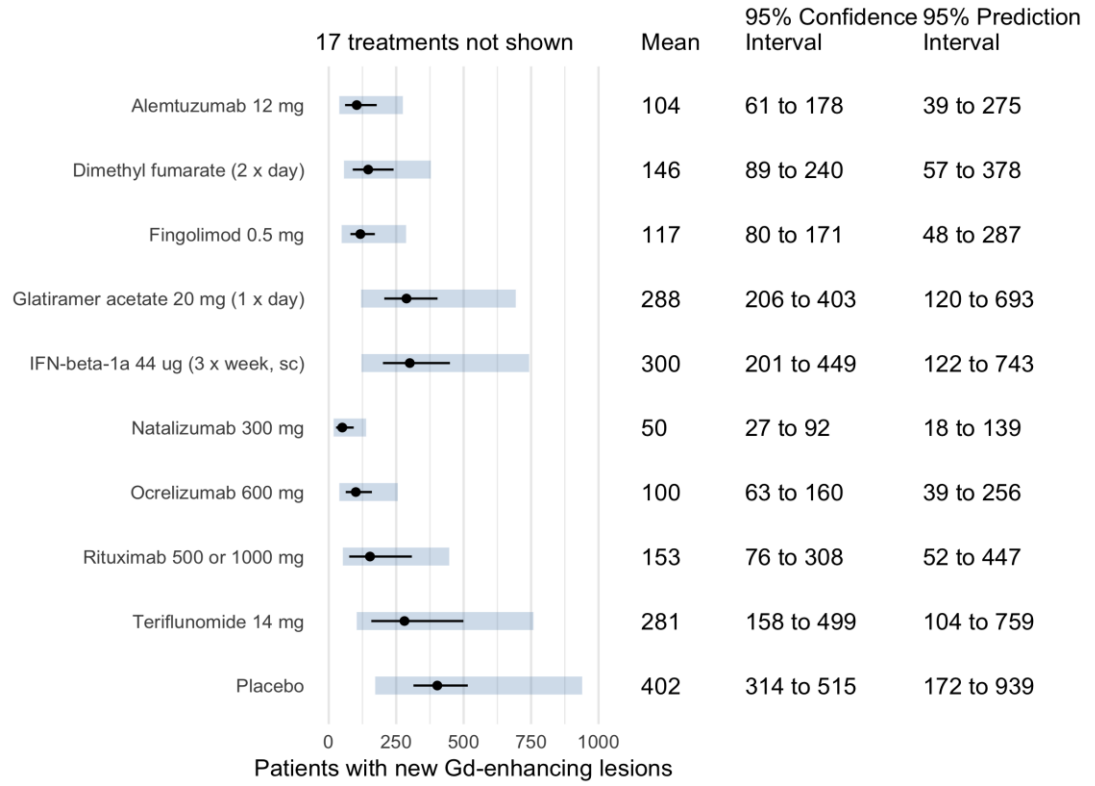
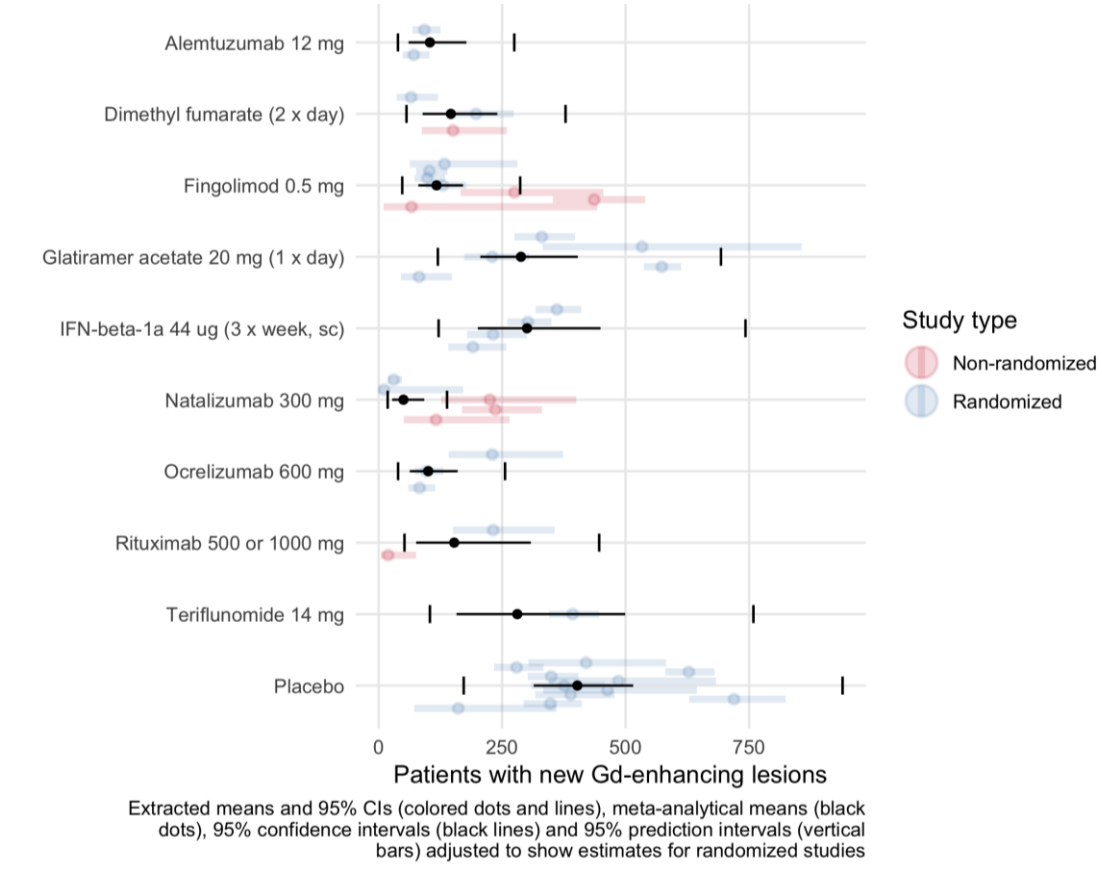


***Figure 15**. Network meta-regression estimates of new T1-weighted Gd-enhancing MRI lesion per 1000 patients*



Residual heterogeneity: $Q_E = 380.9$ (df = 36), p<0.001.

***Figure 16.** Network meta-regression estimates of new T1-weighted Gd-enhancing MRI lesion per 1000 patients, with results from each included study*



Extracted means and 95% CIs (colored dots and lines), meta-analytical means (black dots), 95% confidence intervals (black lines) and 95% prediction intervals (vertical bars) adjusted to show estimates for randomized studies

Figure 17. *Effect estimates of new T1-weighted Gd-enhancing MRI lesions (95% confidence intervals in parentheses).*

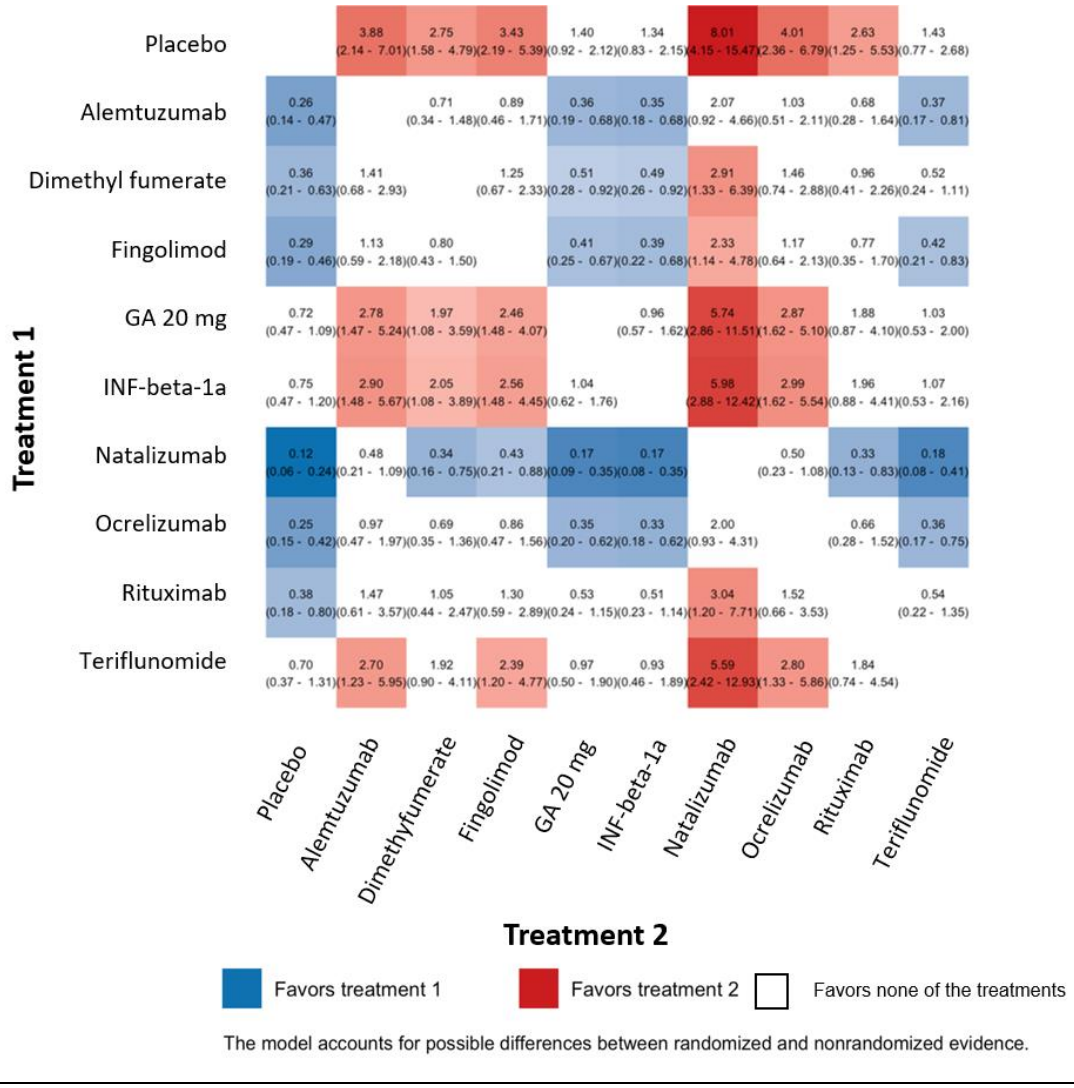


Table 5. *Summary of findings for risk of new Gd-enhancing MRI lesion*

Treatment* *Study type, participants, person years*	**Relative risk** (95% CI)**	**Anticipated risk of new Gd-enhancing MRI lesions over the duration of a typical trial (patients per 1000 patients)**			**Rank**** (P-score)
		With placebo	**With treatment**	**Difference*** (95% CI)**	
Natalizumab *2 RCT; 3 NRS n=872; PY=1 791*	**0.12** (0.06 to 0.24)	402 per 1000	50 per 1000	-352 per 1000 (-375 to -310)	**1** (0.94)
Ocrelizumab *3 RCT n=882; PY=1 552*	**0.25** (0.15 to 0.42)	402 per 1000	100 per 1000	-302 per 1000 (-339 to -241)	**5** (0.73)
Alemtuzumab *2 RCT n=802; PY=1 604*	**0.26** (0.14 to 0.47)	402 per 1000	104 per 1000	-299 per 1000 (-342 to -225)	**6** (0.71)
Fingolimod *4 RCT; 3 NRS n=1 438; PY=2 399*	**0.29** (0.19 to 0.46)	402 per 1000	117 per 1000	-285 per 1000 (-322 to -231)	**7** (0.65)
Dimethyl fumarate *2 RCT; 1 NRS n=855; PY=1 910*	**0.36** (0.21 to 0.63)	402 per 1000	146 per 1000	-256 per 1000 (-313 to -162)	**8** (0.53)
Rituximab *1 RCT; 1 NRS n=189; PY=583*	**0.38** (0.18 to 0.80)	402 per 1000	153 per 1000	-249 per 1000 (-326 to -94)	**9** (0.51)
Teriflunomide *1 RCT n=359; PY=746*	**0.70** (0.37 to 1.31)	402 per 1000	281 per 1000	-122 per 1000 (-244 to 97)	**13** (0.21)
GA 20 mg *5 RCT n=1 577; PY=2 050*	**0.72** (0.47 to 1.09)	402 per 1000	288 per 1000	-114 per 1000 (-196 to 1)	**14** (0.20)
IFN-beta-1a *4 RCT n=1 218; PY=2 309*	**0.75** (0.46 to 1.20)	402 per 1000	300 per 1000	-102 per 1000 (-201 to 47)	**15** (0.18)

RCT, randomised controlled trial; NRS, non-randomised study; n, total number of patients; PY, person years; CI, Confidence Intervals; GA, glatiramer acetate

* See doses for the treatments at the beginning of the chapter

** Relative risk of Gd-enhancing MRI lesions compared to placebo; CIs account for uncertainty on the effect of treatment and placebo

*** CIs on anticipated differences do not account for uncertainty on the effect of placebo

**** Ranked from best (rank 1) to worst by P-score. 17 treatments are not shown and the ranking is therefore not continuous. All treatments are shown in the appendix.

Risk of mortality

We included data from 28 studies of which 26 were RCTs. The studies included 27 treatments, 74 study arms, 22 060 patients and 42 328 patient years (*Appendix 15*).

We studied all-cause mortality. There were very few deaths in the included studies during the duration of a typical trial (approximately 2 years) (30 deaths out of a total of 22 060 patients). Although we performed a full network meta-analysis, we judged that the number of events was too small to support useful conclusions. In the interest of completeness and transparency, details of the analyses as well as a complete ranking list of all interventions used in the analyses are presented in *Appendix 15*. The included studies reported no statistically significant differences in mortality rates.

We report numbers of deaths per 1000 patients and the total number of patients (*Table 6*). Because we studied all-cause mortality, the reported deaths are not necessarily associated with the studied treatments.

Table 6. *Reported number of deaths per 1000 patients*

Treatment	Study type, participants, person years	Reported numbers of deaths per 1000 patients
Alemtuzumab	3 RCT; n=914; PY=1 940	0.0
Cladribine	1 RCT; n=433; PY=799	4.6
Dimethyl fumarate	3 RCT; n=855; PY=1 910	1.2
Fingolimod	7 RCT; n=1 510; PY=2 432	0.0
GA 20 mg	7 RCT; n=2 386; PY=4 477	3
IFN-beta-1a	6 RCT; n=1 433; PY=2 736	2.1
Natalizumab	2 RCT; n=677; PY=1 471	1.5
Ocrelizumab	3 RCT; n=882; PY=1 552	1.1
Placebo	15 RCT; n=3 887; PY=6 363	1.5
Rituximab	1 RCT; 2 NRS; n=303; PY=754	3.3 (homicide)
Teriflunomide	1 RCT; n=842; PY=1 192	2.4

Risk of serious adverse events (SAE)

We included data from 24 studies of which 23 were RCTs. The studies included 27 treatments, 64 study arms, 18 810 patients and 37 265 patient years (*Figure 18*).

We fitted and present results for the full network meta-regression model, but the random effects may not have been estimated correctly (based on visual inspection of profile plots). However, the estimates presented below are largely consistent with those for the simpler naïve network meta-analysis.

We extracted reported SAE data from the RCTs, adhering to the Food and Drug Administration (FDA) definition (which included, but are not limited to, life-threatening events, hospitalisation, and permanent damage) of SAE where possible (79). Most studies did not describe whether relapses were included in the SAE-reporting. We based our analysis on reported "serious adverse event" counts, however there may be differences in how this was defined by the included studies.

Risk of SAE was modelled on the log risk scale and is presented as the number of patients, per 1000, who would be expected to experience one or more serious adverse event over the duration of a typical trial (approximately 22 months; *Figure 19*), with results from each included study shown in *Figure 20*. Relative treatment effect estimates are reported as risk ratios (RRs; *Figure 21*).

The network meta-regression estimates for dimethyl fumarate and natalizumab were inconsistent with the pairwise meta-analysis estimate that is based on direct RCT evidence (i.e., the 95% confidence intervals do not overlap). For dimethyl fumarate, this may be explained by differences in baseline values where the NRS had lower patient age, shorter time since disease onset, higher ARR, and lower EDSS score. For natalizumab baseline values for NRS showed lower patient age, shorter time since disease onset and lower ARR (*Appendix 11*).

The summary of findings table (*Table 7*) presents effect estimates in ranked order (selected treatments compared to placebo). Details of the analyses as well as a complete ranking list of all interventions used in the analyses are presented in *Appendix 16*.

Rituximab, ocrelizumab and fingolimod were ranked as the best three treatment options for this outcome. We estimate probabilities of 94%, 69%, and 65%, respectively, that these are the best of all treatments. We anticipate that 48 of 1000 typical patients treated with rituximab would experience one or more SAE over the duration of a typical trial (95% CI 21 to 110 patients per 1000), compared to 120 per 1000 patients treated with placebo (95% CI 93 to 165 patients per 1000; relative risk 0.40, 95% CI 0.16 to 0.95). Rituximab was estimated to be superior to placebo, cladribine and teriflunomide. The confidence intervals for SAE overlapped across all the other treatments and it is therefore possible that these treatments have similar risk of SAE.

Based on the GRADE method for assessing certainty of evidence in NMA, we judged the certainty of evidence for rituximab to be very low due to the reliance on evidence from NRSs. We did not assess the certainty of the other treatment effects.

Figure 18. *Study design and sample sizes for risk of ≥1 serious adverse event*

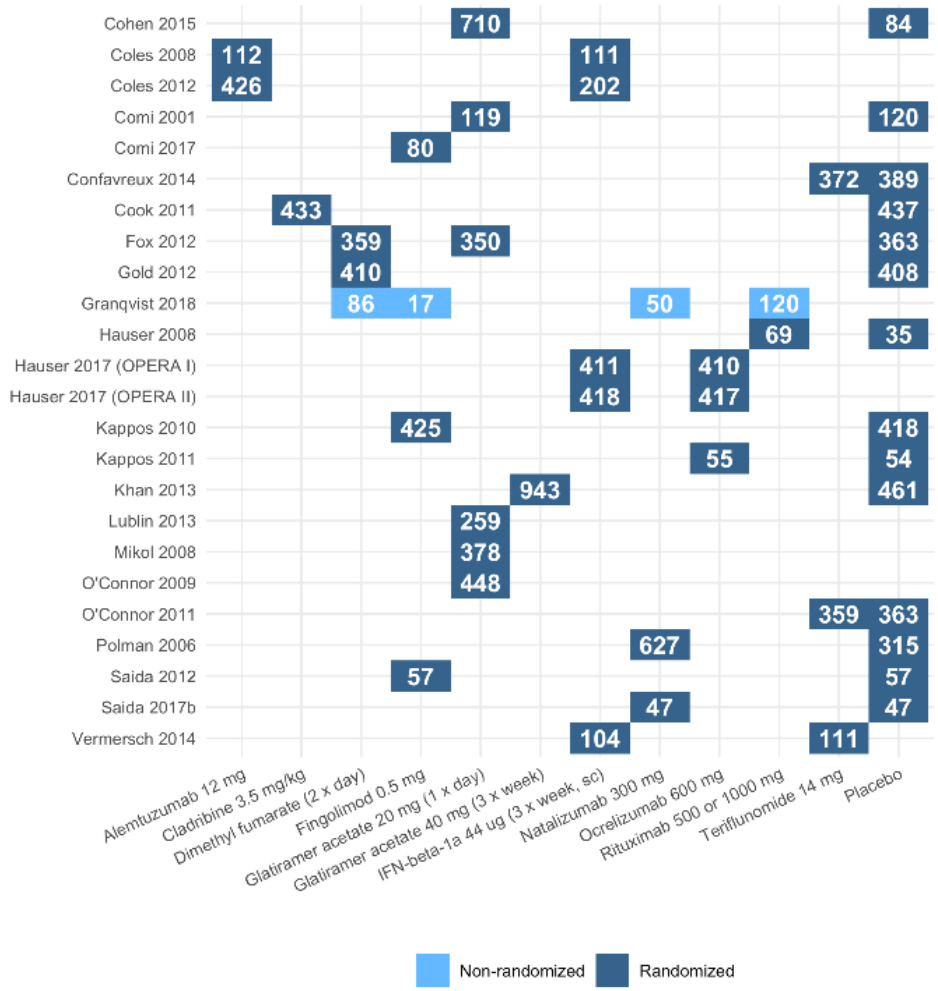


Figure 19. *Network meta-regression estimates for patients with ≥ 1 serious adverse events per 1000 patients*

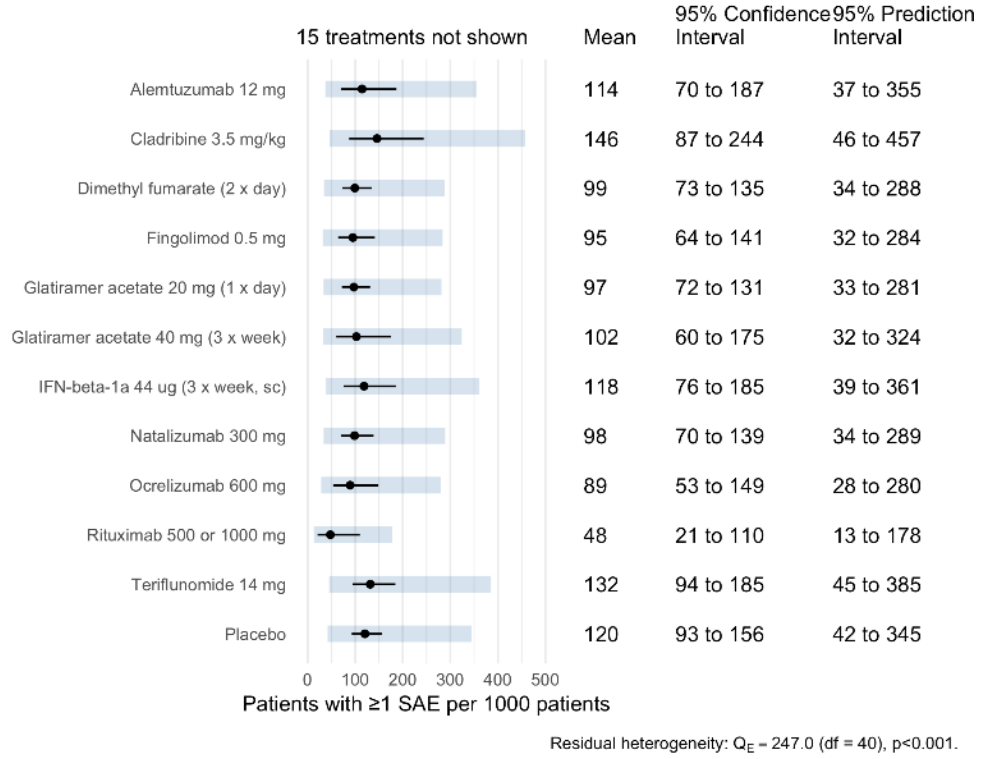


Figure 20. *Network meta-regression estimates for patients with ≥ 1 serious adverse events per 1000 patients with estimates from each included study*

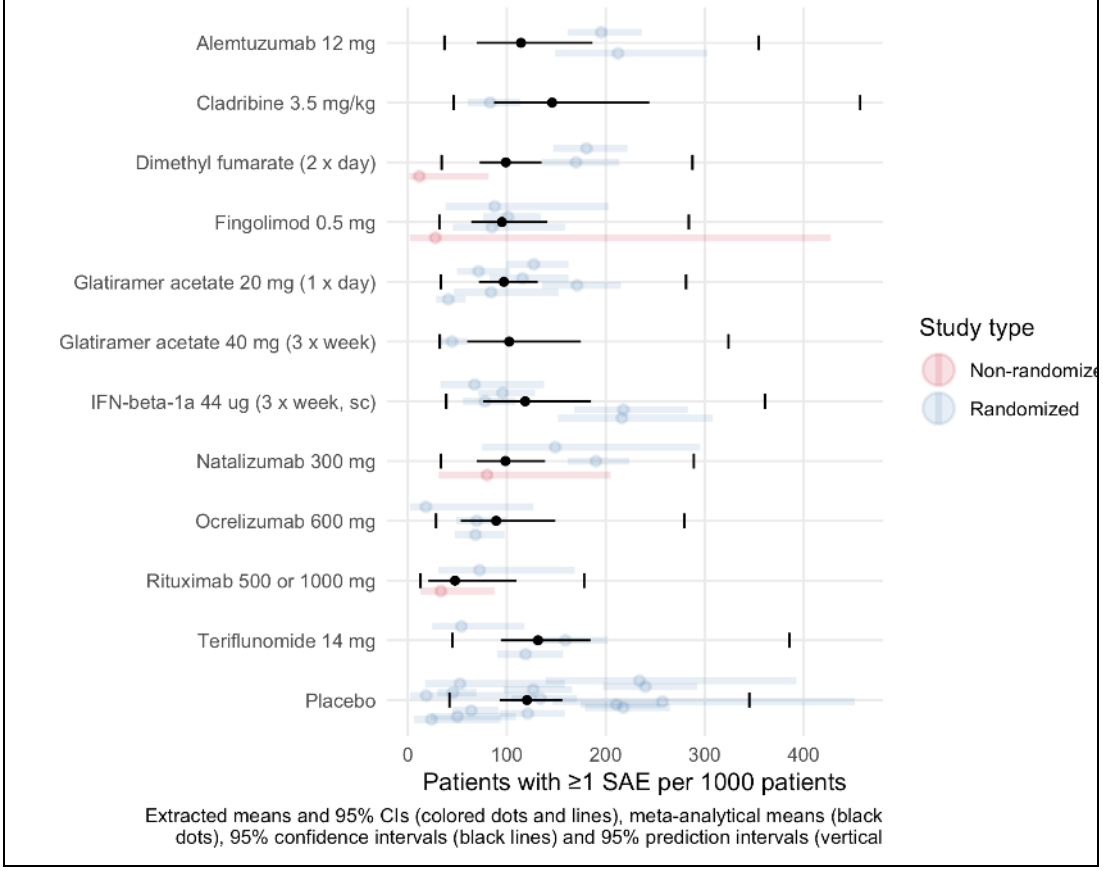


Figure 21. *Effect estimates of SAE ratio (95% confidence intervals in parentheses).*

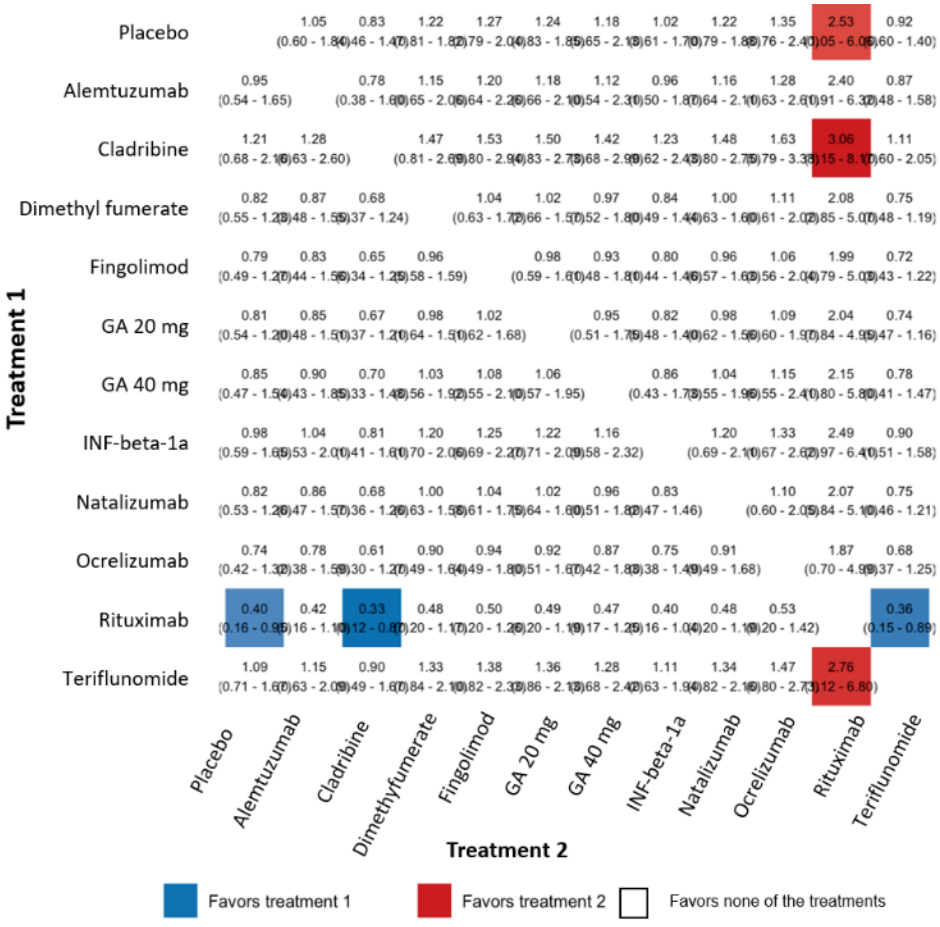


Table 7. *Summary of findings for risk of one or more serious adverse events*

Treatment* *Study type, participants, person years*	**Relative risk** (95% CI)**	**Anticipated risk of ≥1 serious adverse event over the duration of a typical trial (patients per 1000 patients)**			**Rank**** (P-score)
		With placebo	**With treatment**	**Difference*** (95% CI)**	
Rituximab *1 RCT; 1 NRS n=189; PY=583*	**0.40** (0.16 to 0.95)	120 per 1000	48 per 1000	-73 per 1000 (-100 to -11)	**1** (0.94)
Ocrelizumab *3 RCT n=882; PY=1 552*	**0.74** (0.42 to 1.32)	120 per 1000	89 per 1000	-31 per 1000 (-67 to 29)	**4** (0.69)
Fingolimod *3 RCT; 1 NRS n=579; PY=1 072*	**0.79** (0.49 to 1.27)	120 per 1000	95 per 1000	-25 per 1000 (-56 to 21)	**6** (0.65)
GA 20 mg *6 RCT n=2 264; PY=4 365*	**0.81** (0.54 to 1.20)	120 per 1000	97 per 1000	-23 per 1000 (-49 to 11)	**7** (0.64)
Natalizumab *2 RCT; 1 NRS n=724; PY=1 492*	**0.82** (0.53 to 1.26)	120 per 1000	98 per 1000	-22 per 1000 (-50 to 18)	**8** (0.62)
Dimethyl fumarate *2 RCT; 1 NRS n=855; PY=1 910*	**0.82** (0.55 to 1.23)	120 per 1000	99 per 1000	-21 per 1000 (-48 to 15)	**9** (0.62)
GA 40 mg *1 RCT n=943; PY=943*	**0.85** (0.47 to 1.54)	120 per 1000	102 per 1000	-18 per 1000 (-60 to 54)	**11** (0.56)
Alemtuzumab *2 RCT n=538; PY=1 188*	**0.95** (0.54 to 1.65)	120 per 1000	114 per 1000	-6 per 1000 (-50 to 66)	**12** (0.45)
IFN-beta-1a *5 RCT n=1 246; PY=2 364*	**0.98** (0.59 to 1.65)	120 per 1000	118 per 1000	-2 per 1000 (-44 to 65)	**15** (0.41)
Teriflunomide *3 RCT n=842; PY=1 192*	**1.09** (0.71 to 1.67)	120 per 1000	132 per 1000	11 per 1000 (-27 to 64)	**19** (0.29)
Cladribine *1 RCT n=433; PY=799*	**1.21** (0.68 to 2.16)	120 per 1000	146 per 1000	25 per 1000 (-33 to 124)	**22** (0.22)

RCT, randomised controlled trial; NRS, non-randomised study; n, total number of patients; PY, person years; CI, Confidence Intervals; GA, glatiramer acetate

* See doses for the treatments at the beginning of the chapter

** Relative risk of ≥1 serious adverse events; CIs account for uncertainty on the effect of treatment and placebo

*** CIs on anticipated differences do not account for uncertainty on the effect of placebo

**** Ranked from best (rank 1) to worst by P-score. 15 treatments are not shown and the ranking is therefore not continuous. All treatments are shown in the appendix.

Risk of treatment withdrawal due to adverse events, AE

We included data from 21 studies of which 17 were RCTs. The studies included 27 treatments, 55 study arms, 18 978 patients and 40 844 patient years (*Figure 22*).

This outcome was modelled on the log risk scale and is presented as the number of patients, per 1000, who would be expected to discontinue a treatment during a typical trial (of approximately 2 years) due to one or more adverse events (*Figure 23*), with estimates from each included study in *Figure 24.* For all treatments, the network meta-regression estimates were consistent with pairwise meta-analysis estimates based on direct RCT evidence (i.e., the 95% confidence intervals overlapped). Relative treatment effect estimates are reported as risk ratios (RRs; *Figure 25*).

The summary of findings table (*Table 8*) presents effect estimates in ranked order (selected treatments compared to placebo). Details of the analyses as well as a complete ranking list of all interventions used in the analyses are presented in *Appendix 17*.

Rituximab, natalizumab and alemtuzumab were ranked as the best three treatments of interest with respect to this outcome. We estimate probabilities of 92%, 80%, and 74%, respectively, that these are the best of all treatments. We anticipate that 10 of 1000 typical patients treated with rituximab would withdraw from treatment over the duration of a typical trial (95% CI 2 to 43 patients per 1000), compared to 50 of 1000 patients treated with placebo (95% CI 35 to 70 patients per 1000; relative risk 0.19, 95% CI 0.04 to 0.89). Dimethyl fumarate was estimated to be inferior to placebo with respect to this outcome.

Based on the GRADE method for assessing certainty of evidence in NMA, we judged the certainty of evidence for rituximab to be low due to the reliance on evidence from NRSs. We did not assess the certainty of the other treatment effects.

Figure 22. *Study design and sample sizes for risk of treatment withdrawal due to adverse events*

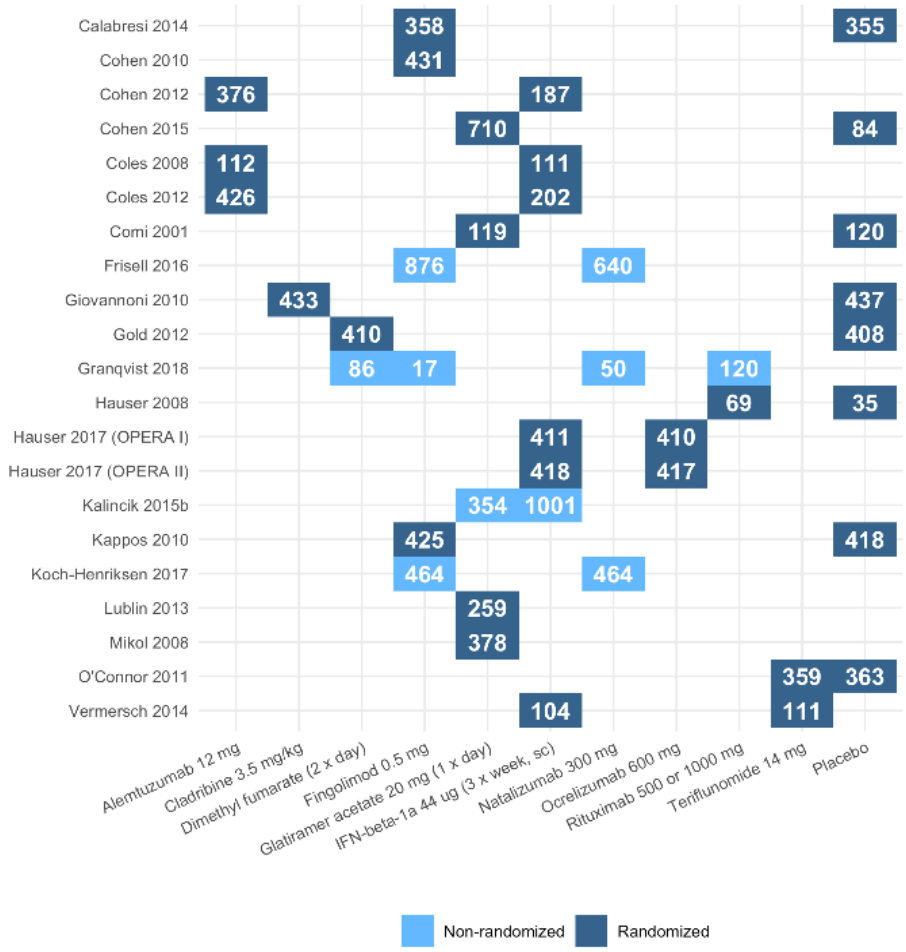


Figure 23. *Network meta-regression estimates of risk of treatment withdrawal due to adverse events*

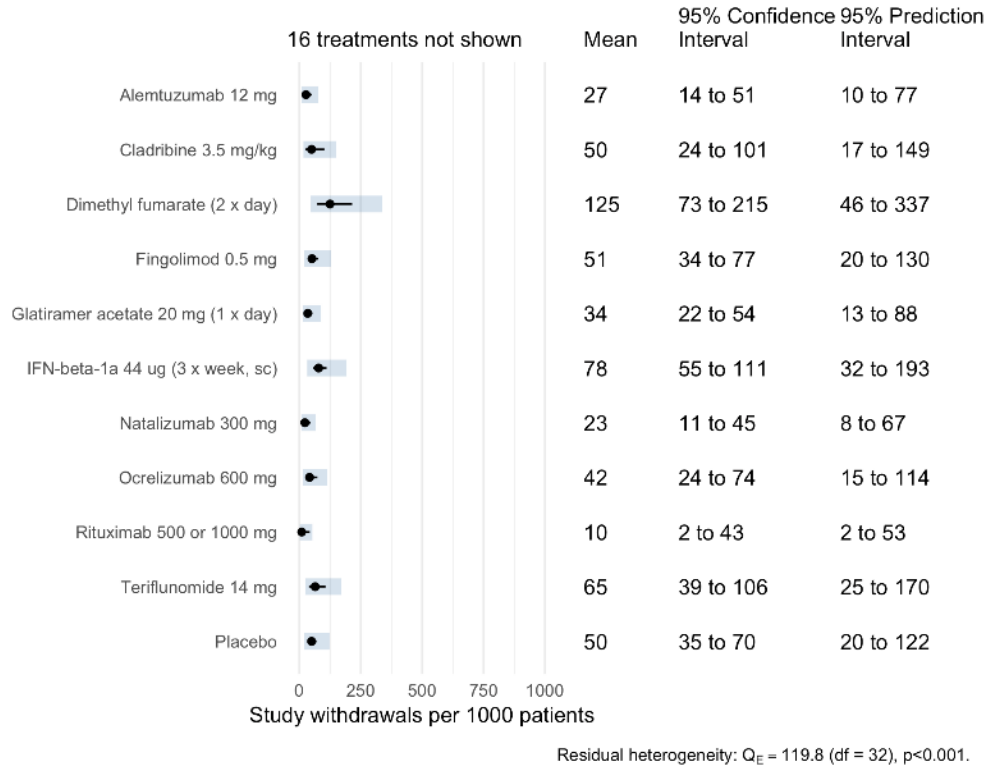


Figure 24. *Network meta-regression estimates of risk of treatment withdrawal due to adverse events with estimates from each included study*

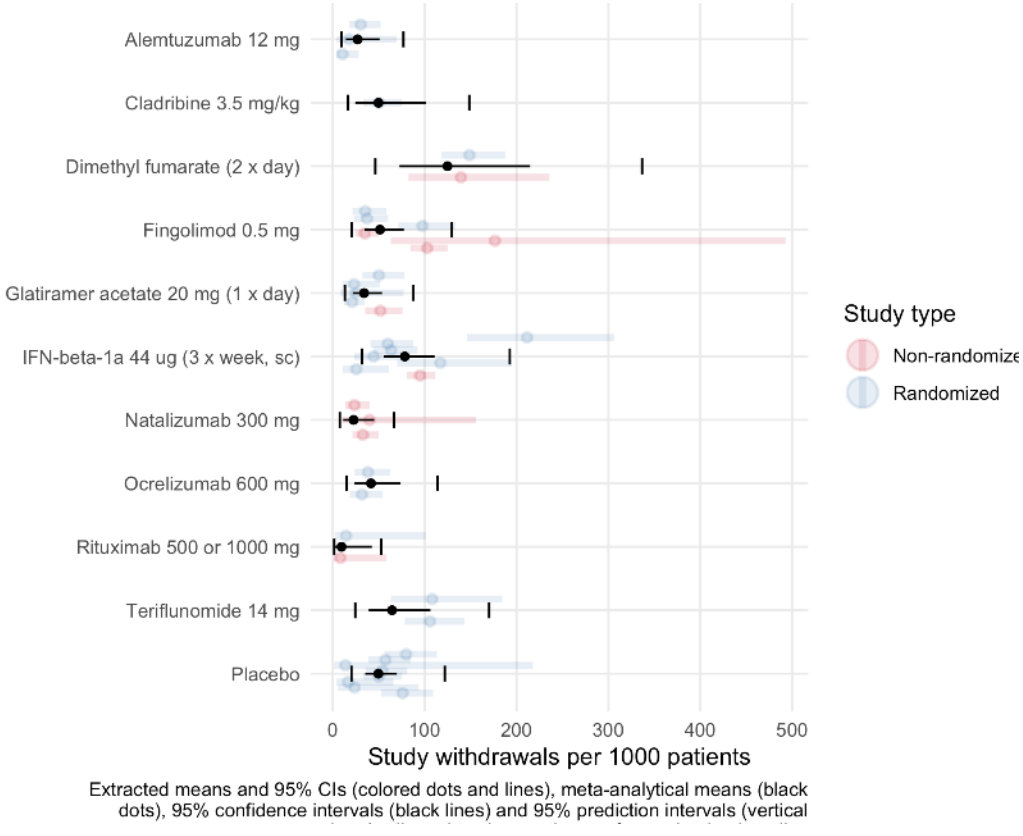


Figure 25. *Effect estimates of relative risk for treatment withdrawal due to adverse events (95% confidence intervals in parentheses).*

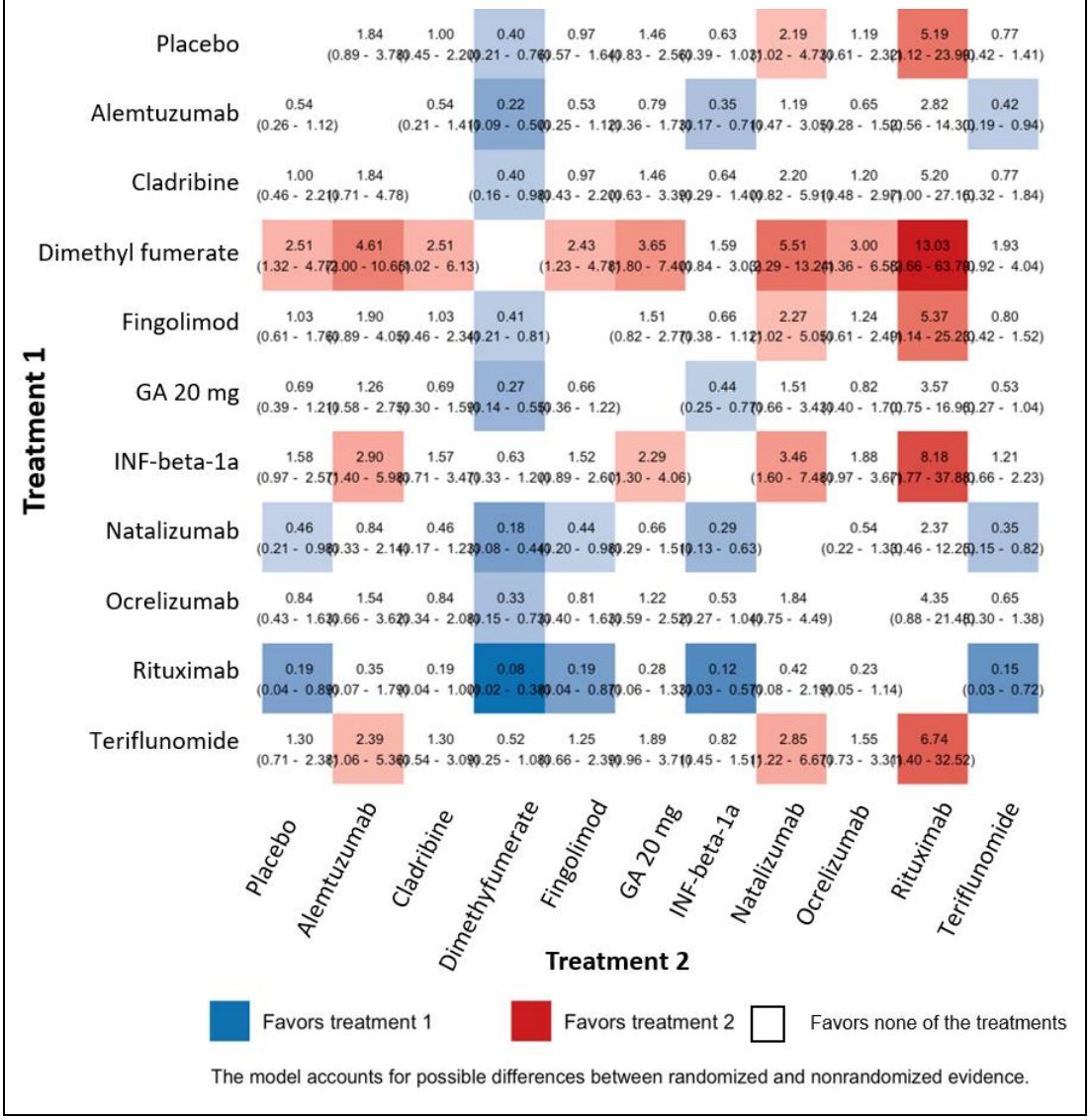


Table 8. *Summary of findings for treatment withdrawal due to AE*

Treatment* *Study type, participants, person years*	**Relative risk** (95% CI)**	**Risk of treatment withdrawal due to AE over the duration of a typical trial (patients per 1000 patients)**			**Rank**** (P-score)
		With placebo	**With treatment**	**Difference*** (95% CI)**	
Rituximab *1 RCT; 1 NRS n=189; PY=583*	**0.19** (0.04 to 0.89)	50 per 1000	10 per 1000	-40 per 1000 (-48 to -7)	**1** (0.92)
Natalizumab *3 NRS n=1 154; PY=2 597*	**0.46** (0.21 to 0.98)	50 per 1000	23 per 1000	-27 per 1000 (-38 to -5)	**5** (0.80)
Alemtuzumab *3 RCT n=914; PY=1 940*	**0.54** (0.26 to 1.12)	50 per 1000	27 per 1000	-23 per 1000 (-35 to 1)	**6** (0.74)
Glatiramer acetate *4 RCT; 1 NRS n=1 820; PY=3 406*	**0.69** (0.39 to 1.21)	50 per 1000	34 per 1000	-16 per 1000 (-28 to 4)	**8** (0.66)
Ocrelizumab *2 RCT n=827; PY=1 527*	**0.84** (0.43 to 1.63)	50 per 1000	42 per 1000	-8 per 1000 (-26 to 24)	**10** (0.55)
Cladribine *1 RCT n=433; PY=799*	**1.00** (0.46 to 2.21)	50 per 1000	50 per 1000	0 per 1000 (-25 to 52)	**13** (0.45)
Fingolimod *3 RCT; 3 NRS n=2 571; PY=4 687*	**1.03** (0.61 to 1.76)	50 per 1000	51 per 1000	2 per 1000 (-15 to 28)	**14** (0.44)
Teriflunomide *2 RCT n=470; PY=848*	**1.30** (0.71 to 2.38)	50 per 1000	65 per 1000	15 per 1000 (-11 to 57)	**16** (0.31)
IFN-beta-1a *6 RCT; 1 NRS n=2 434; PY=6 441*	**1.58** (0.97 to 2.57)	50 per 1000	78 per 1000	29 per 1000 (6 to 61)	**19** (0.20)
Dimethyl fumarate *1 RCT; 1 NRS n=496; PY=1 192*	**2.51** (1.32 to 4.77)	50 per 1000	125 per 1000	75 per 1000 (23 to 165)	**22 (0.05)**

RCT, randomised controlled trial; NRS, non-randomised study; n, total number of patients; PY, person years; CI, Confidence Intervals; GA, glatiramer acetate

* See doses for the treatments at the beginning of the chapter

** Relative risk of treatment withdrawal due to adverse events; CIs account for uncertainty on the effect of treatment and placebo

*** CIs on anticipated differences do not account for uncertainty on the effect of placebo

**** Ranked from best (rank 1) to worst by P-score. 17 treatments are not shown and the ranking is therefore not continuous. All treatments are shown in the appendix.

Risk of specific serious adverse events

We extracted incidences of specific serious adverse events (PML, thyroid diseases, liver diseases, cancer, heart diseases and serious infections) from the included studies. Such events were rare, and often imprecisely reported.

We performed network meta-regression for risk of cancer only (*Appendix 18*). In the interest of transparency, we present results for the full network meta-regression model, however two of the variance components may not have been estimated correctly, so the estimates may not be reliable. In addition, we extracted specific types of SAE from all included studies, and present the numbers per 1000 patients (*Table 9*).

Specific serious adverse events were generally uncommon in the included studies, which reported no statistically significant differences in specific serious adverse events. None of the included studies reported any cases of progressive multifocal leukoencephalopathy (PML). This may be due to the studies being too small or having short duration.

Table 9. *Reported number of specific serious adverse events per 1000 patients.*

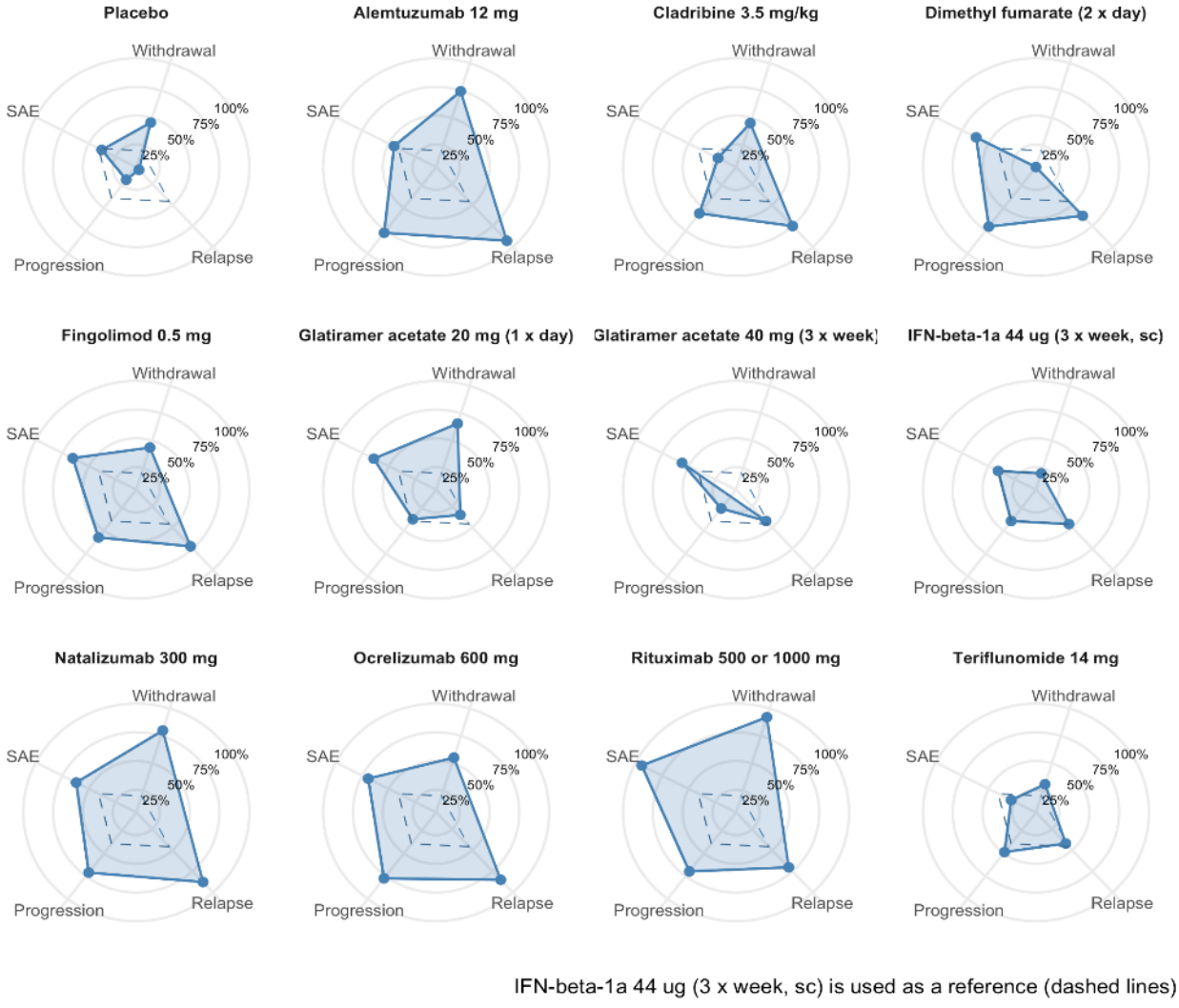
Treatment	Studies	No of patients in treatment arm	Serious events per 1000 patients					
			PML	Thyroid disease	Liver disease	Cancer	Heart disease	Infections
Alemtuzumab 12 mg	Cohen 2012; Coles 2008, Coles 2012	915	0.0	7.7	4.4	4.4	0.0	28.4
Cladribine 3.25	Cool 2011	433	0.0	0.0	0.0	4.6	0.0	4.6
Dimethyl fumarate	Gold 2012	416	0.0	0.0	0.0	0.0	0.0	19.2
Fingolimod 0,5 mg	Alping 2016; Calbresi 2014; Cohen 2010; Kappos 2010	1354	0.0	0.0	0.0	10.3	3.0	9.6
Glatiramer acetate 20 mg	Boiko 2018; Lublin 2013	383	0.0	0.0	7.8	7.8	7.8	2.6
IFNβ-1a 44 µg	Cohen 2012; Coles 2008 Coles 2012; Hauser 2017; Vermersch 2014	1433	0.0	0.0	6.3	3.5	0.0	22.3
Natalizumab 300 mg	Poleman 2006	627	0.0	0.0	0.0	8.0	0.0	0.0
Ocrelizumab 600 mg	Hauser 2017; Kappos 2011	882	0.0	0.0	0.0	4.5	0.0	13.6
Rituximab 500 or 1000 mg	Alping 2016; Hauser 2008	183	0.0	0.0	0.0	0.0	0.0	10.9
Teriflunomide 14 mg	Confavreux 2014; O'Connor 2011; Vermersch 2014	839	0.0	0.0	0.0	4.8	0.0	13.1
Placebo	Boiko 2018; Calbresi 2014; Confraveux 2014; Cook 2011; Gold 2012; Hauser 2008; Kappos 2010; Kappos 2011; O'Connor 2011; Poleman 2006	2804	0.0	0.0	0.0	8.6	0.4	13.9

Radar plot for selected outcomes

We plotted estimated probabilities of superiority (*P*-scores) of each selected treatment with respect to two safety outcomes (withdrawal from study drug, and serious adverse event) and two effectiveness outcomes (annualised relapse rate, and disability progression) as radar plots (*Figure 26*).

In general, treatments with larger polygons are more likely to be superior in terms of the four outcomes. Each radar plot also shows a polygon for IFNbeta-1a, for reference purpose. Note that data on treatment withdrawal was not available for the 40 mg dose of glatiramer acetate, so the area of the polygon for this treatment cannot be compared with those for the other treatments (see section "*How we present the findings", pp 22*, for an explanation of P-scores and how they can be interpreted).

Figure 26. *Radar plots of treatments based on P-scores (larger values and polygon areas are better).*



Juridiske aspekter ved off label-bruk av rituksimab i MS-behandling

This chapter is only available in Norwegian.

Mål

Å belyse juridiske problemer eller utfordringer ved off label-bruk av rituksimab til MS-behandling.

Sammendrag

Rituksimab brukes off label i MS-behandling. Et lignende preparat, ocrelizumab, har markedsføringstillatelse, men er så langt ikke besluttet innført i norsk spesialisthelsetjeneste. Et overordnet spørsmål for dette kapittelet blir om det er noen juridiske problemer eller utfordringer ved fortsatt bruk av rituksimab til MS-behandling når det finnes et lignende preparat for denne behandlingen med markedsføringstillatelse (ocrelizumab).

Ettersom rettskildene er få når det gjelder juridiske aspekter knyttet til off label-bruk av legemidler, har denne delen av metodevurderingen i stor grad måttet lene seg på alminnelige helserettslige prinsipper og generelle momenter og betraktninger vedrørende off label-bruk av legemidler.

Både i norsk rett og i EU-retten, gjøres det et skille mellom retten til å markedsføre legemidler og retten til å forskrive legemidler. Innvilget markedsføringstillatelse innebærer en rett til å selge/markedsføre et preparat i tråd med de vilkår som fremgår av tillatelsen, mens forskrivning av legemidler ligger innenfor legens frie forskrivningsrett. Ettersom legemidler med markedsføringstillatelse har vist at de tilfredsstiller krav til kvalitet, sikkerhet og effekt, for de tilstander som tillatelsen omfatter, vil dette legge føringer for forskrivningen av legemidler. Markedsføringstillatelsen er ikke bindende for forskriver og det er derfor ingen juridiske hindre, utover kravet til forsvarlighet, for om leger kan forskrive rituksimab for MS. Videre kjenner vi ikke til noen bestemmelse som positivt og eksklusivt avgrenser myndighetenes anbefalinger om bruk og forskrivning av legemidler, hvilket betyr at innføring av ocrelizumab i spesialisthelsetjenesten ikke er til hinder for at bruk av rituksimab ved behandling av MS kan anbefales.

EU-retten legger ikke føringer for off label-bruk av legemidler. Ulike stater innad i EU har derfor ulik regulering og praktisering av off label-bruk av legemidler. Men ser vi til Europa er det slik at prinsippet om pasientsikkerhet skal ha presedens over eksempelvis økonomiske hensyn. Det kan argumenteres for at et legemiddel med markedsføringstillatelse skal være foretrukket fremfor off label-preparater, nettopp fordi pasient-

sikkerheten er bedre ivaretatt gjennom kravene til markedsføringstillatelse. Disse hensynene vil imidlertid ikke i like stor grad gjøre seg gjeldende dersom det viser seg at dokumentasjonen for rituksimabs effekt og sikkerhet ved MS-behandling er tilstrekkelig overbevisende.

Off label-bruk faller inn under pasientskadeerstatningens virkeområde i Norge.

Innledning

Med "off label"-bruk av legemidler menes bruk av legemidler utenfor godkjent indikasjon eller bruk utenfor godkjent preparatomtale.[1] Off label-bruk av legemidler kan skje på flere måter. Det kan blant annet innebære bruk på andre sykdommer, i annen dosering eller til en annen pasientgruppe (eksempelvis gravide eller barn) enn legemiddelet har markedsføringstillatelse for. Off label-bruk av legemidler er vanlig i klinisk praksis. Bruken kan være nødvendig for å sikre pasientens behandlingsbehov dersom det ikke foreligger legemidler med markedsføringstillatelse for en gitt sykdom.

I denne metodevurderingen vurderer Folkehelseinstituttet effekt og sikkerhet av legemiddelet rituksimab i behandling av pasienter med multippel sklerose (MS), sammenlignet med andre legemidler som har markedsføringstillatelse. Rituksimab, som har markedsføringstillatelse for behandling av visse kreftformer og revmatoid artritt,[2] har i denne metodevurderingen vist seg å ha god effekt og gunstig bivirkningsprofil ved behandling av MS, selv om evidensgrunnlaget er svakt da det bygger på ikke-randomiserte studier. Rituksimab har vært et billigere alternativ enn andre legemidler på markedet. Bruken av rituksimab har derfor blitt utstrakt blant visse helseinstitusjoner i Norge.[3]

Ocrelizumab er et legemiddel med markedsføringstillatelse for MS og som så langt ikke er besluttet innført i Norge for MS da Bestillerforum har ønsket å gjennomføre en fullstendig metodevurdering for behandling av MS. Bestanddelene i ocrelizumab og rituksimab ligner svært mye på hverandre, og medikamentene har tilnærmet lik effekt og sikkerhetsprofil, som vist i denne metodevurderingen. Evidensgrunnlaget er dog forskjellig da resultatene for ocrelizumab og rituksimab bygger på henholdsvis randomiserte og ikke-randomiserte studier. Et overordnet spørsmål blir om det er noen juridiske problemer eller utfordringer ved fortsatt off label-bruk av rituksimab til MS-behandling når det finnes et alternativt preparat for denne indikasjonen med markedsføringstillatelse (ocrelizumab).

I den videre fremstillingen vil vi, med forskjellig grundighet, behandle følgende tema:

1) Krav til markedsføringstillatelse
2) Legens frie forskrivningsrett
3) Off label-bruk av legemidler. I denne redegjørelsen vil vi blant annet behandle spørsmål knyttet til hvilken betydning markedsføringstillatelsen har for forskrivning av legemidler. Vi vil også fremheve momenter som kan ha betydning i en mer generell vurdering av off label-bruk av legemidler.

[1] Hem, E. og Madsen, S. Bruk av legemidler utenfor godkjent indikasjon. Tidsskr Nor Legeforen 2016; 136: 448.
[2] Felleskatalogen.no. Link: https://www.felleskatalogen.no/medisin/mabthera-roche-561182
[3] Moe, Lasse. Behandler flere MS-pasienter med «off label» som første behandling. Publisert 2018-04-05 11.30: https://www.dagensmedisin.no/artikler/2018/04/05/behandler-flere-ms-pasienter-med-off-label-som-forste-behandling/

4) Redegjørelse av hvordan EU-retten forholder seg til off label-bruk av legemidler.
5) Oppsummering av juridiske aspekter

Markedsføringstillatelse

For at legemidler som er "fremstilt industrielt eller ved bruk av en industriell prosess" skal kunne omsettes, kreves markedsføringstillatelse, jf. legemiddelloven § 8 (1) bokstav a).[4,5] Markedsføringstillatelse gis på grunnlag av en vurdering av preparatets "kvalitet, sikkerhet og effekt" jf. legemiddelloven § 8 (3). Markedsføringstillatelsen retter seg således mot de som selger/markedsfører et legemiddel. Innvilget markedsføringstillatelse innebærer en rett til å selge/markedsføre et preparat i tråd med de vilkår som fremgår av tillatelsen. Dette må ikke forveksles med legens forskrivningsrett da markedsføringstillatelsen ikke regulerer legens forskrivning av legemidler.

Helse- og omsorgsdepartementet har, i medhold av legemiddelloven § 8 (2), gitt utfyllende regler om kravene til markedsføringstillatelse i legemiddelforskriften. Det kreves omfattende testing og dokumentasjon for legemiddelets kvalitet, sikkerhet og effekt før det innvilges markedsføringstillatelse.[6] På bakgrunn av de strenge kravene for å få markedsføringstillatelse, kan det ta flere år å før dette innvilges, og testingen er både dyr og risikofylt for legemiddelprodusentene.

Markedsføring av legemidler for indikasjoner det ikke har markedsføringstillatelse for, er således ikke tillatt. Men idet et legemiddel er gitt markedsføringstillatelse, regulerer ikke lovgivningen uttømmende hvordan legemiddelet skal brukes. Vanlig medisinsk praksis er at forskrivning av medikamenter skjer i samråd mellom lege og pasient, og prinsippet om legens frie forskrivningsrett gjelder. Det må altså gjøres et skille mellom godkjente og ikke godkjente behandlingsalternativ versus innvilget og ikke innvilget markedsføringstillatelse. Dette gjelder for både on- og off label-bruk av legemidler.

Legens frie forskrivningsrett

Legens frie forskrivningsrett følger av Forskrift om rekvirering og utlevering av legemidler fra apotek.[7] Det fremgår av forskriftens § 2-1 (1) at "[l]ege med norsk autorisasjon har rett til å rekvirere legemidler." Rekvirering av legemidler skal forstås som "muntlig, skriftlig eller elektronisk bestilling av legemiddel ved resept eller rekvisisjon", jf. definisjonen i forskriftens § 1-3 bokstav e). For enkelhets skyld brukes begrepet "forskrivning" av legemidler.

Grunnkravet til forskrivning av legemidler fremgår av forskriftens § 1-4. Det kreves av den som forskriver legemidler "skal ha rutiner som sikrer forsvarlig rekvirering av legemidler, som bidrar til forsvarlig mottak og ekspedisjon av resept og rekvisisjon og som bidrar til forsvarlig utlevering av legemidlet fra apoteket", jf. § 1-4 (1). Som ved annen medisinsk behandling, kreves altså at forskrivning av legemidler er forsvarlig. Det

[4] Lov om legemidler m.v. LOV-1992-12-04-132.
[5] Det finnes unntak fra kravet om markedsføringstillatelse gjengitt i kapittel 2 i legemiddelforskriften (FOR-2009-12-18-1839). Dette er imidlertid ikke av videre interesse for denne metodevurderingen.
[6] Se blant annet krav til innhold ved søknad om markedsføringstillatelse i legemiddelforskriften § 3-4
[7] Forskrift av 27. april 1998 nr. 455. Forskrift om rekvirering og utlevering av legemidler fra apotek, jf. helsepersonelloven § 11.

fremgår av selve formålet med forskriften at den skal "sikre forsvarlig rekvirering av legemidler", jf. § 1-1.

Forskrivning av legemidler off label ligger innenfor legens frie forskrivningsrett.[8] Men retten til fri forskrivning skal utøves innenfor rammen av det som er forsvarlig, jf. *Forskrift om legemidler fra apotek § 1-4 jf. § 1-1*. Forsvarlighetskravet gjelder både for on label- og off label-bruk av legemidler. Det kan anføres at markedsføringstillatelse vil legge visse føringer for forskrivning av legemidler. Men den eksklusive retten til forskrivning tilligger likevel legen, og blir legens vurdering i enhver behandlingssituasjon. Det går med andre ord et prinsipielt skille mellom retten til å markedsføre et legemiddel, og retten til å forskrive et legemiddel.

Off label-bruk av legemidler

Off label-bruk av legemidler er svært beskjedent behandlet i juridisk teori og praksis. Selve off label-bruken av legemidler er ikke eksplisitt lovregulert i norsk rett, men den blir hjemlet i kravet om å yte forsvarlig helsehjelp, jf. spesialisthelsetjenesteloven § 2-2 og helsepersonelloven § 4 (1), og prinsippet om helsepersonells plikt til å yte best mulig helsehjelp.

Det er utbredt og allment akseptert med bruk av legemidler off label. Som nevnt innledningsvis, kan off label-bruk av legemidler ofte være det eneste rasjonelle og nødvendige for å ivareta pasienten og dennes behov for helsehjelp. Til eksempel har bruk av legemidler vært utbredt i pediatrien, der utviklingen av legemidler med markedsføringstillatelse har vært lav.[9] Spørsmålet om lovlig off label-bruk har også vært indirekte behandlet av Helsetilsynet i forbindelse med anvendelse av Avastin ved våt aldersrelatert makuladegenerasjon (AMD). Helsetilsynet fremhevet at off label-bruk ikke innebærer at forskrivningen av den grunn er rettsstridig: Bruken av Avastin off label i behandling av våt AMD var *per se* forsvarlig.[10] Men i den konkrete saken, var behandlingen ved St. Olavs Hospital ikke utført på forsvarlig vis.[11]

Momentene vi vil trekke frem i dette avsnittet, viser at det kan være utfordringer knyttet til off label-bruk av legemidler, samtidig som det også kan være betydelige fordeler ved off label-bruk. Rettslig sett er det viktig å presisere at det går et skille mellom retten til å markedsføre legemidler og retten til å forskrive legemidler. Markedsføringstillatelsen gir føringer for forskrivning av legemidler, men det er vanskelig å se at den er bindende.

Systematisk off label-bruk av legemidler

Off label-bruk av legemidler er altså lovlig, og ofte nødvendig, for å yte best mulig helsehjelp. Forskrivning av legemidler skjer i samråd mellom lege og pasient, og legen må følge de krav til forsvarlighet som gjelder for forskrivning av legemidler. Det har imidlertid blitt reist spørsmål ved i hvilken grad utstrakt og systematisk bruk av legemidler

[8] Det finnes visse begrensninger i forskrivningsretten som følger av Forskrift om rekvirering og utlevering av legemidler fra apotek, men disse er ikke av nærmere interesse for det som behandles her.
[9] McIntyre J, Conroy S, Avery A et al. Unlicensed and off label drug use in general practice. Arch Dis Child 2000; 83: 498 – 501. Se også: Kalikstad, Betty og Gramstad, Lars. Medisin for de store – og for de små? Tidsskr Nor Legeforen 2005;125: 1470. Link: https://tidsskriftet.no/2005/06/leder/medisin-de-store-og-de-sma#reference-2
[10] Helsetilsynet.no. Alvorlig øyeinfeksjon etter injeksjonsbehandling med Avastin ved St. Olavs hospital HF. Se s. 17. Link: https://www.helsetilsynet.no/globalassets/opplastinger/tilsyn/varsel_enhet/st_olav_hf_avastin_2017.pdf
[11] Helsetilsynet.no. Alvorlig øyeinfeksjon etter injeksjonsbehandling med Avastin ved St. Olavs hospital HF. Se s. 19-20. Link: https://www.helsetilsynet.no/globalassets/opplastinger/tilsyn/varsel_enhet/st_olav_hf_avastin_2017.pdf

off label er tillatt. Dette spørsmålet er særlig relevant idet det foreligger to legemidler som har tilnærmet lik effekt, der det ene har markedsføringstillatelse og det andre ikke.

Spørsmålet er aktuelt ved MS-behandling fordi legemiddelet ocrelizumab, som har markedsføringstillatelse for behandling av MS, ikke er besluttet innført i Norge da Bestillerforum har ønsket å gjennomføre en fullstendig metodevurdering for behandling av MS. Dersom ocrelizumab blir besluttet innført i spesialisthelsetjenesten, oppstår det et juridisk spørsmål knyttet til om utstrakt og systematisk bruk av rituksimab kan fortsette, da disse to legemidlene er meget like. Er det noen juridiske problemer eller utfordringer ved fortsatt forskrivning av rituksimab off label til MS-behandling når det finnes et alternativt preparat for denne behandlingen med markedsføringstillatelse (ocrelizumab)? Et sentralt spørsmål i en slik vurdering er om og i hvilken grad en markedsføringstillatelse må oppfattes førende og/eller bindende for forskrivningen av legemidler til en definert behandling hvor det gis alternativ behandling med et off label preparat.

Her går det, som nevnt, et prinsipielt skille mellom retten til å markedsføre et legemiddel og retten til å forskrive et legemiddel. Markedsføringstillatelsen kan derfor ikke sies å være bindende for forskrivningen av legemidler. Det kan argumenteres for at markedsføringstillatelsen legger føringer for bruken av legemidler, uten at den stiller krav til forskriveren. Forskrivning av legemidler er en rettighet som tilligger legen i dennes yrkesutøvelse og i samhandling med dennes pasient. Markedsføringstillatelse er retten til å selge/markedsføre et preparat i tråd med de vilkår som fremgår av tillatelsen. Tillatelsen vil derfor kunne sies å være førende for forskrivningen av legemidler, men ikke styrende. I forholdet mellom bruken av rituksimab og ocrelizumab, må tilsvarende resonnement ligge til grunn. Forskrivning av legemidler skjer i samhandling mellom forskriver og pasient. At ocrelizumab har markedsføringstillatelse for behandling av MS vil således være førende, men ikke bindende for forskriver.

I forlengelsen av dette, kan det stilles spørsmål ved om innføring av ocrelizumab i spesialisthelsetjenesten er til hinder for myndighetenes anbefaling, for eksempel i retningslinjene, av rituksimab til bruk i behandling av MS. Vilkår knyttet til salg og markedsføring av legemidler vil være regulert blant annet gjennom markedsføringstillatelsen, som således binder legemiddelfirmaet til de vilkår og begrensninger som er satt av myndighetene blant annet gjennom tillatelsen. Samtidig vil spørsmål om forskrivning og bruk av legemidler være regulert gjennom den generelle helselovgivningen, hvor helsevesenet (herunder legene) er underlagt krav til forsvarlig helsehjelp med tilhørende rett til fri forskrivning. Myndighetene kan her sies å ha en todelt rolle. En som er knyttet til forvaltning og oppfølgning av salg og markedsføring overfor legemiddelselskapene, og en annen overfor helsevesenet i rådgivning/anbefalinger/retningslinjer og oppfølgning av behandling og bruk (herunder forskrivning) av legemidler. Vi kjenner ikke til bestemmelser som positivt og eksklusivt avgrenser myndighetenes anbefaling om bruk og forskrivning av legemidler til de vilkår som er satt overfor legemiddelfirmaene. Det må med andre ord legges til grunn at forvaltningens rolle her er delt i ulike forvaltningsoppgaver. På den ene side tilligger det myndighetene en forvaltningsoppgave i å avklare og eventuelt utstede en markedsføringstillatelse på bakgrunn av en søknad fra et legemiddelfirma, som ikke uten videre vil være direkte begrensende på de motstående forvaltningsoppgavene som ligger i å veilede (og eventuelt utstede råd, veiledere, rundskriv m.v.) i forskrivning av legemidler (eventuelt off label) overfor helsevesenet. Til sist handler forskrivning av legemidler om hva som gir best og forsvarlig helsehjelp, hvilket er en medisinsk vurdering.

Pasientsikkerhet

Et naturlig utgangspunkt ved forskrivning av legemidler vil være å vurdere eller ta i bruk de legemidlene som har markedsføringstillatelse for bestemte indikasjoner, før eventuelt legemidler anvendes off label. Dette er fordi legemidlene etter lang og omfattende testing har vist at de tilfredsstiller kravene til kvalitet, sikkerhet og effekt, som kreves for å få godkjent markedsføringstillatelse. Av hensyn til pasientsikkerheten vil derfor legemidler med godkjent markedsføringstillatelse ofte være det foretrukne alternativet: Det kan argumenteres for at det er viktig å ikke undergrave de prinsipper og ordninger som er etablert for å ivareta pasientsikkerheten, og at pasientsikkerheten ivaretas best gjennom bruk av legemidler som har gjennomgått systematisk og forskriftsmessig testing, slik markedsføringstillatelse krever.

Hva gjelder det konkrete forholdet mellom ocrelizumab og rituksimab, kan det imidlertid hevdes at pasientsikkerheten er tilstrekkelig ivaretatt ved bruken av rituksimab. Rituksimab har blitt brukt i lang tid og har vist både god effekt og god sikkerhetsprofil ved behandling av MS, som vist i denne metodevurderingen. Usikkerheten ligger i evidensgrunnlaget og er diskutert i vurderingen. Rituksimab har tidligere også vært prioritert legemiddel i behandling av MS i Sverige.

På den annen side, er det mulig å bruke en langt enklere argumentasjon. Nå er det en gang slik at rituksimab ikke har markedsføringstillatelse for behandling av MS, mens ocrelizumab har fått dette. Det kan derfor argumenteres for at bruken av rituksimab bør, som et utgangspunkt, tilhøre unntakene - der andre legemidler med markedsføringstillatelse for indikasjonen ikke gir behandlingsresultater, kan legen i samråd med pasienten bruke legemidler off label. Markedsføringstillatelsen utgjør en sikkerhetsmekanisme for bruken av legemidler, som skal ivareta pasientsikkerheten og forhindre utstrakt bruk av eksperimentell behandling som i verste fall kan skade pasienten. Ser vi til Europa, er det slik at prinsippet om pasientsikkerhet skal ha presedens over eksempelvis økonomiske hensyn.[12] Det kan argumenteres for at et legemiddel med markedsføringstillatelse skal være foretrukket fremfor off label-preparater, nettopp fordi pasientsikkerheten er bedre ivaretatt gjennom kravene til markedsføringstillatelse. Disse hensynene vil imidlertid ikke i like stor grad gjøre seg gjeldende dersom det viser seg at dokumentasjonen for rituksimabs kvalitet, sikkerhet og effekt ved MS-behandling er tilstrekkelig overbevisende.

Krav til dokumentasjon

Det kan også stilles spørsmål ved om utstrakt og systematisk bruk av legemidler off label for indikasjoner der det finnes legemidler med godkjent markedsføringstillatelse, på sikt vil lede til en utvanning av kravene til markedsføringstillatelse. Utvanning av reglene for markedsføringstillatelse er ikke en akutt utfordring, men det kan bli en utfordring i et lenger perspektiv. Avastin-saken er et tidligere eksempel. Fortsatt utstrakt bruk av rituksimab ved innføring av ocrelizumab i spesialisthelsetjenesten er et dagsaktuelt eksempel. Og det vil trolig komme flere tilfeller i fremtiden.

Samtidig har det betydning at kravene for å få markedsføringstillatelse er strenge, og det fordrer utstrakt testing og utprøving av et legemiddel for den spesielle indikasjonen

[12] EU Directive 2001/83 is underpinne by the principle that publich health prevails over economic considerations and the system of medicines licensing is fundamental to this. The Court of Justice of the EU (CJEU) has also stated that public health must override any budgetary concerns [Case C-180/96R UK v Commission (BSE)]

det ønskes markedstillatelse for. Dette tar gjerne flere år å gjennomføre, og er naturligvis en lang, kostbar og risikofylt prosess for legemiddelprodusentene. Dersom utstrakt og systematisk bruk av legemidler off label fortsetter når det foreligger fullgode on label-alternativ, kan dette svekke legemiddelprodusentenes incentiver for å utvikle nye legemidler med markedsføringstillatelse. Dette kan på lang sikt skape et dårligere tilbud av legemidler til pasientene.[13]

Prioriteringskriterier for innføring av legemidler i spesialisthelsetjenesten
Bruk av legemidler vil alltid ha en helseøkonomisk side, som sammen med nytte og alvorlighet utgjør de lovforankrede prioriteringskriteriene for den norske spesialisthelsetjenesten[14]. Ved off label-bruk oppstår det stadig situasjoner der legemidler uten markedsføringstillatelse er billig sammenlignet med legemidler on label. Dersom rituksimab kan vurderes å være et kostnadseffektivt behandlingsalternativ til ocrelizumab, og samtidig har god effekt og gunstig bivirkningsprofil, fremkommet fra akseptabelt evidensgrunnlag, tilsier helseøkonomiske hensyn at rituksimab skal være foretrukkent legemiddel ved behandling av MS.[15]

Legemiddelindustriens rolle
Det er heller ikke urimelig å stille spørsmål ved hvorfor fortsatt utprøving av rituksimab ikke ble gjort da det for flere år tilbake i tid viste god effekt ved behandling av MS.[16] Det er ikke ukjent at legemiddelprodusentene unnlater å få markedsføringstillatelse for gamle legemidler på nye indikasjoner, for å sikre god økonomisk gevinst ved å utvikle nye, lignende legemidler, jf. blant annet den tidligere nevnte Avastin-saken, som også har vært aktuell i Europa. Samtidig er det forståelig at Roche ikke velger å gå videre med godkjenning av markedsføringstillatelse for rituksimab, når kravene til markedsføringstillatelse innebærer langt og kostbart arbeid og opphevet patent på legemiddelet fører til at det er lite penger å tjene på salg.

EU-retten

EU-retten stiller krav til markedsføringstillatelse for legemidler før de kan markedsføres i en stat. Men idet et legemiddel er gitt markedsføringstillatelse legger ikke EU-retten føringer for selve forskrivningen av legemidlene internt i staten.

Det betyr med andre ord at EU-retten ikke legger føringer for off label-bruk av legemidler. Ulike stater innad i EU har derfor ulik regulering og praktisering av off label-bruk av legemidler.

Off label-bruk i EU-retten

På samme måte som i norsk rett, krever altså EU-retten at legemidler har fått innvilget markedsføringstillatelse før de kan markedsføres i et medlemsland.[17] Dette følger av direktiv 2001/83 artikkel 6 (1) der det fremgår at "[n]o medicinal product may be

[13] Høeg, 2010.
[14] Meld. St. 34 (2015–2016) Verdier i pasientens helsetjeneste — Melding om prioritering
[15] Hagen, G. et al. *Disease modifying treatments for relapsing remitting multiple sclerosis. A health economic evaluation.* 2019. (Den helseøkonomiske evalueringen er en del av denne metodevurderingen.)
[16] Raknes, G. *Rituksimab eller okrelizumab ved multippel sklerose?*, 2018.
[17] EU-domstolens avgjørelse av 23. januar 2018. Hoffmann-La Roche Ltd m.fl. mot Autorità Garante dellaConcorrenza e del Mercato, avsnitt 53.

placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or an authorisation has been granted in accordance with Regulation (EC) No 726/2004".[18] Avgjørelsen om å gi eller ikke gi markedsføringstillatelse er basert på en vurdering av sikkerhet, kvalitet og effekt, på samme måte som det norske regelverket. Det finnes visse unntak fra utgangspunktet om krav til markedsføringstillatelse, men de er svært begrenset og underlagt strenge krav (og for øvrig ikke av ytterligere interesse for denne metodevurderingen).

Mens godkjenning av legemidler med markedsføringstillatelse er underlagt EU-lovgivningen, er selve bruken av legemidler i den medisinske utøvelsen ikke det: Forskrivningen av legemidler er noe som skjer i forholdet mellom pasient og lege, og reguleres av nasjonal lovgivning og ikke EU-regelverket.[19] Dette inkluderer off label-bruk av medikamenter. EU-lovgivningen regulerer således ikke off label-bruk av legemidler.[20] Ifølge en EU-studie gjort på off label-bruk blant EU-landene fremkommer det at "[o]nce a medicinal product is placed on the market physicians may prescribe the medicinal product off label for a wide variety of conditions in any patient: there is a general expectation that the [health care provider] would prescribe on-label, but there is the freedom of prescription."[21]

Rettspraksis fra EU-domstolen er svært begrenset når det gjelder off label-bruk av legemidler i EU.[22] Dette er nettopp fordi off label-bruk reguleres av nasjonal rett og vanligvis er forbeholdt den enkelte lege i dennes pasientforhold, jf. over. Det er imidlertid noen avgjørelser fra EU-domstolen som kan være relevant å trekke frem.

I saken *Laboratoires CTRS v Commission*, som er en av få saker som kommenterer off label-bruk, bekreftet General Court at off label-bruk av legemidler verken er forbudt i EU eller hører inn under EU-regelverket. Domstolen uttalte at "off-label prescribing is not prohibited, or even regulated, by EU law. There is no provision which prevents doctors from prescribing a medicinal product for therapeutic indications other than those for which a marketing authorisation has been granted."[23] Videre følger det av dommens avsnitt 82 at "off-label prescribing is the sole responsibility of the prescribing physician."[24]

I saken *Novartis Pharma* fremgår det at "the EU rules on pharmaceutical products prohibit neither the off-label prescription of a medicinal product nor its repackaging for such use, but do require that they comply with the conditions laid down in those rules."[25] Betingelsene for off label-bruk skulle blant annet inkludere "the requirement

[18] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.
[19] Marjolein Weda et.al., "Study on off-label use of medicinal products in the European Union," February 2017, s. 31.
[20] Jf. EU-domstolens avgjørelse av 23. januar 2018. Hoffmann-La Roche Ltd m.fl. mot Autorità Garante della Concorrenza e del Mercato, C 179/16, EU:C:2018:25, avsnitt 59, og Novartis Farma SpA v Agenzia Italiana del Farmaco, C 29/17, EU:C:2018:931, avsnitt 67.
[21] Marjolein Weda et.al., "Study on off-label use of medicinal products in the European Union," February 2017, s. 85.
[22] I analysen gjort i EU-rapporten fremgår det også svært lite relevant rettspraksis fra EU-domstolen, etter gjennomgang av aktuell praksis.
[23] General Court, case T-452/14 Laboratoires CTRS v Commission [2015], avsnitt 79.
[24] General Court, case T-452/14 Laboratoires CTRS v Commission [2015], avsnitt 82.
[25] Novartis Pharma SpA v Agenzia Italiana del Farmaco, C-29/17, EU:C:2018:931, avsnitt 67.

of holding an MA [Marketing authorization] and manufacturing authorisation, both authorisations being stated in Articles 6 and 40 of Directive 2001/83 respectively."[26] Det er imidlertid vanskelig å se hvilken videre verdi saken har for reguleringen av off label-bruk i EU.[27]

I *Hoffmann-La Roche-saken,* som var en prejudisiell avgjørelse om tolkningen av art. 101 TFEU i lys av bestemmelsene i direktiv 2001/83/EF ved off label-bruk av legemiddelet Avastin i behandling av visse øyesykdommer, bekreftet domstolen igjen at off label-bruk av legemidler ikke er forbudt i henhold til EUs regelverk. Det følger av avsnitt 56 at "[i]n that respect, it should be noted that Directive 2001/83 does not prohibit the use of medicinal products for therapeutic indications not covered by their MA. Article 5(1) of Directive 2001/83 in fact provides that a Member State may, in order to fulfil special needs, exclude from the provisions of that directive medicinal products supplied in response to a *bona fide* unsolicited order, prepared in accordance with the specifications of an authorised healthcare professional for use by an individual patient under his direct personal responsibility." Under henvisning til *Commission v Poland* (avsnitt 36)[28] og Abcur (avsnitt 56)[29] slo EU-domstolen fast at "[o]n that point, the Court has held that it is apparent from all the conditions set out in that provision, read in the light of the fundamental objectives of that directive, and in particular the objective of seeking to safeguard public health, that the exception provided for in that provision can only concern situations in which the doctor considers that the state of health of his individual patients requires that a medicinal product be administered for which there is no authorised equivalent on the national market or which is unavailable on that market", jf. avsnitt 57.

Domstolen refererer i avsnitt 57 til "that provisions", som omtales i avsnitt 56. I avsnitt 56 presiseres det først at direktiv 2001/83 ikke forbyr off label-bruk. Videre fremheves det at direktivets artikkel 5(1) tvert imot tillater at man kan gjøre unntak for kravene i nevnte direktiv "... in response to a bona fide unsolicited order…": Altså kan man selge et produkt som mangler markedsføringstillatelse under gitte vilkår (direktivets artikkel 5). Dommen legger således ikke føringer for off label-bruk, men sier noe om salg av produkter som mangler markedsføringstillatelse. Heller ikke denne dommen gir derfor ytterligere føringer for reguleringen av off label-bruk av legemidler i EU.

EU-retten er derfor tilbakeholden med å legge føringer for den enkelte stats praktisering av off label-bruk av legemidler. Reguleringen varierer fra stat til stat, der noen har eksplisitte bestemmelser, mens andre ikke har det.

Bruk i Sverige

I Sverige finnes det retningslinjer for off label-bruk av legemidler. Terapeutisk behandling, både on og off label, skal baseres på forskning og klinisk erfaring, og pasienten skal konsulteres og gi sitt informerte samtykke, jf. SFS 2010:659 og SFS 2014:821. På samme måte som i Norge, har legene fri rett til forskrivning av legemidler. Dersom det foreligger tilstrekkelig forskning og klinisk erfaring, er off label-bruk tillatt. Läkemedelverket i Sverige har imidlertid uttalt at «godkjent läkemedel med godkänd indikation

[26] Novartis Pharma SpA v Agenzia Italiana del Farmaco, C-29/17, EU:C:2018:931, avsnitt 68.
[27] Marjolein Weda et.al., "Study on off-label use of medicinal products in the European Union," February 2017, s. 148.
[28] Judgment of 29 March 2012, Commission v Poland, C-185/10, EU:C:2012:181, paragraph 36.
[29] Judgement of 16 July 2015, Abcur, C-544/13 and C-545/13, EU:C:2015:481, paragraph 56.

bör vara førstahandsval».[30] Ansvaret for off label-bruk ligger hovedsakelig hos legen i dennes profesjonelle rolle.[31]

Rituksimab brukes i behandling av MS-pasienter i Sverige. Men anbefalingen om bruk av rituksimab i MS-behandling ble i 2018 tatt bort fra retningslinjene til legemiddelkomiteen i Stockholm. Bakgrunnen for dette var at legemiddelforsikringen ble endret slik at skader ved eventuell off label-bruk ikke dekkes dersom off label-bruken var anbefalt av offentlig myndighet eller helsetjenesten.[32] Off label-bruk faller derimot ikke utenfor pasientskadeerstatningens virkeområde i Norge.

Kildeliste

Artikler

McIntyre J., Conroy S., Avery A et al. *Unlicensed and off label drug use in general practice*. Arch Dis Child 2000; 83: 498 – 501.

Kalikstad, B. og Gramstad, L. *Medisin for de store – og for de små?* Tidsskr Nor Legeforen 2005;125: 1470. https://tidsskriftet.no/2005/06/leder/medisin-de-store-og-de-sma#reference-2

Høeg, E. og Frostelid, T. Systematisk bruk av legemidler utenfor godkjent indikasjon. Tidsskr Nor Legeforen 2010;130: 1452-3. https://tidsskriftet.no/2010/08/kommentar/systematisk-bruk-av-legemidler-utenfor-godkjent-indikasjon

Hem, E. og Madsen, S. Bruk av legemidler utenfor godkjent indikasjon. Tidsskr Nor Legeforen 2016; 136: 448. https://tidsskriftet.no/2016/03/sprakspalten/bruk-av-legemidler-utenfor-godkjent-indikasjon

Marjolein Weda et.al., Study on off-label use of medicinal products in the European Union, February 2017.

Läkemedelverket, "Läkemedelverkets syn på användning av läkemedel utanför det regulatoriske godkännandet", 7. november 2016.

Norske lover

Helsepersonelloven: Lov om helsepersonell m.v. LOV-1999-07-02-64

Helsetilsynsloven: Lov om statlig tilsyn med helse- og omsorgstjenesten m.m. LOV-1984-03-3015

Legemiddelloven: Lov om legemidler m.v. LOV-1992-12-04-132

Menneskerettighetsloven: Lov om styrking av menneskerettighetenes stilling i norsk rett., LOV 1999-05-21-30

Pasient- og brukerrettighetsloven: Lov om pasient- og brukerrettigheter. LOV-1999-07-02-63

Spesialisthelsetjenesteloven: Lov om spesialisthelsetjenesten m.m. LOV-1999-07-02-61

Norske forskrifter

Legemiddelforskriften: Forskrift om legemidler. FOR-2009-12-18-1839

Forskrift om legemidler fra apotek: Forskrift om rekvirering og utlevering av legemidler fra apotek. FOR-1998-04-27-455

EU-lovgivning

EU Directive 2001/83 Directive 2001/83/EC of the EUROPEAN Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

Direktiv 65/65/EEC: Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products

[30] Läkemedelverkets syn på användning av läkemedel utanför det regulatoriske godkännandet 7. november 2016.
[31] Marjolein Weda et.al., "Study on off-label use of medicinal products in the European Union," February 2017, s. 66.
[32] Heyman, Sara. *Rekommendation för ms-behandling tas bort*. Publisert i LäkemedelsVärlden 3. mai 2018. Link: https://www.lakemedelsvarlden.se/behandlingsrekommendation-for-ms-tas-bort/. Se også Hake, Carl-Magnus og Moe, Lasse. *Svensk legemiddelkomité trekker MS-anbefalinger*. Publisert i Dagens Medisin 11. mai 2018. Link: https://www.dagensmedisin.no/artikler/2018/05/11/stockholms-legemiddelkomite-trekker-MS-anbefalinger/

Praksis fra EU-domstolen

Novartis Pharma: Judgement of the Court (First Chamber) 21 November 2018. Novartis Pharma SpA v Agenzia Italiana del Farmaco, C-29/17, EU:C:2018:931

Commission v Poland: Judgment of 29 March 2012, Commission v Poland, C-185/10, EU:C:2012:181

Abcur AB: Judgement of the Court of 16 July 2015, C-544/13 and C-545/13, EU:C:2015:481. Abcur AB v Apoteket Farmaci AB and Apoteket AB

Hoffmann-La Roche: EU-domstolens avgjørelse av 23. januar 2018. Case C-179/16. Hoffmann-La Roche Ltd m.fl. mot Autorità Garante della Concorrenza e del Mercato.

Laboratoires CTRS v Commission: General Court, case T-452/14 Laboratoires CTRS v Commission [2015]

Internett

Dagensmedisin.no: Moe, L.. *Behandler flere MS-pasienter med "off label" som første behandling*.

https://www.dagensmedisin.no/artikler/2018/04/05/behandler-flere-ms-pasienter-med-off-label-som-forste-behandling/ [Publisert 2018-04-05 11.30]

Dagensmedisin.no: Hake, C.-M. Og Moe, L. *Svensk legemiddelkomité trekker MS-anbefalinger*. https://www.dagensmedisin.no/artikler/2018/05/11/stockholms-legemiddelkomite-trekker-MS-anbefalinger/ [Publisert 11. mai 2018]

Felleskatalogen.no: Søkeord: *MabThera*, https://www.felleskatalogen.no/medisin/mabthera-roche-561182 [12.03.2019]

Helsetilsynet.no: Tilsynsrapport etter alvorlig hendelse. Alvorlig øyeinfeksjon etter injeksjonsbehandling med Avastin ved St. Olavs hospital HF. https://www.helsetilsynet.no/globalassets/opplastinger/tilsyn/varsel_enhet/st_olav_hf_avastin_2017.pdf [31.08.2017]

Lakemedelsverlsen.se: Heyman, S. *Rekommendation för ms*-behandling tas bort. https://www.lakemedelsvarlden.se/behandlingsrekommendation-for-ms-tas-bort/ [Publisert 3. mai 2018]

Relis.no: Raknes, G. og Westergren, T. *Rituksimab eller okrelizumab ved multippel sklerose?,* https://relis.no/content/4969/Rituksimab-eller-okrelizumab-ved-multippel-sklerose [Publisert 15.10.2018]

Discussion

Key findings and conclusions

We have systematically collected and reviewed the evidence for clinical effectiveness and general safety issues for disease modifying treatments for relapsing remitting multiple sclerosis, synthesised evidence from randomised controlled trials and non-randomised registry-based studies using network meta-regression, and carefully interpreted the findings. We included rituximab in our analysis as it is used off-label for the treatment of patients with RRMS, even though it does not hold marketing authorisation for RRMS.

We included 35 randomised controlled trials and 11 non-randomised registry-based studies, with a total of almost 30 000 patients. We compared estimates of our predefined outcomes from meta-analysis of randomised controlled trials, of non-randomised registry-based studies, the network meta-regression, and other network meta-analytical models, and judged that the estimates are mutually consistent in most cases, and that where there is inconsistency, it could be explained.

Based on the available evidence and the meta-analysis used: alemtuzumab is most likely to be the best treatment with respect to annual relapse rate; ocrelizumab and alemtuzumab are equally likely to be the best treatments with respect to risk of disability progression. Further, we estimate that rituximab is likely to have the lowest risk of serious adverse events and treatment withdrawal due to adverse events. However, the evidence for rituximab is from one small randomised trial of short duration and one non-randomised study, making this finding uncertain.

Treatment rankings are based on available evidence and model assumptions, and in many cases confidence intervals for the highest-ranked treatments overlap, so rankings should not be interpreted as definitive.

There were very few deaths in the included studies (30 deaths out of a total of 22 060 patients). Although we performed a full network meta-analysis, we judged that the number of events was too small to support useful conclusions regarding mortality risk.

We compiled information of rare, and potentially life-threatening effects of disease modifying treatments from the included studies, but we have not searched other sources or databases that may be more suitable for such information. The risk of specific serious adverse events was not estimated due to the limited data available, but data were retrieved from all included studies. The events were generally uncommon in the included studies, which reported no statistically significant differences in rates of serious adverse events.

The effect estimates of annualised relapse rate and sustained disability progression were used in a health economic analyses that is reported in a separate publication.

Evidence quality

Several working groups have made an effort to develop guidelines for how to assess certainty of effect estimates generated by NMAs and we describe this in detail under Methods. However, the grading of NRS in meta-analyses has not previously been done. We are not confident that the available method offer the best solution for our assessment. One example is that the estimate of ARRR for ocrelizumab versus placebo were evaluated to be of low certainty with the reason that NRS contributed to the estimate. There are no included NRSs presenting results on ocrelizumab, and a low certainty of evidence may seem odd. However, since ocrelizumab is not compared to placebo in any studies, the effect estimate is generated from loops in the network, and these loops includes NRS. The shortest loops are used for grading, and if this loop contains an NRS, as for ocrelizumab, the certainty will be downgraded.

We considered only including NRS for rituximab to avoid the downgrading of other treatments, but both our clinical experts and input from the industry suggested that study types should be the same for all treatments. Hence, the trade-off is that more effect estimates are downgraded. However, as described above, the consistency between the estimates generated by the different models, allows us to suggest that the results are not heavily compromised by including NRSs.

Strengths and weaknesses

Inclusion of non-randomised studies (NRS)

In our network meta-analyses, our most important assumption is the transitivity assumption, i.e. that there is no systematic differences across the included studies other than the treatments studied.

In our assessment, the included RCTs were sufficiently similar for the transitivity assumption to hold. However, we also included NRS which for many reasons may be different from RCTs. Most obvious is the risk of bias due to lack of randomisation, but NRS may also differ from RCTs in other ways, e.g. reporting of adverse events and adherence to treatment. The potential differences between estimates based on RCT and NRS-data were accounted for in the network meta-regression. The high degree of consistency between the estimates of the RCT-based, NRS-based and network meta-regression shows that the regression model is well fitted.

Further, three NRS were the main contributors to the effect estimates of rituximab, and all three NRS were from the Swedish Multiple Sclerosis Register (MS Register). To avoid double-counting patients, we included data from only one NRS for each outcome. If multiple NRSs reported data on the same outcome, we chose the study with the most patients.

A validation of the Swedish MS register (80) found satisfying overlap between the register and hospital charts for EDSS outcomes for rituximab, suggesting that this register is a valid source for results on MS treatments. A potential strength of data from registers is that the population may be less selected, and thus can provide results that are more applicable to MS-patients in general than RCT-findings.

Network meta-analyses

Our estimates are based on network meta-regression analyses. We modelled data arm-wise using network meta-regression rather than the more common alternative approach to network meta-analysis, contrast-wise modelling. We chose the arm-wise model because it allowed us to model possible differences between RCT and NRS evidence. Also, it allowed us to provide estimates for treatments that were part of small disconnected networks, which occurred for some outcomes.

While the model we generally favour attempts to adjust for systematic bias and differences in heterogeneity between RCT and NRS evidence, we did not attempt to model more complex differences. For example, we did not try to model:

- possible systematic differences in the precision of estimates reported by the two types of study
- how estimates from studies may be biased in favour of particular treatments
- differences in patient inclusion criteria definitions (e.g., McDonald 2010 versus 2017)
- definitions of endpoints such as serious adverse events and treatment withdrawal.

However, we judged that there was likely sufficient similarity for the purpose of evidence synthesis, and our work is comparable to recent systematic reviews and network meta-analyses on RRMS.

We also performed simpler analyses using the contrast-wise approach (the naïve NMA and the NMA that includes only RCT evidence). We compared estimates provided by the three models for consistency, and we present estimates from all three models for the purpose of transparency. We found that the estimates were inconsistent only for a few treatments and outcomes, and these differences between the models' estimates seem to have simple and plausible explanations.

Safety data

We had expected that the inclusion of registry-based studies would yield long term follow data on safety outcomes, but this proved not to be the case as the follow up time for patients in these studies were not very different from the RCTs.

Our results on rare serious adverse effects should therefore be interpreted cautiously as the follow up time in the included studies may have been too short to detect important adverse events. Further, it may also be the case that registry based NRS underreport SAEs and that patients participating in RCTs experience few SAEs due to the selection criteria for these studies.

For rare adverse events, it is likely that real world experience or surveillance systems or databases from WHO (VigiBase) or EMA (Eudra Vigilance) may provide stronger data than the types of studies we have included, as illustrated by the recent notice from EMA about restrictions of the use of alemtuzumab (24).

We analysed the risk of experiencing SAEs, and treatment withdrawal due to AEs, from our included studies. The results did not show any specific risk profile for neither of the treatments, but the risk of serious adverse events seemed lower than for placebo. This counter intuitive finding is easily explained by the fact that the definition of SAE includes hospitalisation, thus any treatment that effectively reduces the risk of being hospitalised due to relapses will have a beneficial SAE-profile. For rituximab, the results were based on one small RCT and one NRS from the Swedish registry. It is suggested that reporting of SAE may be under reported to this registry although this has not been validated (personal communication, Andres Svenningsson).

Treatment withdrawal due to adverse events is a typical outcome in RCTs, seen as an indication of which degree a patient finds that the adverse effects outweighs the treatment effect. There may be legitimate concerns that the results for rituximab are driven by NRS evidence from the Swedish registry, which may differ in important ways from RCT evidence (see *Network meta-analysis,* which outlines the degree to which we attempted to model such differences in our statistical analysis). However, reporting of treatment withdrawal to the Swedish MS registry is a first priority for the Swedish neurologist and data on this outcome is therefore considered relatively solid (personal communication, Anders Svenningsson).

Safety profile of natalizumab

Natalizumab is recognized as an effective therapy available for RRMS, but is also associated with PML (16). Ho *et al* showed that the risk of PML was increased in patients both with (2.7 per 1000 patients) and without (less than 0.07 per 1000 patients) antibodies against JVC (81).

In our included studies, no events of PML were reported, which is not surprising given the relatively low number of participants and short follow up.

Safety profile of alemtuzumab

Alemtuzumab has been associated with thyroid disorders and studies show that a 5-year incidence of thyroid adverse events in phase 3 clinical trials is up to 40.7% (summarised in a Belgian consensus group on diagnosis and management of thyroid disorders in alemtuzumab (82)). The seriousness of the type, frequency, and course of thyroid dysfunction was studies in a cohort of alemtuzumab-treated patients with MS in the United Kingdom (17). In our report we counted eight cases of serious thyroid disease per 1000 patients in the alemtuzumab groups, while none in the other groups. However, the scarcity of data did not allow us to perform solid statistical analyses or draw any firm conclusions.

In addition to thyroid events, alemtuzumab has recently been linked to fatal or life-threatening cases of HLH, other immune-mediated conditions, and various cardiovascular events (25). Based on these reports, EMA has advised to restrict the use of alemtuzumab in new patients, while it is being reviewed (24).

Safety profile of ocrelizumab vs rituximab

A review by Menge *et al* (83) specifically discusses the risk of long-term depletion of B-cells using ocrelizumab and rituximab, underlining that repeated long-term B-cell depletion may lead to exhaustion of adaptive immune responses. Potential effects of this may be difficult to capture in a clinical trial. The safety profile of a treatment may also differ depending on the indication. This can be exemplified by ocrelizumab showing no increased incidences over placebo of malignancies in the treatment of rheumatoid arthritis of up to 5 year follow-up (84) while in the ORATORIO trial (85) where ocrelizumab was used to treat primary progressive multiple sclerosis, 11 malignancies were reported in the ocrelizumab treated patients (n=486), compared to 2 in the placebo-group (n=239). Hence, we should be careful extrapolating long-term safety data from other indications, for either ocrelizumab or rituximab. We have therefore not included safety data for rituximab in the treatment of other indications in this assessment.

Rituximab has a better ranking for both outcomes, but due to the uncertainty around the effect estimates we cannot rule out the possibility that ocrelizumab is the better drug.

The molecular difference between ocrelizumab and rituximab is mostly related to the degree of chimerisation, ocrelizumab being more humanized than rituximab. It has been shown that rituximab treatment is associated with a high degree (37%) of anti-drug-antibodies, which is correlated with efficacy of B-cell depletion (86). In contrast, anti-human antibodies were found in only 0.4% of patients treated with ocrelizumab (66). However, the clinical relevance of anti-drug-antibodies or reduced B-cell depletion remains uncertain (86).

Consistency with other reviews

The ICER report from 2017 (14) analysed outcomes overlapping with ours: ARR, confirmed disease progression (combined 12 and 24 weeks), treatment withdrawal and serious adverse events. Their estimates for ARR ratio and confirmed disability progression for treatments against placebo were consistent with ours. They also reported that specific SAEs were uncommon and not statistically different from placebo. However, they identified life-threatening harms from post-marketing data which we have not included. All effect estimates for ARR for treatments compared to placebo were slightly lower in our report compared to the results of Li et al (87), but the ranking of treatments was similar. Further, our ranking for ARR, CDP and SAE were all similar to those reported by McCool et al (77), while the ranking for treatment discontinuation due to adverse events differed slightly.

Need for further research

There is substantial uncertainty about the comparative effectiveness of the various disease-modifying treatments for MS. More and better evidence, preferably in the form of RCTs are needed to enable more firm conclusions. This is particularly the case for rituximab, where we only identified one small RCT. Two RCTs where rituximab is one of the treatments, are currently registered at clinicaltrial.gov.

Further, we have identified numerous ongoing clinical trials, as well as preliminary results presented in ECTRIMS-2018 abstracts, where safety is one of the most important outcomes. When more study results become available, we expect to have more evidence with regards to the safety issues for MS treatments. It may therefore be valuable to perform an updated systematic review of only safety issues within two years.

Methods used in the evaluation of clinical effectiveness and safety

We evaluated clinical effectiveness and safety following the protocol and its amendment (*Appendix 3*), except as described in section *Protocol deviations — statistical analysis*.

Search methods for identification of studies

An information specialist performed a literature search to identify studies according to the inclusion and exclusion criteria. We performed the following searches:

1. An updated systematic search based on the previous Norwegian HTA (3). We limited the search to year of publication 2015-2018 (23.05.2018). The medicines that were included are listed under "Inclusion criteria". RCT limitation.
2. A search of medicines with marketing authorisation for RRMS but not included in the previous HTA (cladribine and ocrelizumab). No date limitation (search date 07.06.2018). RCT limitation.
3. A search of the use of rituximab as a disease-modifying treatments for multiple sclerosis. No date limitation (search date 22.05.2018). No study design limitation.
4. A search for registry studies of all included treatments (search date 12.10.2018).
5. A search for ongoing clinical trials (search date 20.08.2018).
6. A search for systematic reviews on serious adverse effects (search date 15.01.2019).
7. A hand search for relevant abstracts from the ECTRIMS meeting in Berlin 2018 in Multiple Sclerosis Journal 2018; 24:(S2).

Search strategy

For search 1 to 6 we systematically searched the literature using databases listed in *Appendix 19*. The information specialist (in collaboration with the project team) conducted the literature search using index terms (where possible; Medical Subject Headings and EMTREE terms), and free text terms related to the population and the interventions of interest. The search strategy was peer reviewed. The complete search strategy is shown in *Appendix 19*. All searches were be performed using the generic names of the medicines.

Selection of studies

We based the selection of studies on the following criteria:

Population

Men and women aged 18 and above diagnosed with relapse-remitting multiple sclerosis (RRMS) (as for the previous report) who were treatment naïve or not, at the start of the trial.

Intervention

All disease-modifying treatments approved by the National System for Managed Introduction of New Health Technologies within the Specialist Health Service, including ocrelizumab, except interferons and peg-interferon (due to low priority use). In addition, rituximab was included as an off-label medicine for the indication. For all included medicines, see *Table 10*. The patient partners had wanted to see stem cell transplantation as one of the interventions, but this was not included in the assessment.

Table 10. *Included medicines*

Active substance (Brand/generic name) *First authorisation date in Norway*	**Approved indication***	**Administration method and dose**	**Posology**
Alemtuzumab (Lemtrada) *September 2013*	RRMS	I.V.: 10 mg/ml, concentrate for solution for infusion	1st treatment course: 12 mg/day on 5 consecutive days 2nd treatment course: 12 mg/day on 3 consecutive days, 12 months after first course If needed: 3rd and 4th treatment course: 12 mg/day on 3 consecutive days, at least 12 months after the prior course
Cladribine (Mavenclad) *August 2017*	RRMS	Oral: 10 mg tablets.	Recommended cumulative dose: 3,5 mg/kg body weight over 2 years, administered as one treatment course of 1,75 mg/kg per year. Each treatment course consists of two treatment weeks (week 1: beginning of first month, week 2: beginning of second month). Following completion of two treatment courses, no further treatment is required In years 3 and 4.
Dimethyl fumarate (Tecfidera) *January 2014*	RRMS	Oral: 120 mg or 240 mg, gastro-resistant hard capsules.	Recommended maintenance dose: 240 mg, orally twice daily
Fingolimod (Gilenya) *March 2011*	RRMS	Oral: 0,5 mg, hard capsules.	0,5 mg capsule, orally once daily
Glatiramer acetate (Copaxone/ Copemyl) *February 2004 (20 mg)* *January 2015 (40 mg)*	RRMS	S.C.: 20 mg/ml or 40 mg/ml, solution for injection, pre-filled syringe (1 ml).	20 mg (= one pre-filled syringe), subcutaneous injection, once daily or 40 mg (= one pre-filled syringe), subcutaneous injection, three times weekly, with at least 48 hours apart
Natalizumab (Tysabri) *June 2006*	RRMS	I.V.: 300 mg, concentrate for solution for infusion	300 mg, once every 4 weeks
Ocrelizumab (Ocrevus) *January 2018*	RRMS, PPMS	I.V.: 300 mg, concentrate for solution for infusion.	Initial doses: 600 mg administered at two separate infusions of 300 mg each (first 300 mg, then 300 mg 2 weeks later). Subsequent doses: 600 mg, once every 6 months, starting 6 months after the first infusion of the initial dose.

Rituximab (MabThera/ Tixathon) *March 2014*	NHL, CLL, RA, GPA, MPA**	I.V.: 10 mg/ml, concentrate for solution for infusion.	Posology from included studies for RRMS: Usual dose: 500-1000 mg, every 6-12 months
Teriflunomide (Aubagio) *August 2013*	RRMS	Oral: 14 mg, film-coated tablets.	14 mg, once daily

** Approved indication according to the Norwegian Medicines Agency*
*** NHL: non-Hodgkin's lymphoma, CLL: chronic lymphocytic leukaemia, RA: rheumatoid arthritis, GPA: granulomatosis with polyangiitis (Wegener's), MPA: microscopic polyangiitis*

Comparison

As comparators, we used medicines in *Table 10* as well as interferons or placebo.

Outcomes

We included the following outcomes:

- Annualised clinical relapse rate
- Risk of confirmed disability progression, defined as a sustained increase in patient's EDSS score. Typically assessed as disability progression sustained over 12 or 24 weeks (12- or 24-CDP). We chose to estimate a single disability progression outcome, and used the longest confirmation time when a study reported more than one.
- Change in EDSS score
- Risk of new lesions detected using Magnetic Resonance Imaging (MRI). We estimated the risk of experiencing one or more lesions, as detected using T1-weighted Gd-enhanced MRI.
- Risk of mortality
- Risk of serious adverse events (SAE). We analysed the SAE as reported in the RCTs, where we assumed the FDA definition (79). For rituximab, the a contributing study was one NRS (70). In this study, they reported adverse events according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, which has 5 steps. We used the steps 3-4 in the analyses. Also, we did not adjust for SAE from relapses. Hence, the risk of SAE results may be considered as a result of clinical effect rather than providing information about the safety profile of the treatments.
- Risk of treatment withdrawal due to adverse events (AE)
- Risk of selected serious adverse events (cancer, PML, thyroid diseases, infections)

Annualised relapse rate and confirmed disability progression were the clinical effect estimates used in the health economic evaluation. The patient partners commented on the importance of long-term safety issues.

Study design

We included the following study designs:

- For the updated search (based on the previous Norwegian HTA (3)) and for the new medicines, RCTs and NRS were included. We limited the NRS search to include studies using national- or hospital-based registers, or chart reviews as data source.
- In addition:

- We retrieved systematic reviews and meta-analysis to check the included primary studies and references to ensure our search had captured all relevant studies
- We identified companion studies and used them to search for updated data
- We registered the trial registry number when available
- We included studies presenting pooled data, trial extensions, post-hoc analyses and interim analyses to search for the most updated data from relevant primary studies

Exclusion criteria

- Reports on the cellular and molecular mechanisms of the medicines
- Daclizumab have been withdrawn from market and were therefore not included
- All interferons, including peg-interferon, were excluded due to low-priority use, but were included as comparators for the included medicines
- Mitoxantrone were excluded due to limited use
- Rituximab for sub-cutaneous delivery was excluded since this has not been used for the present indication
- Studies of pregnant women

Selection of publications

The studies in this HTA were selected through two steps. In both steps, two persons worked independently, assessing articles against the described inclusion criteria. In the first step, two persons read all titles and abstracts retrieved by the literature search and selected potentially relevant full-texts. In the second step, the two persons read all the selected full text articles to decide which articles should be included in the HTA. Any disagreements throughout this work were solved either through discussion or by involving a third person.

Risk of bias and quality of included studies

Two researchers assessed for the risk of bias using the Cochrane Collaboration tool (88) for the randomised controlled trials and a checklist for cohort studies from the Handbook of Norwegian Institute of Public health (4) for the NRS. Risk of bias was rated as low risk of bias, unclear risk of bias, or high risk of bias. Any disagreements were solved either through revising or by involving a third person.

Data extraction

One researcher extracted the data from the selected publications and a second verified the findings. The following data were extracted:

Study characteristics

- Information on publication (author names, year of publication)
- Description of study (design and setting, clinical trial identification, source of funding)
- Participant characteristics (number of participants in the trial, age, gender, MS diagnosis, length of disease, and status of disease, e.g. by EDSS)

- Description of intervention and comparator (i.e. dose, frequency)
- Outcomes (number of events, methods used to ascertain outcome data, estimates of risk, length of follow-up).
- Baseline characteristics

Measures of treatment effect

All included outcomes were extracted from the studies by two researches. The statistician used the extracted data and double checked occasionally with the original paper.

Data analyses

We analysed the extracted data as described in the protocol and its amendment, except as where detailed in the protocol deviations section below.

Treatment definition

We did not pre-specify how we would define treatments but followed an approach similar to that used in the previous FHI report on disease-modifying drugs for relapsing-remitting multiple sclerosis (3). We considered a treatment to be a unique combination of drug name, dose, and regimen because we anticipated dose-response relationships. We modelled a combination therapy of an interferon and glatiramer acetate as a distinct treatment. Dose and regimen information were not clearly reported by all studies, particularly among registry studies. Where this information was lacking, we imputed dose and regimen based on regulator-approved doses and regimens. Evidence about the safety and effectiveness of rituximab is supported mostly by registry studies, which did not clearly report dose and regimen. Following advice from our panel of experts, we modelled rituximab as a single treatment in the networks. However, there is likely heterogeneity in dose and regimen between the one RCT that studied rituximab, and within and between the registry studies. We modelled placebo and "untreated" as distinct treatments. We treated brand and generic versions of the same drug as a single treatment (if dose and regimen were identical). We modelled OPERA I and II (66) as distinct trials.

Measures of treatment effect

The results section for each outcome explains how the outcome was defined and the treatment effect estimates used. Briefly, event rates (e.g., annualised relapse rate) were modelled on the log rate scale, with relative treatment effect estimates analysed as rate ratios; dichotomous events were modelled on the log risk scale, with relative treatment effect estimates reported as risk ratios (RRs); and change in EDSS was measured on a continuous scale.

Dealing with missing data

We planned in our original protocol to include only randomised evidence and to address missing data for dichotomous outcomes (e.g., disability progression) by imputing that patients lost to follow-up experienced the outcome event. The project plan was subsequently amended to also include non-randomised registry evidence, for which pa-

tients could not be lost to follow-up. To avoid treating the two types of available evidence differently, we chose not to impute that patients lost to follow-up experienced events. We planned not to address missing data for continuous outcomes (e.g., annualised relapse rate), and did not do so.

Imputation

For annualised relapse rate, log rates and standard errors on log rates were imputed for studies that reported annualised relapse rates as point estimates and confidence intervals by assuming the sampling distribution of mean log rate is approximately normal on the log scale, following §7.7.7.3 of the Cochrane Handbook (89). Imputation was performed for studies that reported number of relapses and total time at risk using the "escalc" function of the "metafor" package (i.e., a Poisson-like method); one-half event counts were added to zero event counts. Imputation was performed for studies that only reported point estimates of mean annualised relapse rate by assuming the reported rate was computed by the study authors by dividing the number of events by total time at risk; total time at risk was itself imputed as the product of sample size and study duration; the "escalc" function was then used. Total time at risk was imputed for studies that reported median time on study by imputing mean time on study using the method of Wan et al. (90) and multiplying the result by the sample size.

For dichotomous outcomes (e.g., disability progression), log risk and standard error on log risk were computed using the "escalc" function of the "metafor" package; one-half event counts were added to zero event counts. For risks reported as means and confidence intervals, standard error on log risk was imputed by assuming the sampling distribution of mean log risk is approximately normal on the log scale, following §7.7.7.3 of the Cochrane Handbook (89).

Standard error on mean change in EDSS was imputed for studies reporting standard deviations via division by the square root of the sample size. Standard error on mean change in EDSS was imputed for studies reporting confidence intervals by assuming the sampling distribution of mean change in EDSS is approximately normal.

To avoid introducing additional treatments in the network merely to distinguish brand from generic versions of the same treatment, study arms that compared brand and generic versions of the same treatment were pooled within studies using inverse variance-weighted meta-analytic estimates of continuous outcomes, or by pooling event counts for dichotomous outcomes.

We planned to base 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), but in some cases had to use data reported as "modified" intention to treat or similar.

Assessment of possible publication bias

We inspected funnel plots of the arm-wise data extracted from the included studies, plotting for each treatment supported by at least three studies a measure of treatment effect (e.g., log risk of disability progression) and its associated standard error. We

treated these analyses as exploratory. We planned not to perform formal statistical tests of asymmetry and did not perform such tests.

Assessment of transitivity assumption

For each outcome, we assessed the validity of the transitivity assumption (that there were no systematic differences across the included studies other than the treatments studied) by extracting study- and arm-level data on the following variables: blinding method (double, rater-only, or unblinded); lead country; study duration; number of centres; number of countries; total sample size; RCT study phase; study sponsorship (public or industry); treatment experience for enrolment (experienced or naïve); minimum and maximum age for enrolment; diagnosis method; minimum and maximum EDSS for enrolment; relapse criterion for enrolment; average patient age at baseline; patient gender; patient race; mean time since disease onset; annualised relapse rate at baseline; treatment experience at baseline (experienced or naïve); average baseline EDSS; average number of gadolinium-enhancing lesions at baseline; average lesion volume on T_1-weighted MRI at baseline; average lesion volume on T_2-weighted MRI at baseline; and normalized brain volume at baseline. We inspected plots of the extracted data and performed exploratory regression analyses to test the null hypotheses of no association with treatment comparison (for study-level data) or treatment (for arm-level data).

Network meta-analyses

Conventional meta-analysis synthesises evidence from studies that each compare a single pair of treatments (e.g., a treatment of interest versus placebo). NMA is a generalisation of conventional meta-analysis to the case where there are multiple treatments, and therefore multiple pairs of treatments that may be compared (91). In the common case, each study included in an NMA directly compares some but not all treatments, and the studies form a network of evidence (i.e., each trial studies at least one treatment that is also studied by at least one other trial).

NMA allows treatment effects to be estimated for all possible pairs of treatments, including those that have not been directly compared in any of the studies. However, this is only possible if certain assumptions hold. For example, an NMA model may assume that it would be theoretically possible for a given patient to have been randomised to any arm of any included study. Such rigid assumptions can be relaxed using random effects models, in which each study is assumed to come from a distribution of studies that are generally similar to one another but nonetheless differ (e.g. due to differences in inclusion criteria), and network meta-regression in which adjustment can be made for important differences between study arms and studies. If the assumptions underpinning an NMA are violated, important inconsistency will be observed between the treatment effect estimates extracted from the included studies and the NMA estimates. A substantial amount of NMA work involves assessing the validity of the assumptions made prior to performing the analysis and evaluating any eventual inconsistency.

For most outcomes we performed NMA using three different frequentist models. The simplest model is a naïve NMA that assumes there are no important differences between studies. This assumption may be invalid because we included a mix of randomised controlled trials (randomised evidence; RCTs) and non-randomised studies (NRS), which may provide estimates that differ in important ways. In exploratory analyses, we fitted a second model, which was simply the naïve model with non-randomised evidence excluded. The third, and most complex model, which we favour, is a network meta-regression model that models possible differences between randomised and non-randomised evidence. Important differences between the models used are outlined in *Table 11*.

Table 11. *Network meta-analysis models*

	Naïve network meta-analysis[1]	Network meta-analysis of RCTs[2]	Network meta-regression[3]
Based only on studies that are assumed *a priori* to provide high-certainty evidence		✓	
Includes all available evidence			✓
Models multi-arm trials[4]	✓	✓	✓
Preserves original patient allocation[5]	✓	✓	
Models distinction between RCTs and registry studies			✓
Facilitates analysis of studies that form disconnected networks[6]			✓

Notes:
1. The naïve network meta-analyses (NMAs) presented in this report assume that there are no important differences between studies. This assumption is likely invalidated by the inclusion of a mix of randomised and non-randomised evidence.
2. This report also presents NMAs based only on RCT evidence. The model used is identical to that used in the naïve NMA, but non-randomised evidence is excluded. Treatment effects cannot be estimated for outcomes that are only supported by non-randomised evidence.
3. The report favours results from network meta-regressions based on a multilevel linear mixed-effects model that accounts for differences between the randomised and non-randomised evidence. If necessary, simplified models were used.
4. Trials with more than two arms induce a correlation structure that is accounted for by all methods.
5. Contrast-wise data are entered into the network meta-analyses; arm-wise data are entered into the network meta-regression.
6. Disconnected networks occur when, for example, there are studies that directly compare treatments A and B, and treatments C and D, but where there are no studies that directly compare treatments A or B to treatments C or D. Disconnected networks are also formed if single-arm results are included.

Naïve NMAs, and NMAs of RCTs only, were performed using a model proposed by Rücker (92). We performed these analyses using the "netmeta" R package (93), described further in (94).

Network meta-regressions were performed using a multivariate linear mixed-effects model, as implemented in the "metafor" R package (95). This model includes fixed effects that model systematic differences between treatments and systematic differences between randomised and non-randomised evidence, and random effects that model heterogeneity between studies and between randomised and non-randomised evi-

dence. The model can be viewed as a frequentist arm-wise version of the class of models proposed by Efthimiou et al. (96) to combine randomised and non-randomised evidence in an NMA. We gratefully acknowledge Wolfgang Viechtbauer, author of the "metafor" package, who suggested the model (personal communication). Because this model is quite complex, we did not attempt to model other sources of variation such as possible over-precision of the NRS, nor interactions between treatment and evidence type. For some outcomes the network meta-regression model was over-parameterized and could not be fitted. In such cases we attempted to simplify the model and report the model used alongside the results.

Because the three models generally used different data, and the "netmeta" package does not provide model fit statistics such as Akaike information criterion, we did not formally compare model fits. We inspected profile plots for the network meta-regression models to verify that the variance components were estimated correctly. In cases where profile plots lacked clear maxima that were correctly estimated, we report the analyses in the appendices: they should be treated as exploratory and estimates should be interpreted with appropriate caution.

For each outcome, we computed a P-score for each treatment, to quantify the extent of certainty that one treatment is better than another treatment (averaged over all competing treatments), and ranked the treatments from best (rank 1) to worst by P-score (97). Because there are generally more treatments in the networks than treatments of interest, reported rankings may not begin at 1 and the ranks may not be contiguous. We present full ranking lists in the appendices.

Assessment of inconsistency

Following Efthimiou et al. (96), for each comparison and where possible we used forest plots to assess inconsistency in estimates of "absolute" treatment effects between:

- Direct randomised evidence
- Indirect randomised evidence
- Direct non-randomised evidence
- Indirect non-randomised evidence
- Naïve network evidence
- Network evidence from randomised evidence alone
- Network meta-regression

We judged inconsistency in in estimates of "absolute" treatment effects using two different treatments as a reference: placebo and interferon-beta-1a 44 ug (3 × week sc). In a given forest plot, we judged there to be inconsistency if 95% confidence intervals computed for these sources of evidence did not overlap. We comment on any inconsistency observed when presenting the results.

Presentation of results

For each outcome, we present a graph that shows the network of direct evidence supporting the analysis. Each treatment is represented by a graph vertex, and each direct comparison is represented by a graph edge. Edges are color-coded to indicate whether the comparison was studied in an RCT or NRS. The precision (inverse-variance) of each

direct treatment effect estimate is indicated by edge transparency: opaque edges indicate high-precision estimates (e.g., study arms with many patients), while translucent edges indicate low-precision estimates (e.g., study arms with few patients).

Following Methodological Expectations of Cochrane Intervention Reviews (MECIR) standards (98), we expressed relative effect estimates in absolute terms as follows. Annualised relapse rate ratios comparing each treatment to placebo were re-expressed as annualised relapse rates; a meta-analytical estimate of mean relapse rate on placebo was used as the reference. For dichotomous outcomes (e.g., disability progression), risk ratios comparing each treatment to placebo were re-expressed as the number of patients per 1000 patients who would be expected to experience the event; a meta-analytical estimate of mean risk on placebo was used as the reference. We did not re-express change in EDSS, as this relative treatment effect was judged to be directly interpretable. All estimates reported for network meta-regressions are adjusted for evidence type (we report estimates we would anticipate from randomised controlled trials rather than registry studies).

In the summary of findings tables (see below), confidence intervals on relative treatment effect estimates account for uncertainty on the effect of both treatments in the comparison. Confidence intervals on absolute effect estimates assume a point estimate for the reference treatment (i.e., placebo) and therefore only account for uncertainty on the absolute effect of the treatment of interest. Judgements about "statistical significance" may therefore differ between relative and absolute treatment effects.

For each treatment of interest, we also present a radar plot of P-scores for the following outcomes to facilitate treatment comparison across multiple efficacy and safety outcomes in a single figure: annualised relapse rate, risk of disability progression, risk of serious adverse event, and risk of study withdrawal due to adverse event.

Protocol deviations — statistical analysis

We planned to present net heat plots to aid inconsistency assessment. However, the "netmeta" package was unable to do this due to the large number of treatments included in the network.

We planned to assess network and within- and between-design homogeneity and consistency via decompositions of Cochrane's Q statistic using the "netmeta" package. However, the "netmeta" package does not facilitate modelling of possible differences between randomised and non-randomised evidence via regression. Such statistics would therefore not be useful for interpreting the network meta-regression models we generally prefer.

In the original protocol, we planned to perform subgroup, sensitivity, or regression meta-analyses for the two primary outcomes, for example with respect to risk of bias and type of intervention (e.g., drug mechanism). However, amending the project to include both randomised and non-randomised evidence substantially expanded the complexity of the project. To ensure the project could be completed within a reasonable timeframe we chose not to perform such exploratory analyses. However, we did perform sensitivity analysis by comparing NMAs of RCTs alone (which we assume *a priori*

provide high certainty evidence) and NMAs that use randomised and non-randomised evidence (which we assume *a priori* provide low certainty evidence).

In the case of sparse count data, we planned to switch from frequentist to Bayesian methods. We would have done this for the cancer and mortality outcomes. However, we judged that Bayesian analyses would not meaningfully change the results.

We planned to estimate reference values for use in computing "absolute" effect estimates using data from placebo arms published in studies that were included in the previous report but not eligible for inclusion in this project. However, the network meta-regression models that we generally favour include an intercept term corresponding to the reference treatment, which means it is not necessary to use external data to estimate reference values. Readers may calculate "absolute" measures of effect using their own reference values via the relative treatment effect estimates we report.

Grading the certainty of estimates

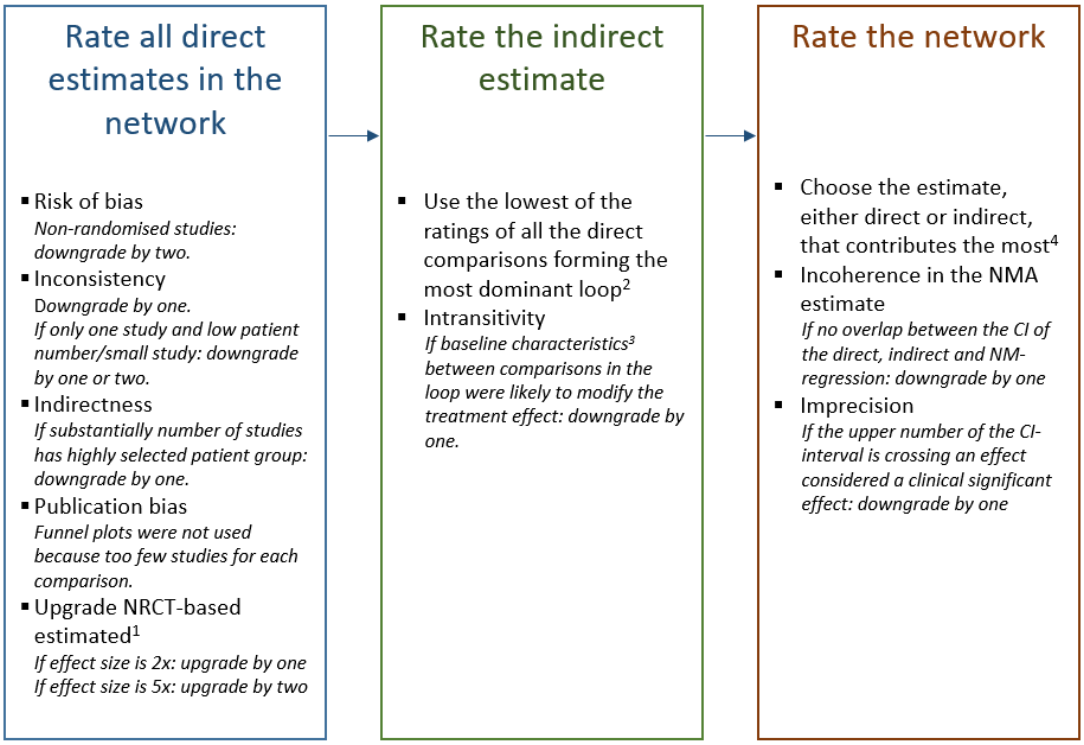
We used GRADE-NMA (75;76) to assess the certainty of the estimates, and performed the assessment for the comparison of the nine included medicines to placebo. Hence, we did not separately assess the in-between comparisons of the different treatments.

We rated the certainty of estimates for annual relapse rate ratio and relative risk of disability progression, both against placebo, the two outcomes used in the economic evaluation. We did not rate the certainty of evidence for all treatments for the other outcomes. To provide certainty of evidence statements for rituximab (given it is a treatment of particular interest in this report), we GRADEd this treatment if it was ranked among the three best treatments for the other outcomes we report.

We followed the strategy shown in *Figure 27* (adapted from (76) and modified to our purpose). First, we assessed all direct evidence contributing to the entire NMA ("*Rate all direct estimates in the network*"). Second, we assessed the indirect evidence that constituted the fewest comparisons (loops of lowest order) or a medicine-placebo comparison in the NMA ("*Rate the indirect estimate*"). Where there were multiple paths between a pair of treatments, we defined the dominant path to be the one with the least total sampling variance. Third, we rated the network ("*Rate the network*") by evaluating the inconsistency between the relative treatment effect estimates from the network meta-regression and the direct and indirect estimates (incoherence), and the confidence interval in the network meta-regression (imprecision). Publication bias was analysed using funnel plot. However, we did not assess this in our grading due to the few publications for each comparison.

We used the GRADE definitions (75) in *Table 12*. We adapted the summary of findings table from Yepes-Nunes et al (74).

Figure 27. *GRADE the network meta-analyses estimates*



[1]To avoid upgrading of an estimate based on a mixture of RCT and NRS, we upgrade based on effect size in this step
[2]«The most dominant loop» was the one with the least total sampling variance
[3]We focused on baseline characteristics as time since disease onset, annualised relapse rate and average EDSS score
[4]Judged to be the estimate with the narrowest confidence interval

Table 12. *GRADE definitions*

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

References

1. Compston A, Coles A. Multiple sclerosis. Lancet 2008;372(9648):1502-17.
2. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17(2):162-73.
3. Couto E, Hamidi V, Ringerike T, Odgaard-Jensen J, Harboe I, Klemp M. NIPH Systematic Reviews. In: Medicines Used for Multiple Sclerosis - A Health Technology Assessment. Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH); 2016.
4. Folkehelseinstituttet. Slik oppsummerer vi forskning. Håndbok. 2014. Available from: https://www.fhi.no/kk/oppsummert-forskning-for-helsetjenesten/slik-oppsummerer-vi-forskning/
5. Spelman T, Frisell T, Piehl F, Hillert J. Comparative effectiveness of rituximab relative to IFN-beta or glatiramer acetate in relapsing-remitting MS from the Swedish MS registry. Multiple Sclerosis Journal 2018;24(8):1087-95.
6. McKay KA, Kwan V, Duggan T, Tremlett H. Risk factors associated with the onset of relapsing-remitting and primary progressive multiple sclerosis: a systematic review. Biomed Res Int 2015;2015:817238.(doi):10.1155/2015/817238. Epub 2015 Jan 31.
7. Koch-Henriksen N, Sorensen PS. The changing demographic pattern of multiple sclerosis epidemiology. Lancet Neurol 2010;9(5):520-32. doi: 10.1016/S474-4422(10)70064-8.
8. Trust MS. Expanded Disability Status Scale (EDSS)[cited]. Available from: http://www.mstrust.org.uk/atoz/edss.jsp
9. Gasperini C, Prosperini L, Tintore M, Sormani MP, Filippi M, Rio J, et al. Unraveling treatment response in multiple sclerosis: A clinical and MRI challenge. Neurology 2019;92(4):180-92.
10. Tintore M, Rovira A, Rio J, Otero-Romero S, Arrambide G, Tur C, et al. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. Brain 2015;138(Pt 7):1863-74.
11. NICE. Multiple sclerosis in adults: management. Clinical guideline [CG186]: NICE [cited]. Available from: http://www.nice.org.uk/guidance/CG186
12. Ziemssen T, De Stefano N, Pia Sormani M, Van Wijmeersch B, Wiendl H, Kieseier BC. Optimizing therapy early in multiple sclerosis: An evidence-based view. Mult Scler Relat Disord 2015;4(5):460-9. doi: 10.1016/j.msard.2015.07.007. Epub Jul 17.
13. Helsedirektoratet. Sykdomsmodulerende behandling av aktiv inflammatorisk multippel sklerose (MS): Helsedirektoratet [cited]. Available from: https://helsedirektoratet.no/retningslinjer/multippel-sklerose/seksjon?Tittel=sykdomsmodulerende-behandling-av-aktiv-1338#pasienter-med-aktiv-inflammatorisk-multippel-sklerose-(ms),-definert-som-nylig-klinisk-attakk-eller-påvisning-av-nye-lesjoner-ved-mr,-bør-tilbys-sykdomsmodulerende-legemiddelbehandling.anbefaling
14. ICER. Disease-Modifying Therapies for Relapsing-Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value: ICER [cited]. Available from: https://icer-review.org/wp-content/uploads/2016/08/CTAF_MS_Final_Report_030617.pdf

15. Dong-Si T, Gheuens S, Gangadharan A, Wenten M, Philip J, McIninch J, et al. Predictors of survival and functional outcomes in natalizumab-associated progressive multifocal leukoencephalopathy. Journal of neurovirology 2015;21(6):637-44.
16. Vermersch P, Kappos L, Gold R, Foley JF, Olsson T, Cadavid D, et al. Clinical outcomes of natalizumab-associated progressive multifocal leukoencephalopathy. Neurology 2011;76(20):1697-704.
17. Pariani N, Willis M, Muller I, Healy S, Nasser T, McGowan A, et al. Alemtuzumab-Induced Thyroid Dysfunction Exhibits Distinctive Clinical and Immunological Features. The Journal of clinical endocrinology and metabolism 2018;103(8):3010-8.
18. McClain KL, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosisUpToDate: UpToDate [cited 02.05.2019]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis?search=Hemophagocytic%20lymphohistiocytosis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
19. Sepulveda FE, de Saint Basile G. Hemophagocytic syndrome: primary forms and predisposing conditions. Curr Opin Immunol 2017;49:20-6.
20. Ramos-Casals M, Brito-Zeron P, Lopez-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet 2014;383(9927):1503-16.
21. McClain KL. Treatment and prognosis of hemophagocytic lymphohistiocytosisUpToDate: UpToDate [cited 02.05.2019]. Available from: https://www.uptodate.com/contents/treatment-and-prognosis-of-hemophagocytic-lymphohistiocytosis?search=Hemophagocytic%20lymphohistiocytosis&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2#H526310
22. Saarela M, Senthil K, Jones J, Tienari PJ, Soilu-Hanninen M, Airas L, et al. Hemophagocytic lymphohistiocytosis in 2 patients with multiple sclerosis treated with alemtuzumab. Neurology 2018;90(18):849-51.
23. Myro AZ, Bjerke G, Zarnovicky S, Holmoy T. Diffuse alveolar hemorrhage during alemtuzumab infusion in a patient with multiple sclerosis: a case report. BMC Pharmacol Toxicol 2018;19(1):75.
24. Use of multiple sclerosis medicine Lemtrada restricted while EMA review is ongoing [press release]. The European Medicine Agency, : The European Medicine Agency, , 12.04.2019 2019.
25. European Medicines Agency. Assessment report on provisional measures - Lemtrada. European Medicines Agency,: European Medicines Agency,; 2019. EMA/249094/2019. Available from: https://www.ema.europa.eu/en/documents/referral/lemtrada-article-20-referral-assessment-report-provisional-measures_en.pdf
26. Grytten N, Torkildsen O, Myhr KM. Time trends in the incidence and prevalence of multiple sclerosis in Norway during eight decades. Acta neurologica Scandinavica 2015;132(199):29-36.
27. Berg-Hansen P, Moen SM, Harbo HF, Celius EG. High prevalence and no latitude gradient of multiple sclerosis in Norway. Mult Scler 2014;20(13):1780-2. doi: 10.177/1352458514525871. Epub 2014 Mar 6.
28. Kingwell E, Marriott JJ, Jette N, Pringsheim T, Makhani N, Morrow SA, et al. Incidence and prevalence of multiple sclerosis in Europe: a systematic review. BMC Neurol 2013;13:128.(doi):10.1186/471-2377-13-128.
29. Coles AJ, Compston DA, Selmaj KW, Lake SL, Moran S, Margolin DH, et al. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med 2008;359(17):1786-801. doi: 10.056/NEJMoa0802670.
30. Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-

modifying therapy: a randomised controlled phase 3 trial. Lancet 2012;380(9856):1829-39. doi: 10.016/S0140-6736(12)61768-1. Epub 2012 Nov 1.
31. Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet 2012;380(9856):1819-28. doi: 10.016/S0140-6736(12)61769-3. Epub 2012 Nov 1.
32. Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, Sorensen PS, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. New England Journal of Medicine 2010;362(5):416-26.
33. Cook S, Vermersch P, Comi G, Giovannoni G, Rammohan K, Rieckmann P, et al. Safety and tolerability of cladribine tablets in multiple sclerosis: The CLARITY (CLAdRIbine Tablets treating multiple sclerosis orallY) study. Multiple Sclerosis Journal 2011;17(5):578-93.
34. Comi G, Cook SD, Giovannoni G, Rammohan K, Rieckmann P, Sorensen PS, et al. MRI outcomes with cladribine tablets for multiple sclerosis in the CLARITY study. JNeurol 2013;260(4):1136-46.
35. Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012;367(12):1098-107.
36. Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med 2012;367(12):1087-97.
37. Ernst FR, Barr P, Elmor R, Wong SL. Relapse outcomes, safety, and treatment patterns in patients diagnosed with relapsing-remitting multiple sclerosis and initiated on subcutaneous interferon beta-1a or dimethyl fumarate: a real-world study. Current Medical Research and Opinion 2017;33(12):2099-106.
38. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010;362(5):387-401. doi: 10.1056/NEJMoa0909494. Epub 2010 Jan 20.
39. Calabresi PA, Radue EW, Goodin D, Jeffery D, Rammohan KW, Reder AT, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): A double-blind, randomised, placebo-controlled, phase 3 trial. The Lancet Neurology 2014;13(6):545-56.
40. Saida T, Kikuchi S, Itoyama Y, Hao Q, Kurosawa T, Nagato K, et al. A randomized, controlled trial of fingolimod (FTY720) in Japanese patients with multiple sclerosis. Mult Scler 2012;18(9):1269-77. doi: 10.177/1352458511435984. Epub 2012 Feb 21.
41. Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med 2010;362(5):402-15. doi: 10.1056/NEJMoa0907839. Epub 2010 Jan 20.
42. Comi G, Stefano N, Freedman M, Barkhof F, Uitdehaag B, Vos M, et al. Subcutaneous interferon beta-1a in the treatment of clinically isolated syndromes: 3-year and 5-year results of the phase III dosing frequency-blind multicentre REFLEXION study. Journal of neurology, neurosurgery and psychiatry 2017;88(4):285-94.
43. O'Connor P, Filippi M, Arnason B, Comi G, Cook S, Goodin D, et al. 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. Lancet Neurol 2009;8(10):889-97. doi: 10.1016/S474-4422(09)70226-1. Epub 2009 Sep 2.
44. Lublin FD, Cofield SS, Cutter GR, Conwit R, Narayana PA, Nelson F, et al. Randomized study combining interferon and glatiramer acetate in multiple sclerosis. AnnNeurol 2013;73(3):327-40.

45. Lublin F, Cofield S, Cutter G, Gustafson T, Krieger S, Narayana P, et al. Long-term follow-up of a randomized study of combination interferon and glatiramer acetate in multiple sclerosis: efficacy and safety results up to 7 years. Multiple sclerosis and related disorders 2017;18:95-102.
46. Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. AnnNeurol 2013;73(6):705-13.
47. Calabrese M, Bernardi V, Atzori M, Mattisi I, Favaretto A, Rinaldi F, et al. Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing-remitting multiple sclerosis. Multiple sclerosis (Houndmills, Basingstoke, England) 2012;18(4):418-24.
48. Rinaldi F, Perini P, Atzori M, Favaretto A, Seppi D, Gallo P. Disease-modifying drugs reduce cortical lesion accumulation and atrophy progression in relapsing-remitting multiple sclerosis: results from a 48-month extension study. Mult Scler Int 2015.
49. Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging--measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. Ann Neurol 2001;49(3):290-7.
50. Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology 1995;45(7):1268-76.
51. Mikol DD, Barkhof F, Chang P, Coyle PK, Jeffery DR, Schwid SR, et al. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. Lancet Neurol 2008;7(10):903-14. doi: 10.1016/S474-4422(08)70200-X. Epub 2008 Sep 11.
52. Cohen J, Belova A, Selmaj K, Wolf C, Sormani M, Oberyé J, et al. Equivalence of Generic Glatiramer Acetate in Multiple Sclerosis: a Randomized Clinical Trial. JAMA neurology 2015;72(12):1433-41.
53. Boiko A, Lashch N, Sharanova S, Zakharova M, Trifonova O, Simaniv T, et al. A Comparative Placebo-Controlled Clinical Trial of the Efficacy and Safety of Glatiramer Acetate 20 mg in Patients with Remitting Multiple Sclerosis: first-Year Study Results. NeurosciBehavPhysiol 2018;48(3):351-7.
54. Kalincik T, Jokubaitis V, Izquierdo G, Duquette P, Girard M, Grammond P, et al. Comparative effectiveness of glatiramer acetate and interferon beta formulations in relapsing-remitting multiple sclerosis. Multiple Sclerosis Journal 2015;21(9):1159-71.
55. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006;354(9):899-910.
56. Gobbi C, Meier DS, Cotton F, Sintzel M, Leppert D, Guttmann CRG, et al. Interferon beta 1b following natalizumab discontinuation: One year, randomized, prospective, pilot trial. BMC Neurol 2013;13(101).
57. Zecca C, Riccitelli GC, Calabrese P, Pravata E, Candrian U, Guttmann CR, et al. Treatment satisfaction, adherence and behavioral assessment in patients de-escalating from natalizumab to interferon beta. BMC Neurol 2014;14:38.
58. Saida T, Kira JI, Kishida S, Yamamura T, Ohtsuka N, Ling Y, et al. Safety and Efficacy of Natalizumab in Japanese Patients with Relapsing-Remitting Multiple Sclerosis: Open-Label Extension Study of a Phase 2 Trial. Neurology and Therapy 2017;6(1):39-55.

59. Fox RJ, Cree BAC, De Seze J, Gold R, Hartung HP, Jeffery D, et al. MS disease activity in RESTORE: A randomized 24-week natalizumab treatment interruption study. Neurology 2014;82(17):1491-8.
60. Frisell T, Forsberg L, Nordin N, Kiesel C, Alfredsson L, Askling J, et al. Comparative analysis of first-year fingolimod and natalizumab drug discontinuation among Swedish patients with multiple sclerosis. Multiple Sclerosis Journal 2016;22(1):85-93.
61. Guger M, Enzinger C, Leutmezer F, Kraus J, Kalcher S, Kvas E, et al. Real-life clinical use of natalizumab and fingolimod in Austria. Acta neurologica Scandinavica 2018;137(2):181-7.
62. Kalincik T, Horakova D, Spelman T, Jokubaitis V, Trojano M, Lugaresi A, et al. Switch to natalizumab versus fingolimod in active relapsing-remitting multiple sclerosis. AnnNeurol 2015;77(3):425-35.
63. Koch-Henriksen N, Magyari M, Sellebjerg F, Soelberg Sorensen P. A comparison of multiple sclerosis clinical disease activity between patients treated with natalizumab and fingolimod. MultScler 2017;23(2):234-41.
64. Lanzillo R, Carotenuto A, Moccia M, Sacca F, Russo CV, Massarelli M, et al. A longitudinal real-life comparison study of natalizumab and fingolimod. Acta neurologica Scandinavica 2017;136(3):217-22.
65. Prosperini L, Sacca F, Cordioli C, Cortese A, Buttari F, Pontecorvo S, et al. Real-world effectiveness of natalizumab and fingolimod compared with self-injectable drugs in non-responders and in treatment-naive patients with multiple sclerosis. JNeurol 2017;264(2):284-94.
66. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. New England Journal of Medicine 2017;376(3):221-34.
67. Kappos L, Li D, Calabresi PA, O'Connor P, Bar-Or A, Barkhof F, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet 2011;378(9805):1779-87. doi: 10.016/S0140-6736(11)61649-8. Epub 2011 Oct 31.
68. Hauser SL, Waubant E, Arnold DL, Vollmer T, Antel J, Fox RJ, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. New England Journal of Medicine 2008;358(7):676-88.
69. Alping P, Frisell T, Novakova L, Islam-Jakobsson P, Salzer J, Bjorck A, et al. Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. AnnNeurol 2016;79(6):950-8.
70. Granqvist M, Boremalm M, Poorghobad A, Svenningsson A, Salzer J, Frisell T, et al. Comparative Effectiveness of Rituximab and Other Initial Treatment Choices for Multiple Sclerosis. JAMA Neurology 2018;75(3):320-7.
71. O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med 2011;365(14):1293-303. doi: 10.056/NEJMoa1014656.
72. Vermersch P, Czlonkowska A, Grimaldi LM, Confavreux C, Comi G, Kappos L, et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: A randomised, controlled phase 3 trial. MultScler 2014;20(6):705-16.
73. Confavreux C, O'Connor P, Comi G, Freedman MS, Miller AE, Olsson TP, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): A randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Neurology 2014;13(3):247-56.
74. Yepes-Nunez JJ, Li SA, Guyatt G, Jack SM, Brozek JL, Beyene J, et al. Development of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Summary of Findings (SoF) Table for Network Meta-analysis. Journal of clinical epidemiology 2019.
75. Puhan MA, Schunemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect

estimates from network meta-analysis. BMJ (Clinical research ed) 2014;349:g5630.
76. Brignardello-Petersen R, Bonner A, Alexander PE, Siemieniuk RA, Furukawa TA, Rochwerg B, et al. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. Journal of clinical epidemiology 2018;93:36-44.
77. McCool R, Wilson K, Arber M, Fleetwood K, Toupin S, Thom H, et al. Systematic review and network meta-analysis comparing ocrelizumab with other treatments for relapsing multiple sclerosis. Multiple sclerosis and related disorders 2019;29:55-61.
78. Wiendl H, Meuth SG. Pharmacological Approaches to Delaying Disability Progression in Patients with Multiple Sclerosis. Drugs 2015;75(9):947-77.
79. What is a Serious Adverse Event?: FDA [cited]. Available from: https://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm
80. Alping P, Piehl F, Langer-Gould A, Frisell T. Validation of the Swedish Multiple Sclerosis Register: Further Improving a Resource for Pharmacoepidemiologic Evaluations. Epidemiology (Cambridge, Mass) 2019;30(2):230-3.
81. Ho PR, Koendgen H, Campbell N, Haddock B, Richman S, Chang I. Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies. Lancet Neurol 2017;16(11):925-33.
82. Decallonne B, Bartholome E, Delvaux V, D'Haeseleer M, El Sankari S, Seeldrayers P, et al. Thyroid disorders in alemtuzumab-treated multiple sclerosis patients: a Belgian consensus on diagnosis and management. Acta neurologica Belgica 2018;118(2):153-9.
83. Menge T, Dubey D, Warnke C, Hartung HP, Stuve O. Ocrelizumab for the treatment of relapsing-remitting multiple sclerosis. Expert Rev Neurother 2016;16(10):1131-9.
84. Emery P, Rigby W, Tak PP, Dorner T, Olech E, Martin C, et al. Safety with ocrelizumab in rheumatoid arthritis: results from the ocrelizumab phase III program. PLoS One 2014;9(2):e87379.
85. Montalban X, Hauser SL, Kappos L, Arnold DL, Bar-Or A, Comi G, et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. New England Journal of Medicine 2017;376(3):209-20.
86. Dunn N, Juto A, Ryner M, Manouchehrinia A, Piccoli L, Fink K, et al. Rituximab in multiple sclerosis: Frequency and clinical relevance of anti-drug antibodies. Multiple Sclerosis Journal 2018;24(9):1224-33.
87. Li H, Hu F, Zhang Y, Li K. Comparative efficacy and acceptability of disease-modifying therapies in patients with relapsing-remitting multiple sclerosis: a systematic review and network meta-analysis. J Neurol 2019.
88. Chapter 8: Assessing risk of bias in included studies: Cochrane tools [cited December]. Available from: https://handbook-5-1.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm
89. Cochrane handbook[cited 12/02/2015]. Available from: http://handbook.cochrane.org/
90. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC medical research methodology 2014;14:135.
91. Salanti G, Higgins JP, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. Statistical methods in medical research 2008;17(3):279-301.
92. Rucker G. Network meta-analysis, electrical networks and graph theory. Research synthesis methods 2012;3(4):312-24.
93. Rucker G, Kran U, König J, Efthimiou O, Schwarzer G. netmeta: Network Meta-Analysis using Frequentist Method. R package version 1.0-1[cited 21.05.2019]. Available from: https://github.com/guido-s/netmeta

94. Schwarzer G, Carpenter J, G R. Meta-Analysis with R (Use-R!): Sprinter International Publishing; 2015.
95. Viechtbauer. Conducting Meta-Analyses in R with the metafor Package. Journal of Statistical Software 2010;36(3):48.
96. Efthimiou O, Mavridis D, Debray TP, Samara M, Belger M, Siontis GC, et al. Combining randomized and non-randomized evidence in network meta-analysis. Statistics in medicine 2017;36(8):1210-26.
97. Rucker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC medical research methodology 2015;15:58.
98. Higgins JP, Lasserson T, Chandler J, Tovey D, Churchill R. Standards for the conduct and reporting of new Cochrane Intervention Reviews, reporting of protocols and the planning, conduct and reporting of updates. Methodological Expectations of Cochrane Intervention Reviews (MECIR), Version 1.07: Cochrane Community [cited 21.05.2019]. Available from: https://community.cochrane.org/mecir-manual

Appendices – General

Appendix 1. Progress log

Logg og tid brukt i rapporten		
LOGG	Forslag til metode innsendt/ metodevarsel publisert på nyemetoder.no	30.01.2018
	Metodevurdering bestilt av Bestillerforum RHF	23.04.2018
	Start metodevurdering	15.05.2018
	Fageksperter kontaktet første gang	19.06.2018
	Brukerrepresentant kontaktet første gang	Juni 2018
	Første møte med faggruppe	Juni 2018
	LIS/sykehusinnkjøp kontaktet for første gang	Juni 2018
	Dato for rapport sendt til eksterne fagfeller (gjelder rapporter fra FHI)	Mai 2019
	Dato for rapport sendt til ekstern produsent	Ikke aktuelt
	Dato for rapport sendt til sekretariatet for Bestillerforum RHF	Juni 2019
TID	Tid brukt til å innhente ytterligere dokumentasjon fra produsent	Ikke aktuelt
	Tid brukt til å innhente ytterligere dokumentasjon fra andre aktører	Ikke aktuelt
	Totalt antall dager i påvente av dokumentasjon	Ikke aktuelt
	Totalt antall dager til saksbehandling (total tid hos utrederinstans)	400

Appendix 2. Table of abbreviations

AE	Adverse events
ARR	Annualised relapse rate
ARRR	Annualised relapse rate ratio
CIS	Clinical isolated syndrome
CNS	Central nervous system
DMT	Disease-modifying treatment
ECTRIMS	European committee for treatment and research in multiple sclerosis
EDSS	Expanded Disability Status Scale
EMA	European Medicine Agency
EQ-5D	EuroQoL-5 Dimensions
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HLH	Haemophagocytic lymphohistiocytosis
HTA	Health technology assessment
IFN	Interferon
JCV	John Cunningham virus
MRI	Magnetic Resonance Imaging
MS	Multiple sclerosis
NMA	Network meta analyses
NRS	Non-randomised study
PML	Progressive multifocal leukoencephalopathy
PPMS	Primary progressive multiple sclerosis
PRAC	Pharmacovigilance Risk Assessment Committee
P-score	The mean extent of certainty that a treatment is better than competing treatments
QALY	Quality adjusted live years
RCT	Randomised controlled trials
RR	Risk ratios
RRMS	Relapsing remitting multiple sclerosis
SAE	Serious adverse events
SPMS	Secondary progressive MS

Appendix 3. Project plan and amendment

The project plan was published in September 2018, and is found here:

https://www.fhi.no/globalassets/dokumenterfiler/prosjekter/id2018_004-project-plan-rrms-with-amendment.pdf

The amendment was made in February 2019 and is found at the end of the project plan.

Appendices – Study selection

Appendix 4. Description of included randomised controlled trials

Study	Interventions and control	Follow up / History	Eligibility criteria	Baseline characteristics	Outcomes and definitions
ALEMTUZUMAB					
CAMMS223 (Coles 2008); NCT00050778; RCT; Phase 2; Rater-blinded; Multicenter (49 centres, Europe and US)	Alemtuzumab, n=113 12 mg, i.v., daily, 5 consecutive days at month 1, 3 consecutive days at months 12 and 24 Alemtuzumab, n=110 24 mg, i.v., daily, 5 consecutive days at month 1, 3 consecutive days at months 12 and 24 IFNβ-1a, n=111 44 µg, s.c., three times a week	3 years / Treatment-naive	**Age:** Not given in eligibility criteria **Diagnosis:** RRMS (McDonald criteria) with an onset of symptoms no more than 36 months before the time of screening **EDSS:** 0-3,0 **Lesions:** One or more enhancing lesions on MRI **Relapses:** ≥ 2 relapses during the previous 2 years.	Alemtuzumab 12 mg **Age:** 31,9 ± 8,0; **Female:** 64,3%; **EDSS:** 1,9 ± 0,74 Alemtuzumab 24 mg **Age:** 32,2 ± 8,8; **Female:** 64,5%; **EDSS:** 2,0 ± 0,73 IFNβ-1a **Age:** 32,8 ± 8,8; **Female:** 64,0%; **EDSS:** 1,9 ± 0,83	**Relapses:** New or worsening symptoms with an objective change in neurologic examination attributable to multiple sclerosis that lasted for at least 48 hours, that were present at normal body temperature, and that were preceded by at least 30 days of clinical stability. **Disability:** An increase of at least 1,5 points for patients with a baseline score of 0 and of 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. **Lesions:** Changes in lesion burden (as seen on T2-weighted MRI), and brain volume (as measured by the Losseff method on T1-weighted MRI8). **Mortality; SAE; Withdrawal due to SAE**
CARE MS II (Coles 2012); NCT00548405; RCT; Phase 3; Rater-blinded; Multicenter (194 academic medical centres and clinical practices, 23 countries, incl Europe, Canada, and US)	Alemtuzumab 12 mg, n=436 12 mg, i.v., daily, 5 consecutive days at month 0, 3 consecutive days at months 12 Alemtuzumab 24 mg, n=173 24 mg, i.v., daily, 5 consecutive days at month 0, 3 consecutive days at months 12 IFNβ-1a, n=231 44 µ, s.c., Three times a week	2 years / Treatment-experienced	**Age**: 18-50 years **Diagnosis:** RRMS (McDonald criteria) with disease duration up to 5 years **EDSS:** 0-5,0 **Lesions:** had cranial and spinal MRI lesions **Relapses:** ≥ 2 relapses during the previous 2 years and at least one in the previous year.	Alemtuzumab 12 mg **Age:** 34,8 ± 8,36; **Female:** 281; **EDSS:** 2,7 ± 1,26; **Duration of onset:** 4,5 ± 2,68 years since first clinical events Alemtuzumab 24 mg **Age:** 35,1 ± 8,4; **Female:** 120; **EDSS:** 2,7 ± 1,17; **Duration of onset:** 4,3 ± 2,77 years since first clinical events IFNβ-1a **Age:** 35,8 ± 8,77; **Female:** 131 **EDSS:** 2,7 ± 1,21; **Duration of onset:** 4,7 ± 2,86 years since first clinical events	**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 the baseline EDSS score was 0) confirmed over 6 months. **Mortality; SAE; Lesions; Withdrawal due to SAE**
CARE-MS I (Cohen 2012); NCT00530348; RCT; Phase 3; Rater-blinded; Multicenter (101 centers 16 countries, including Europe, Canada, and US)	Alemtuzumab, n= 386 12 mg, i.v., daily, 5 consecutive days at baseline, and at 3 consecutive days at month 12 IFNβ-1a, n=195 44 µ, s.c., Three times a week	2 years / Treatment-naive	**Age:** 18-55 years **Diagnosis:** RRMS (McDonald criteria) with disease duration up to 5 years **EDSS:** 0-3,0 **Lesions:** Cranial abnormalities on MRI attributable to MS **Relapses:** ≥ 2 relapses during the previous 2 years.	Alemtuzumab **Age:** 33,0 ± 8,0; **Female:** 243; **EDSS:** 2,0 ± 0,8; **Duration from onset:** 2,1 ± 1,4 years IFNβ-1a **Age:** 33,2 ± 8,5; **Female:** 122; **EDSS:** 2,0 ± 0,8; **Duration from onset:** 2,0 ± 1,3	**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. **Mortality; SAE; Lesions; Withdrawal due to SAE**

Appendix 4. Description of included randomised controlled trials

Study	Interventions and control	Follow up / History	Eligibility criteria	Baseline characteristics	Outcomes and definitions
CLADRIBINE					
CLARITY (Giovanni 2010, Cook 2011, Comi 2013); NCT00213135; RCT; Phase 3; Double blind; Multicenter (155 clinical centers, 32 countries)	Cladribine, n=433 3,5 mg/kg, oral, daily, given 4-5 consecutive days at 4-week intervals Cladribine, n=456 5,25 mg/kg, oral, daily, given 4-5 consecutive days at 4-week intervals Placebo, n=437 Oral, Daily, Given 4-5 consecutive days at 4-week intervals	8 years / Mixed	**Diagnosis:** RRMS (McDonald criteria) **EDSS:** ≤ 5,5 **Lesions:** had lesions consistent with MS on MRI (Fazekas criteria) **Relapses:** ≥ 1 relapse within 12 months before study entry	*From Giovanni 2010* Placebo **Age:** 38,7 ± 9,9 years; **Female:** 288; **Weight:** 70,3 ± 15,4 kg; **EDSS:** 2,9 ± 1,3; **Duration from onset:** 8,9 ± 7,4 years Cladribine 3,5 mg/kg **Age:** 37,9 ± 10,2 years; **Female:** 298; **Weight:** 68,1 ± 14,6 kg; **EDSS:** 2,8 ± 1,2; **Duration from onset:** 7,9 ± 7,2 years Cladribine 5,25 mg/kg **Age:** 39,1 ± 9,9 years; **Female:** 312; **Weight:** 69,3 ± 14,8 kg; **EDSS:** 3,0 ± 1,4; **Duration from onset:** 9,3 ± 7,3 years	**Relapse:** an increase of 2 points in at least one functional system of the EDSS or an increase of 1 point in at least two functional systems (excluding changes in bowel or bladder function or cognition) in the absence of fever, lasting for at least 24 hours and to have been preceded by at least 30 days of clinical stability or improvement. T**ime to sustained progression of disability:** the time to a sustained increase (for at least 3 months) of at least 1 point in the EDSS score or an increase of at least 1,5 points if the baseline EDSS score was 0. **Mortality; SAE; Lesions; Withdrawal due to SAE**
DIMETHYL FUMARATE					
DEFINE (Gold 2012); NCT00420212; RCT; Phase 2; Double-blind; Multicenter (198 sites, 28 countries)	Dimethyl fumarate, n = 411 240 mg; oral, twice daily (BID) Dimethyl fumarate , n = 416 240 mg, oral, tree times daily (TID) Placebo: n = 410 Oral	2 years / Mixed	**Age:** 18-55 years **Diagnosis:** RRMS (McDonald criteria) **EDSS:** 0,0 to 5,0 **Lesions:** ≥ 1 gadolinium-enhancing lesion within 6 weeks before randomization or **Relapses:** ≥1 clinically documented relapse within 12 months before randomization	Dimethyl fumarate (BID) **Age:** 38,1 ± 9,1 years; **Female:** 296; **Weight:** 70,7 ± 18,5 kg; **EDSS:** 2,40 ± 1,29; **Duration from onset:** 5,6 ± 5,4 years (since diagnosis) Dimethyl fumarate (TID) **Age:** 38,8 ± 8,8 years; **Female:** 306; **Weight:** 71,3 ± 16,9 kg; **EDSS:** 2,36 ± 1,19; **Duration from onset:** 5,1 ± 5,3 years (since diagnosis) Placebo **Age:** 38,5 ± 9,1 years; **Female:** 306; **Weight:** 71,7 ± 17,0 kg; **EDSS:** 2,48 ± 1,24; **Duration from onset:** 5,8 ± 5,8 years (since diagnosis)	**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 in-creased score sustained for at least 12 weeks. **Mortality; SAE; Lesions; Withdrawal due to SAE**
CONFIRM (Fox 2012) NCT00451451; RCT; Phase 3; Partly blinded/Rater-blinded; Multicentre (200 sites, 28 countries)	Dimethyl fumarate, n=359 240 mg, oral, twice daily (BID) Dimethyl fumarate, n=345 240 mg, oral, three times daily (TID) Glatiramer acetate, n=350 20 mg, s.c., 1x daily Placebo: n=363 Oral	2 years / Mixed	**Age:** 18-55 years **Diagnosis:** RRMS (McDonald criteria) **EDSS:** 0 to 5 **Relapse:** at least one clinically documented re-lapse in the previous 12 months or **Lesions:** at least one gadolinium-enhancing lesion 0 to 6 weeks before randomization Comment: one patient in the Dimethyl fumarate BID group had an EDSS-score higher than 5.	Dimethyl fumarate BID **Age:** 37,8 ± 9,7 years; **Female:** 245; **Weight:** 71,9 ± 17,9 kg; **EDSS:** 2,6 ± 1,2; **Duration from onset:** 4,9 ± 5,1 years Dimethyl fumarate TID **Age:** 37,8 ± 9,7 years; **Female:** 250; **Weight:** 72,5 ± 17,8 kg: **EDSS:** 2,5 ± 1,2; **Duration from onset:** 4,6 ± 5,2 years Glatiramer acetate **Age:** 36,7 ± 9,1 years; **Female:** 247; **Weight:** 71,4 ± 19,1 kg; **EDSS:** 2,6 ± 1,2; **Duration from onset:** 4,4 ± 4,7 years Placebo **Age:** 36,9 ± 9,2 years; **Female:** 251; **Weight:** 72,6 ± 16,9 kg; **EDSS:** 2,6 ± 1,2; **Duration from onset:** 4,8 ± 5,0 years	**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 point in patients with a baseline score of 0, confirmed at least 12 weeks later. **Mortality; SAE; Lesions; Withdrawal due to SAE**

Appendix 4. Description of included randomised controlled trials

Study	Interventions and control	Follow up / History	Eligibility criteria	Baseline characteristics	Outcomes and definitions
FINGOLIMOD					
FREEDOMS (Kappos2010); NCT00289978; RCT; Phase 3; Double-blind; Multicenter (138 centers, 22 countries)	Fingolimod, n = 425 0,5 mg, oral, once daily Fingolimod, n = 429 1,25 mg, oral, once daily Placebo: n = 418 Oral, once daily	2 years / Mixed	**Age:** 18-55 years **Diagnosis:** RRMS (McDonald criteria) **EDSS:** 0,0-5,5 **Relapses:** ≥ 1 relapse in the previous year or ≥ 2 relapses in the previous 2 years	Fingolimod 1,25 mg **Age:** 37,4 ± 8,9 years; **Female:** 295; **EDSS:** 2,4 ± 1,4; **Duration from onset:** 8,4 ± 6,9 years (from first MS symptom to randomisation) Fingolimod 0,5 mg **Age:** 36,6 ± 8,8 years; **Female:** 296; **EDSS:** 2,3 ± 1,3; **Duration from onset:** 8,0 ± 6,6 years (from first MS symptom to randomisation) Placebo **Age:** 37,2 ± 8,6 years; **Female:** 298; **EDSS:** 2,5 ± 1,3; **Duration from onset:** 8,1 ± 6,4 years (from first MS symptom to randomisation)	**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. **Mortality; SAE; Lesions; Withdrawal due to SAE**
FREEDOMS II (Calabresi 2014); NCT00355134; RCT; Phase 3; Double-blind; Multicenter (117 academic and tertiary referral centres, 8 countries)	Fingolimod, n=370 1.25 mg, oral, once daily Fingolimod, n=358 0.5 mg, oral, once daily Placebo, n=355 Oral, once daily	2 years / Mixed	**Age:** 18–55 years **Diagnosis:** relapsing-remitting multiple sclerosis (McDonald criteria) **EDSS:** 0.0–5.5 **Relapses:** ≥1 confirmed relapses during the preceding year (or ≥ 2 confirmed relapses during the previous 2 years) **Other:** no relapse or steroid treatment within 30 days before randomisation IFNβ or glatiramer acetate therapy had to be stopped at least 3 months before randomization, and natalizumab treatment at least 6 months before randomization.	Fingolimod 1,25 mg: **Age:** 40,9 ± 8,9; **Female:** 281; **BMI:** 27,41 ± 5,956; **EDSS:** 2,5 ± 1,3; **Duration from onset:** 10,8 ± 8,2 (years from first symptom to randomisation) Fingolimod 0,5 mg: **Age:** 40,6 ± 8,4; **Female:** 275; **BMI:** 27,74 ± 5,952; **EDSS:** 2,4 ± 1,3; **Duration from onset:** 10,4 ± 8,0 (years from first symptom to randomisation) Placebo: **Age:** 40,1 ± 8,4; **Female:** 288; **BMI:** 27,67 ± 6,458; **EDSS:** 2,4 ± 1,3; **Duration from onset:** 10,6 ± 7,9 (years from first symptom to randomisation)	**Relapses:** A relapse was confirmed when it was accompanied by an increase of at least half a stem (0,5) on the EDSS, an increase of 1 point on two differential functional systems of the EDSS, or 2 points on one of the functionsla systems (excluding bowel, bladder, or cerebral systems). **Degree of disability; Mortality; SAE; Lesions; Withdrawal due to SAE**

Appendix 4. Description of included randomised controlled trials

Study	Interventions and control	Follow up / History	Eligibility criteria	Baseline characteristics	Outcomes and definitions
Saida 2012; NCT00537082); RCT; Phase 2; Double-blind; Multicenter Japan	Fingolimod, n=57 0,5 mg, oral, daily Fingolimod, n=57 1,25 mg, oral, daily Placebo: n=57 Oral, daily	0.5 years / Unclear	**Age:** 18-60 years **Diagnosis:** RRMS (McDonald criteria) **EDSS:** 0,0-6,0 **Relapses:** ≥ 1 relapse in the previous year or ≥ 2 relapses in the previous 2 years **Lesions:** ≥ 1 gadolinium-enhancing lesion within 30 days before study commencement	Placebo **Age:** 35,0 ± 8,9; **Female:** 39; **Weight (BMI):** 20,8 ± 2,8; **EDSS:** 2,1 ± 1,7; **Duration from onset:** 8,2 ± 7,3 (time from first MS symptom to randomisation) Fingolimod 0,5 mg **Age:** 35,0 ± 9,0; **Female:** 40; **Weight (BMI):** 21,8 ± 3,3; **EDSS:** 2,3 ± 1,9; **Duration from onset:** 8,2 ± 6,8 (time from first MS symptom to randomisation) Fingolimod 1,25 mg **Age:** 36,0 ± 9,3; **Female:** 39; **Weight (BMI):** 21,8 ± 3,8; **EDSS:** 1,8 ± 1,7; **Duration from onset:** 7,1 ± 5,3 (time from first MS symptom to randomisation)	**Relapses; Degree of disability; Mortality; SAE; Lesions**
TRANSFORMS (Cohen 2010); NCT00340834; RCT; Phase 3; Double-blind; Multicenter (172 centres, 18 countries)	Fingolimod, n=436 0,5 mg, oral, daily Fingolimod , n=431 1,25 mg, oral, daily Interferon β-1a: n=435 30 µg, i.m., weekly	1 year / Mixed	**Age:** 18 -55 years **Diagnosis:** RRMS (McDonald criteria) **EDSS:** 0,0-5,5 **Relapses:** ≥ 1 relapse during the previous year or ≥ 2 relapses during the previous 2 years	Fingolimod 1,25 mg **Age:** 35,8 ± 8,4; **Female:** 293; **EDSS:** 2,21 ± 1,31; **Duration from onset:** 7,3 ± 6,0 years (interval from onset of symptoms to randomisation) Fingolimod 0,5 mg **Age:** 36,7 ± 8,87; **Female:** 282; **EDSS:** 2,24 ± 1,33; **Duration from onset:** 7,5 ± 6,2 years (interval from onset of symptoms to randomisation) Placebo **Age:** 36,0 ± 8,3; **Female:** 295; **EDSS:** 2,19 ± 1,26; **Duration from onset:** 7,4 ± 6,3 years (interval from onset of symptoms to randomisation)	**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. **SAE; Lesions; Withdrawal due to SAE**

Appendix 4. Description of included randomised controlled trials

Study	Interventions and control	Follow up / History	Eligibility criteria	Baseline characteristics	Outcomes and definitions
GLATIRAMER ACETATE					
BEYOND (O'Connor 2009); NCT00099502; RCT; Phase 3; Rater-blinded; Multicentre (198 centres, 26 countries worldwide)	Glatiramer acetate, n=448 20 mg, s.c., Daily IFNβ-1b, n=897 250 µg, s.c., every other day IFNβ-1b, n=899 500 µg, s.c., every other day	2-3,5 years / Treatment-naive	**Age:** 18-55 years **Diagnosis:** RRMS (McDonald criteria) **EDSS:** 0 to 5.0 **Relapses:** ≥1 relapse in the year before entry into the study	IFNβ-1b 500 µg **Age:** 35,9 (36; 28-43) years; **Female (no):** 629; **EDSS:** 2,33 (2; 1,5-3,0); **Duration from onset:** 5,4 (3; 1-8) IFNβ-1b 250 µg **Age:** 35,8 (35; 28-43) years; **Female (no):** 627; **EDSS:** 2,35 (2; 1,5-3,0); **Duration from onset:** 5,3 (3; 1-7) Glatiramer acetate **Age:** 35,2 (35; 27-43) years; **Female (no.):** 306; **EDSS:** 2,28 (2; 1,5-3,0); **Duration from onset:** 5,1 (3; 1-7) *Numbers are mean (median; IQ range)*	**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. A neurological event was deemed as a relapse only if it was associated with an increase in EDSS. **Degree of disability; Mortality; SAE; Lesions**
CombiRx (Lublin 2013, Lublin 2017); NCT00211887; RCT; Phase 3; Double-blind; Multicenter (68 sites, both private practice and academic USA and Canada)	Glatiramer acetate **+** IFNβ-1a n=499 20 mg **+** 30 µg s.c. **+** i.m. Daily **+** Weekly Glatiramer acetate **+** placebo n=259 20 mg **+** placebo s.c. **+** i.m. Daily **+** Weekly Placebo **+** IFNβ-1a n=250 placebo **+** 30 µg s.c. **+** i.m. Daily **+** Weekly	3 years / Treatment-naïve	**Age:** 18-60 years **Diagnosis:** RRMS (Poser or McDonald cirteria) **EDSS:** 0,0-5,5 **Relapses:** at least 2 exacerbations in the prior 3 years, where 1 exacerbation could be an MRI change.	Glatiramer acetate + IFNβ-1a **Age:** 37,1 ± 9,4 years; **Female:** 372; **EDSS:** 1,9 ± 1,2; **Duration from onset:** 1,1 ± 3,1 years duration of disease Placebo + IFNβ-1a **Age:** 37,6 ± 10,2 years; **Female:** 173; **EDSS:** 2,0 ± 1,2; **Duration from onset:** 1,4 ± 4,0 years duration of disease Glatiramer acetate + placebo **Age:** 39,0 ± 9,5; **Female:** 185; **EDSS:** 1,9 ± 1,2; **Duration from onset:** 1,0 ± 2,9 years duration of disease	**Relapse:** New or worsening neurologic symptoms that lasted at least 24 hours without fever or infec-tion, preceded by 30 days of stability. Only the protocol defined relapses were included in the primary analyses (PDE). **Confirmed progression:** A 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. **Mortality; SAE; Lesions; Withdrawal due to AE**

Appendix 4. Description of included randomised controlled trials

Study	Interventions and control	Follow up / History	Eligibility criteria	Baseline characteristics	Outcomes and definitions
GALA (Khan 2013); RCT; Phase 3; Double-blind: Multicentre (142 sites, 17 countries (incl USA, Bulgaria, Croatia, Germany, Poland, Romania, and Ukraine)	Glatiramer acetate: n=943 40mg, s.c., three times a week Placebo: n=461 40 mg mannitol in water; s.c., three times a week	1 year / Mixed	**Age:** 18 to 55 years **Diagnosis:** RRMS (McDonald criteria) **EDSS:** ≤ 5.5 **Relapses:** have ≥ 1 documented relapse in the 12 months prior to screening, or ≥ 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 T_1 gadolinium enhancing lesion in an MRI performed within 12 months of screening. **Other:** relapse-free for ≥ 30 days.	Glatiramer acetate **Age:** 37.4 ± 9.4; **Female:** 641; **EDSS:** 2.8 ± 1.2; **Duration from onset:** 7.7 ± 6.7 (years from onset of MS symptom) Placebo **Age:** 38.1 ± 9.2; **Female:** 313; **EDSS:** 2.7 ± 1,2; **Duration from onset:** 7.6 ± 6.4 (years from onset of first MS symptom)	**Relapse:** 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. **Degree of disability; Mortality; SAE; Lesions; Withdrawal due to AE**
(Calabrese 2012, Rinaldi 2015); RCT; Phase 4; Rater-blinded; Single-centre (Italy)	Glatiramer acetate, n = 55 20 mg , s.c., daily IFNβ-1a, n = 55 44 µg, s.c., three times weekly IFNβ-1a, n = 55 30 µg, i.m., weekly Reference population, n=50 DMD-untreated patients	2 years / Unclear	**Age:** 18 -55 years **Diagnosis:** RRMS (McDonald/Polman criteria) **EDSS:** ≥ 5,0	Interferon β-1a s.c. **Age:** 35,9 ± 9,1; **Female:** 32; **EDSS:** 1,9 ± 1,0 (1,0-5,0); **Duration from onset:** 5,7 ± 4,9 Interferon β-1a i.m. **Age:** 34,8 ± 9,6; **Female:** 32; **EDSS:** 1,9 ± 0,8 (1,0-5,0); **Duration from onset:** 5,3 ± 5,1 Glatiramer acetate **Age:** 38,9 ± 10,2; **Female:** 35; **EDSS:** 2,1 ± 1,1 (1,0-5,0); **Duration from onset:** 5,5 ± 6,1 DMD-untreated **Age:** 39,6 ± 11,8; **Female:** 36; **EDSS:** 1,3 ± 0,9 (1,0-2,0); **Duration from onset:** 6,0 ± 4,8	**Relapses; Degree of disability; Lesions**
(Comi 2001); RCT; Double-blind; Multicenter (29 centres, 7 countries (incl Europe and Canada))	Glatiramer acetate, n=119 20 mg, s.c., daily Placebo, n=120 s.c., daily	9 months / Unclear	**Age:** 18-50 years **Diagnosis:** RRMS **EDSS:** 0-5.0 **Relapses:** ≥ 1 documented relapse in the preceding 2 years **Lesions:** ≥ 1 enhancing lesion on screening brain MRI. **Other:** MS diagnosis for at least 1 year	Glatiramer acetate **Age:** 34,1 ± 7,4; **EDSS:** 2,3 ± 1,1; **Duration from onset:** 7,9 ± 5,5 (years disese duration) Placebo **Age:** 34,0 ± 7,5; **EDSS:** 2,4 ± 1,2; **Duration from onset:** 8,3 ± 5,5 (years disese duration)	**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 exami-nation 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. **Degree of disability; SAE; Lesions; Withdrawal due to AE**

Appendix 4. Description of included randomised controlled trials

Study	Interventions and control	Follow up / History	Eligibility criteria	Baseline characteristics	Outcomes and definitions
(Johnson 1995); RCT; Phase 3; Double-blind; Multicenter (11 centres, USA)	Glatiramer acetate, n =125 20 mg, s.c., daily Placebo, n=126 s.c., daily	2 years / Treatment-naive	**Age:** 18-45 years **Diagnosis:** RRMS (Poser-criteria) **EDSS:** 0,0-5,0 **Relapses:** ≥ 2 clinically documented relapses in the 2 years before entry, onset of the first relapse at least 1 year before randomization **Other:** a period of neurologic stability and freedom from corticosteroid therapy of at least 30 days prior to entry.	Glatiramer acetate **Age:** 34,6 ± 6,0; **Female:** 88; **EDSS:** 2,8 ± 1,2; **Duration from onset:** 7,3 ± 4,9 years Placebo **Age:** 34,3 ± 6,5; **Female:** 96; **EDSS:** 2,4 ± 1,1; **Duration from onset:** 6,6 ± 5,1 years	**Relapses:** The appearance or reappearance of one or more neurologic abnormalities persisting for at least 48 hours and immediately proceeded by a rela-tively 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.
REGARD (Mikol 2008); NCT00078338; RCT; Rater-masked; Multicenter (81 centres, 14 countries (incl North and South America, and Europe)	Glatiramer acetate, n=378 20 mg, s.c., daily IFNβ-1a, n=386 44 µg, s.c., three times per week	8 years / Treatment-naive	**Age:** 18-60 years **Diagnosis:** RRMS patients (McDonald criteria) **EDSS:** 0,0 to 5,5 **Relapses:** ≥ 1 relapse in the preceding 12 months **Other:** Clinically stable or neurologically improving during the 4 weeks before randomization.	Glatiramer acetate **Age:** 36.8; **Female:** 272; **EDSS:** 2.33; **Duration from onset:** NA IFNβ-1a **Age:** 36.7; **Female:** 267; **EDSS:** 2.35; **Duration from onset**: NA	**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. **Mortality; SAE; Lesions; Withdrawal due to AE**

Appendix 4. Description of included randomised controlled trials

Study	Interventions and control	Follow up / History	Eligibility criteria	Baseline characteristics	Outcomes and definitions
NATALIZUMAB					
AFFIRM (Polman 2006); NCT000273; RCT; Phase 3; Double-blinded; Multi-centre (99 centres in Europe, North America, Australia, and New Zealand)	Natalizumab, n=627 300 mg, i.v., every 4 weeks Placebo, n=315 i.v., every 4 weeks	Unclear	**Age:** 18-50 years **Diagnosis:** RRMS **EDSS:** 0-5.0 **Lesions:** showing lesions consistent with MS on MRI **Relapses:** ≥1 medially documented relapse within 12 months before the study began	Natalizumab **Age:** 35,6 ± 8,5; **Female:** 449; **EDSS:** 2,3 ± 1,2; **Duration from onset; median (range):** 5,0 (0-34) Placebo **Age:** 36,7 ± 7,8; **Female:** 211; **EDSS:** 2,3 ± 1,2; **Duration from onset; median (range):** 6,0 (0-33)	**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). **Mortality; SAE; Lesions; Withdrawal due to AE**
(Gobbi 2013, Zecca 2014); NCT01144052); RCT; Pilot; Rater blinded; Single center (Switzerland)	Natalizumab, n=10 300 mg, i.v., monthly IFNβ-1b, n=9 250 mg, s.c., every other day (De-escalate natalizumab to IFN)	Treatment experienced	**Age:** 18-60 years **Diagnosis:** RRMS (McDonald's criteria) , **Relapses:** Patients had to be free of disease activity while on natalizumab (free from relapses and disability progression for at least 6 months and no gadolinium enhancing lesions on base-line MRI) **Other:** Patients on natalizumab and feared or were at significant risk for progressive multifocal leucoencephalopathy	Natalizumab: **Age**: 43 (20-60) years; **Female (no.):** 6; **EDSS**: 3 (1,5-3,5) ; **Duration from onset**: 10 (5-17) years IFNβ: **Age**: 39 (24-48) years; **Female:** 3; **EDSS**: 3 (1,5-3,5); **Duration from onset**: 12 (2-23) years (*Numbers are median (range))*	**Relapse:** Newly developing neurological symptoms or reactivation of pre-existing neurological deficits for a minimum of 24 hours in the absence of an increase in body temperature or infections occuring at least 30 days after the preceding episode. Relapses were confirmed when an increase of at least 1 point in at least one functional system was recorded. **Degree of disability; SAE; Lesions; Withdrawal due to AE**

Appendix 4. Description of included randomised controlled trials

Study	Interventions and control	Follow up / History	Eligibility criteria	Baseline characteristics	Outcomes and definitions
OCRELIZUMAB					
OPERA I and II (Hauser 2017); NCT01247324m NCT01412333; RCT; Phase 3; Double blind; Multicenter ((OPERA I: 141 sites, OPERA II 166 sites), 32 and 24 countries)	**OPERA I:** Ocrelizumab, n=410 600 mg, i.v., every 24 weeks IFNβ-1a, n= 411 44 µg, s.c., three times weekly **OPERA II:** Ocrelizumab, n=417 600 mg, i.v., every 24 weeks IFNβ-1a, n=418 44 µg, s.c., three times weekly Note: Ocrelizumab were administered as two 300 mg infusions on days 1 and 15 for the first dose, and as a single single 600 mg infusion thereafter.	8 years / Mixed	**Age:** 18-55 years **Diagnosis:** MS (according to 2010 revised McDonald criteria) **EDSS score:** 0-5.5, **Relapses:** at least 2 documented clinical relapses within 1 year before screening, **Lesions:** MRI showing abnormalities consistent with MS **Other:** no neurological worsening for at least 30 days before screening and baseline	**OPERA I** Ocrelizumab **Age:** 37,1 ± 9,3 years; **Female:** 270; **EDSS:** 2,86 ± 1,24; **Duration from onset:** 3,82 ± 4,80 years since diagnosis IFNβ-1a **Age:** 36,9 ± 9,3 years; **Female:** 272; **EDSS:** 2,75 ± 1,29; **Duration from onset:** 3,71 ± 4,63 years since diagnosis **OPERA II** Ocrelizumab **Age:** 37,2 ± 9,1 years; **Female:** 271; **EDSS:** 2,78 ± 1,3; **Duration from onset:** 4,15 ± 4,95 years since diagnosis IFNβ-1a **Age:** 37,4 ± 9,0; **Female:** 280; **EDSS:** 2,84 ± 1,38; **Duration from onset:** 4,13 ± 5,07 years since diagnosis	**Disability progression:** an increase from the baseline EDSS score of at least 1,0 point (or 0,5 points if the baseline EDSS score was >5,5) **Disability improvement:** an reduction from the baseline EDSS score of at least 1,0 point (or 0,5 points if the baseline EDSS score was >5,5) **Mortality; SAE; Lesions; Withdrawal due to AE**
(Kappos 2011); NCT00676715; RCT; Phase 2; Double-blind; Multicenter (79 20 countries, North America, east-central Europe, Asia, western Europe, and Latin America)	Ocrelizumab, n=56 (but 1 not treated, n=55 in ITT) 600 mg, i.v., day 1 and 15 (This is information on the first cycle only: 300 mg on day 1 and 15) Ocrelizumab, n=55 2000 mg, i.v., day 1 and 15 (This is information on the first cycle only: 1000 mg on day 1 and 15) Placebo, n=54 i.v., day 1 and 15	0.5 (1) year) / Mixed	**Age:** 18 - 55 years, **Diagnosis:** RRMS **EDSS:** 1-6 **Relapses:** ≥ 2 relapses in previous 3 years **Other:** Evidence of previous MS activity with 6 T2 leasions or 2 relapses in the year before screening	Ocrelizumab 600 mg: **Age:** 35,6 ± 8,5 years; **Female:** 35; **EDSS:** 3,5 ± 1,5; **Duration from onset:** 3,6 (0,1-16,5) years since diagnosis; median (range) Ocrelizumab 2000 mg: **Age:** 38,5 ± 8,7 years; **Female:** 38; **EDSS:** 3,4 ± 1,3; **Duration from onset:** 4,4 (0,1-19,2) years since diagnosis; median (range) Placebo: **Age:** 38,0 ± 8,8 years; **Female:** 36; **EDSS:** 3,2 ± 1,4; **Duration from onset:** 2,7 (0,1-19,2) years since diagnosis; median (range)	**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. **Mortality; SAE; Lesions; Withdrawal due to AE**
RITUXIMAB					
(Hauser 2008); NCT00097188; RCT; Phase 2; Double-blind; Multicenter (32 centers, USA and Canada)	Rituximab, n=69 1000 mg, i.v. Infusion on study days 1 and 15 Placebo, n=35 i.v.	48 weeks / Mixed	**Age:** 18-55 years **Diagnosis:** RRMS **EDSS:** 0.5 **Relapses:** at least 1 relapse during the preceding year	Rituximab **Age:** 39,6 ± 8,7 years; **Female:** 52; **EDSS (median; range):** 2,5 (0-5); **Duration from onset:** 9,6 ± 6,4 years Placebo **Age:** 41,5 ± 8,5 years; **Female:** 29; **EDSS (median; range):** 2,5 (0-5); **Duration from onset:** 9,6 ± 7,1 years (from onset)	**Relapses; Mortality; Degree of disability; SAE; Lesions; Withdrawal due to AE**

Appendix 4. Description of included randomised controlled trials

Study	Interventions and control	Follow up / History	Eligibility criteria	Baseline characteristics	Outcomes and definitions
TERIFLUNOMIDE					
TEMSO (O'Connor 2011); NCT00134563; RCT; Phase 3; Double-blind; Multicenter (127 centres, 21 countries (incl North America and Europe))	Teriflunomide, n=365 7 mg, oral, daily Teriflunomide, n=358 14 mg, oral, daily Placebo, n=363 Oral, daily	Mixed	**Age:** 18 -55 years **Diagnosis:** RRMS (McDonald criteria) with or without progression **EDSS:** ≤ 5,5 **Relapses:** ≥ 2 relapses in the previous 2 years or ≥ 1 relapse during the preceding year, but no relapse in the 60 days before randomization	Teriflunomide 7 mg **Age:** 37,4 ± 9,0 years; **Female:** 255; **EDSS:** 2,68 ± 1,34; **Duration from onset:** 8,8 ± 6,8 years from first symptom of MS Teriflunomide 14 mg **Age:** 37,8 ± 8,2 years; **Female:** 255; **EDSS:** 2,67 ± 1,24; **Duration from onset:** 8,7 ± 6,7 years from first symptom of MS Placebo **Age:** 38,4 ± 9,0 years; **Female:** 275; **EDSS:** 2,68 ± 1,34; **Duration from onset:** 8,6 ± 7,1 years from first symptom of MS	**Relapses:** The appearance of a new clinical sign or symptom, or clinical worsening of a previ-ous 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. **Mortality; SAE; Lesions; Withdrawal due to AE**
TENERE (Vermersch 2014); NCT00883337; RCT; Phase 3; Rater-blinded; Multicentre	Teriflunomide, n=109 7 mg, oral, daily Teriflunomide, n=111 14 mg, oral, daily IFNβ-1a, n=104 Titrated up to 44 µg, s.c., three times per week	Up to 48 weeks / Mixed	**Age:** ≥ 18 years **Diagnosis:** RRMS (McDonald criteria) with or without progression **EDSS:** ≤ 5,5 **Relapses:** relapse free for 30 days prior to randomisation.	IFNβ1a **Age:** 37,0 ± 10,6; **Female:** 71; **EDSS:** 2,0 ± 1,2; **Duration from onset:** 7,7 ± 7,6 years (since first symptoms of MS) Teriflunomide 7 mg **Age:** 35,2 ± 9,2; **Female:** 70; **EDSS:** 2,0 ± 1,2; **Duration from onset:** 7,0 ± 6,9 years (since first symptoms of MS) Teriflunomide 14 mg **Age:** 36,8 ± 10,3; **Female:** 78; **EDSS:** 2,3 ± 1,4; **Duration from onset:** 6,6 ± 7,6 years (since first symptoms of MS)	**Relapses:** A new clinical sign/symptom or clinical worsening of a previous sign/symptom (previously stable for at least 30 days) that per-sisted 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. **Degree of disability; Mortality; SAE; Withdrawal due to AE**
TOWER (Confavreux 2014); NCT00751881; RCT; Phase 3; Double-blind; Multicenter (189 centres (mainly hospital-based), 26 countries)	Teriflunomide, n=408 7 mg, oral, daily Teriflunomide, n=372 14 mg, oral, daily Placebo, n=389 Oral, daily	Up to 48 weeks / Mixed	**Age:** 18–55 years **Diagnosis:** RRMS (McDonalds criteria) **EDSS:** ≤ 5.5 **Relapses:** ≥ 1 relapse in the previous year, or ≥ 2 relapses in the previous 2 years, and no relapse in the 30 days before randomisation.	Placebo **Age:** 38,1 ± 9,1; **Female:** 273; **EDSS:** 2,69 ± 1,36; **Duration from onset:** 7,64 ± 6,7 years from first symptom of MS Teriflunomide 7 mg **Age:** 37,4 ± 9,4; **Female:** 300; **EDSS:** 2,71 ± 1,39; **Duration from onset:** 8,18 ± 6,75 years from first symptom of MS Teriflunomide 14 mg **Age:** 38,2 ± 9,4; **Female:** 258; **EDSS:** 2,71 ± 1,35; **Duration from onset:** 8,18 ± 6,73 years from first symptom of MS	**Relapse:** New or worsening clinical signs or symptoms lasting at least 24 h with-out fever. Defines as 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 per-sisted for at least 12 weeks. **Degree of disability; SAE; Withdrawal due to AE**

NOTES: All numbers under baseline characteristics are mean±SD unless otherwise stated

Appendix 5. Description of included register studies

Study	Treatment	History/follow-up	Eligibility criteria	Baseline characteristics	Outcomes and definitions
STOPMS (Alping 2016); Observational study; MS-register; Multicentre (3 centres), Sweden	Rituximab n=114 Fingolimod n=142	Treatment-experienced Follow-up: **Rituximab:** 1,24 (0,75-2,02) years **Fingolimod:** 1,82 (1,40-2,36) years *Numbers are median (IQR)*	**Diagnosis:** RRMS **Other:** JCV-positive, switching from natalizumab to rituximab or fingolimod	Rituximab **Age:** 40,17 (33,74-50,44) years; **Female:** 73; **EDSS:** 2,00 (1,00-3,50); **Duration from onset:** 8,00 (4,53-11,84) years since diagnosis Fingolimod **Age:** 40,79 (33,73-47,73) years; **Female:** 86; **EDSS:** 2,50 (1,50-3,50); **Duration from onset:** 7,88 (5,20-11,22) years since diagnosis *Numbers are median (IQR)*	**Lesions (**MRI gadolinium-enhancing T1 lesions and new cerebral T2 lesions as compared with a referance MRI scan after DMT switch), **Clinical relapses, AE, Discontinuation of therapy** (the date for the last administration of the drug plus 6 months for RTX and 1 month for FGL)
Ernst 2017; Chart review; medical charts; Multicentre, USA	IFNβ-1a n=143 s.c. Dimethyl fumarate n=307 p.o.	Mixed Follow-up: 2 years	**Age:** >18 years **Diagnosis:** RRMS, diagnosed within 1 year prior to treatment with IFN or DMF **Treatment:** IFNβ-1a or DMF, initiated between 1st April 2012 and 31st March 2014	IFNβ-1a **Age:** 42,9 ± 12,4 years; **Female:** 102; **Duration from onset:** 385,0 ± 1058,3 days since MS diagnose Dimethyl fumarate **Age:** 46,6 ± 11,8 years; **Female:** 239; **Duration from onset:** 594,0 ± 1795,9 days since MS diagnose *Numbers are mean ± SD*	**Discontinuation of therapy** (a patient discontinuing their medication and not switching to another medication or restarting their current medication within 30 days), **relapse**.
Frisell 2016; Observational study; MS-register; Sweden	Natalizumab n=640 Fingolimod n=876	Mixed Follow-up: 1 year	All patients in the Immunomodulation and MS Epidemiology Study (IMSE), starting treatment with natalizumab or fingolimod between 1st August 2011 and 31st October 2013	Natalizumab **Female:** 489; **BMI:** 24,5 ± 4,8; **EDSS:** 2,4 ± 1,7; **Duration from onset:** 7,0 ± 6,6 years Total fingolimod: **Female:** 595; **BMI:** 24,6 ± 4,5; **EDSS:** 2,5 ± 1,7; **Duration from onset:** 9,8 ± 6,7 years a) Fingolimod after natalizumab: **Female:** 344, **BMI:** 24,6 ± 4,9; **EDSS:** 2,7 ± 1,9, **Duration from onset:** 10,9 ± 6,1 years b) Fingolimod, natalizumab-naïve: **Female:** 423; **BMI:** 24,5 ± 4,1; **EDSS:** 2,4 ± 1,6; **Duration from onset:** 8,9 ± 7,1 years	**Discontinuation of therapy**
Granqvist 2018; Observational study; MS-register; Multicentre (3 centres), Sweden	Natalizumab n=50 Dimethyl fumarate n= 86 Rituximab n=120 Fingolimod n=17 IFNβ + glatiramer acetate n=215	Treatment-naïve Follow-up: ≥ 7 months to ≤ 4,33 years	No inclusion criteria listed.	Rituximab **Age:** 37,8 (28,7-48,8) years; **Female:** 79; **EDSS:** 2,0 (1,0-2,5); **Duration from onset:** 1,0 (0,3-1,9) months IFNβ + glatiramer acetate **Age:** 35,1 (28,6-43,5) years; **Female:** 144; **EDSS:** 1,5 (1,0-2,0); **Duration from onset:** 1,2 (0,5-2,8) months Dimethyl fumarate **Age:** 33,1 (28,2-39,1) years; **Female:** 62; **EDSS:** 1,5 (1,0-2,0); **Duration from onset:** 0,9 (0,5-1,5) months Fingolimod **Age:** 31,7 (23,6-39,6) years; **Female:** 11, **EDSS:** 1,8 (1,0-2,5); **Duration from onset:** 1,2 (0,6-2,5) months Natalizumab **Age:** 29,4 (22,6-35,6) years; **Female:** 34; **EDSS:** 1,5 (1,0-2,5); **Duration from onset:** 1,0 (0,5-1,9) months *Numbers are median (IQR)*	**Discontinuation of therapy, Relapse, Lesions, AE**

Appendix 5. Description of included register studies

Study	Treatment	History/follow-up	Eligibility criteria	Baseline characteristics	Outcomes and definitions
Guger 2018; Observational study; MS-register (AMSTR), Austria	Natalizumab n=246 Fingolimod n=332	Mixed Follow-up: 24 months	All patients who started treatment with natalizumab or fingolimod in the AMSTR from 2011 and stayed on therapy for at least 24 months	Natalizumab **Age:** 34,1 ± 10,3 years, **Female:** 174; **EDSS:** 2,5 ± 1,6; **Duration from onset:** 6,6 ± 5,7 years (duration of MS at treatment start) Fingolimod **Age:** 39,3 ± 9,8 years; **Female:** 226; **EDSS:** 2,7 ± 1,5; **Duration from onset:** 9,9 ± 7,2 years (duration of MS at treatment start) *Numbers are mean ± SD*	**EDSS, ARR, relapses** (new or worsening neurological symptoms lasting for ≥24 hours in absence of fever)
ACTRN12605000455662 (Kalincik 2015a), Observational study, MS-register; Multicenter (66 centres), 26 countries in North- and South America, West-Asia, Australia, Europe	Natalizumab Matched: n=407 Fingolimod Matched: n=171	Treatment-experienced **Follow-up:** Natalizumab: 21 (12-34) months Fingolimod: 14 (8-20) months *Numbers are median (quartiles)*	**Diagnosis:** RRMS **Other:** Switched therapy from IFNβ or glatiramer acetate to natalizumab or fingolimod after on-treatment relapse and/or progression of disability documented within the preceding 6 months. **Treatment:** minimum 3 month persistence on NTZ or FGL	Natalizumab **Age:** 37 ± 9 years; **Female:** 301; **EDSS:** 3,4 ± 1,5; **Duration from onset:** 9,4 ± 6,2 years Fingolimod **Age:** 38 ± 10 years; **Female:** 126; **EDSS:** 3,1 ± 1,7; **Duration from onset:** 9,5 ± 8,0 years	**ARR, Relapses** (occurrence of new symptoms or exacerbation of existing symptoms persisting for ≥24 hours, in the absence of concurrent illness or fever, and occurring ≥ 30 days after a previous relapse), **EDSS** (Progress: increase of ≥1 EDSS step (≥1,5 EDSS steps if baseline EDSS was 0) sustained for ≥6 months. Regression: decrease of ≥1 EDSS step (1,5 EDSS step if baseline EDSS was 1,5) sustained for ≥6 months
ACTRN12605000455662 (Kalincik 2015b), Observational study, MS-register; Multicenter (49 centres), 22 countries in North- and South America, West-Asia, Australia, Europe	IFNβ-1a i.m. n=832 IFNβ-1a s.c. n=1379 IFNβ-1b n=633 Glatiramer acetate n=482	Treatment-naïve Follow-up: 3,7(2,2-6,3) years *Numers are median (IQR)*	**Diagnosis:** RRMS **Treatment:** interferon or glatirmaer acetate as a first-ever disease-modifying agent **Other:** at least 6-month persistence on the initial therapy, time from initial symptoms to treatment start <10 years, at least 1 relapse recorded during the 2 years preceding the treatment initiation, and availability of minimal dataset	IFNβ-1a i.m. **Age:** 32,8 ± 10,0 years; **Female:** 591; **EDSS:** 2 (1,0-2,5) (median; IQR); **Duration from onset:** 2,9 ± 2,6 years IFNβ-1a s.c. **Age:** 33,5 ± 9,4 years; **Female:** 965; **EDSS:** 2 (1,5-3,0); **Duration from onset:** 2,9 ± 2,6 IFNβ-1b **Age:** 34,6 ± 9,4 years, **Female:** 256; **EDSS:** 2 (1,0-3,0); **Duration from onset:** 2,9 ± 2,6 years Glatiramer acetate **Age:** 35,1 ± 8,9 years; **Female:** 352; **EDSS:** 2 (1,0-2,5); **Duration from onset:** 3,2 ± 2,7 *EDSS are median (IQR), otherwise: mean ± SD*	**Relapse** (occurrence of new symptoms or exacerbation of existing symptoms persisting for >24 hours in the absence of concurrent illness or fever, and occurrring ≥30 days after a previous relapse),

Appendix 5. Description of included register studies

Study	Treatment	History/follow-up	Eligibility criteria	Baseline characteristics	Outcomes and definitions
Koch-Henriksen 2017; Observational study; MS-register; Denmark	Natalizumab Matched: n=464 Fingolimod Matched: n=464	Mixed Follow-up: ≤3,75 years	All patients who started treatment with natalizumab or fingolimod from 1st July 2011 up to 31st March 2015	Natalizumab **Age:** 38,7 ± 10,1 years; **Female:** 70,5%; **EDSS:** 3,15 ± 1,6, **Duration from onset:** 7,78 ± 6,2 years (mean duration of MS at treatment start) Fingolimod **Age:** 39,3 ± 10,1 years; **Female:** 70,5%; **EDSS:** 3,08 ± 1,5, **Duration from onset:** 7,69 ± 6,3 years (mean duration of MS at treatment start) *Numbers are mean ± SD*	**Relapses** (new or worsening neurological symptoms occurring within days or weeks with duration of ≥ 24 hours in the absence of fever), **EDSS**
Lanzillo 2017; Observational study; MS-centre; Italy	Natalizumab n=108 Fingolimod n=71	Mixed Follow-up: 24 months	**Diagnosis:** RRMS **Treatment:** ≥24 consecutive months with either NTZ or FGL	Natalizumab **Age:** 33,89 ± 10,046 years; **EDSS:** 3,3 ± 1,03; **Duration from onset:** 92,9 ± 78,22 months Fingolimod **Age:** 40,70 ± 10,728 years; **EDSS:** 3,5 ± 1,09, **Duration from onset:** 141,5 ± 104,67 months *Numbers are mean ± SD*	**Relapses** (occurrence of new symptoms or exacerbation of existing symptoms persisting for ≥ 24 hours, in the absence of concurrent illness or fever, and occurring ≥ 30 days after a previous relapse), **EDSS**
Prosperini 2017; Observational study; MS-centre; Italy	Natalizumab Dataset A: n=110 Dataset B: n=40 Fingolimod Dataset A: n=110 Dataset B: n=40 IFNβ/glatirmaer acetate Dataset A: n=110 Dataset B: n=40	Mixed: Dataset A: treatment-experienced Dataset B: Treatment-naïve Follow-up: 24 months	Not listed inclusion criteria	*Dataset A | dataset B* INFβ/Glatiramer acetate **Age:** 36,7 ± 8,8 | 32,2 ± 8,9 years; **Female:** 77 | 27; **EDSS:** 2,7 ± 1,3 | 2,1 ± 0,9; **Duration from onset:** 8,5 ± 5,8 | 2,1 ± 1,7 years since first symptom Fingolimod **Age:** 36,1 ± 9,2 | 32,1 ± 9,3 years, **Female:** 75 | 25; **EDSS:** 2,6 ± 1,1 | 2,1 ± 0,9; **Duration from onset:** 7,8 ± 5,8 | 2,3 ± 2,9 years since first symptom Natalizumab **Age:** 37,2 ± 9,4 | 30,4 ± 7,8 years; **Female:** 83 | 24; **EDSS:** 2,7 ± 1,1 | 2,1 ± 0,8; **Duration from onset:** 8,5 ± 5,8 | 2,2 ± 2,2 years since first symptom *Numbers are mean ± SD*	**Relapse** (any new neurological symptom, not associated with fever or infection, lasting for ≥24 h and accompanied by new neurological signs), **disability** (worsening: ≥1,5-point increase [if baseline EDSS score was 0], ≥1,0-point increase [if baseline EDSS score was ≤5.5], or ≥0,5-point increase [if baseline EDSS score was ≥5,5] confirmed 6 months apart), **radiological activity** (occurence of ≥1 GD-enhancing lesion or ≥1 new T2-hyperintense lesions)
Spelman 2018; Observational study; MS-register; Sweden	Rituximab n=461	Treatment-experienced Follow-up: 2 years	**Age:** ≥18 years **Diagnosis:** RRMS **EDSS:** no requirement **Relapses:** no requirement **Other:** minimum 3 months persistence on the index DMT	Rituximab **Age:** 41,5 (34,5-48,5) years; **Female:** 343; **EDSS:** 2,0 (1,5-3,0); **Duration from onset:** 10,6 (7,4-15,0) years disease duration IFNβ or glatimer acetate **Age:** 40,0 (33,1-45,7) years; **Female:** 699; **EDSS:** 2 (1,5-3,0); **Duration from onset:** 9,9 (6,4-12,8) years disease duration *Numbers are median (IQR)*	**Relapse, disability progression**

Appendix 6. Risk of bias assessment of included studies

Risk of Bias of included randomised controlled trials

Risk of bias tool from Cochrane handbook was used (88). Rating used in the assessment:

Low risk of bias +
High risk of bias –
Unknown risk of bias ?
"Medium" refers to the assessment tool used in the previous HTA.

Reference	Random sequence generation (selection bias)	Allocation concealment (selection bias	Blinding of participants and personnel (performance bias	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Overall
Boiko 2018	?	?	+	+	+	+	?	?
Calabrese 2012	Assessed in Couto 2016							+
Calabresi 2014a	Assessed in Couto 2016							+
Cohen 2010	Assessed in Couto 2016							+
Cohen 2012	Assessed in Couto 2016							+
Cohen 2015	+	+	+	+	?	+	+	?
Coles 2008	Assessed in Couto 2016							+
Coles 2012	Assessed in Couto 2016							+
Comi 2001	Assessed in Couto 2016							+
Comi 2013	+	+	+	+	+	+	+	+
Comi 2017b	?	?				+	?	
Relapses			?	?	–			–
Degree of disability			?	?	–			–
Lesions			+	+	–			–
Serious adverse events			–	–	?			–
Confavreux 2014	Assessed in Couto 2016							+
Cook 2011	?	?	+	+	+	+	?	+
Fox 2012	Assessed in Couto 2016							+
Fox 2014	Assessed in Couto 2016							+
Giovannoni 2010	+	+	+	+	+	+	?	+
Gobbi 2013	Assessed in Couto 2016							+
Gold 2012	Assessed in Couto 2016							+
Hauser 2008	?	?	+	+	–	+	?	–
Hauser 2017	+	+	+	+	+	+	+	+
Johnson 1995	Assessed in Couto 2016							medium
Kappos 2010	Assessed in Couto 2016							+
Kappos 2011	Assessed in Couto 2016							–
Khan 2013	Assessed in Couto 2016							+

Lublin 2013	Assessed in Couto 2016							+
Lublin 2017	+	+	+	+	?	+	+	+
Mikol 2008	Assessed in Couto 2016							+
O'Connor 2009	Assessed in Couto 2016							+
O'Connor 2011	Assessed in Couto 2016							medium
Polman 2006	Assessed in Couto 2016							+
Rinaldi 2015	+	+	+	+	–	+	+	+
Saida 2012	Assessed in Couto 2016							medium
Saida 2017b	+	+	+	+	+	+	?	+
Vermersch 2014	Assessed in Couto 2016							medium
Zecca 2014	Assessed in Couto 2016							medium

Quality assessment of included non-randomised studies

The table below gives the risk of bias of the registry studies (based on a checklist for cohort studies from the Handbook of Norwegian Institute of Public health (4). Rating used in the assessment low risk, unclear risk and high risk of bias.

	Alping 2016	Ernst 2017	Frisell 2016	Granqvist 2018	Guger 2018	Kalincik 2015a	Kalincik 2015b	Koch-Henriksen 2017	Lanzillo 2017	Prosperini 2017	Spelman 2018
Were the groups comparable for important background factors?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Were the exposed individuals representative of a defined population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the control group(s) selected from the same population as the exposed group(s)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the study prospective?	Yes	No	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes
Was exposure and outcome measured equally and reliably in the groups?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were many enough people in the cohort followed-up?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
An analysis of attrition was done to explain whether those who have abandoned the study differ from those who have been followed-up?	Uncertain	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Uncertain
Was the follow-up time long enough to show positive and/or negative outcomes?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were known, possible confounding factors taken into account in the design and/or analysis of the study?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the person who assessed the results (endpoints) blinded to who was exposed and who was not exposed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Overall assessment	*Low risk*	*Low risk*	*Low risk*	*Low risk*	*Low risk*	*Low risk*	*Low risk*	*Low risk*	*Low risk*	*Low risk*	*Low risk*

Appendix 7. Unpublished results, Spelman 2018 (5)

One of the included studies presented results on rituximab where the comparators were both interferon and glatiramer acetate. Spelman kindly provided the results of rituximab vs each of the comparators for relapse rate and discontinuation. The results used in the present HTA are:

Propensity score matched sample as described in Spelman, T., Frisell, T., Piehl, F., & Hillert, J. (2018). Comparative effectiveness of rituximab relative to IFN-β or glatiramer acetate in relapsing-remitting MS from the Swedish MS registry. Multiple Sclerosis Journal, 24(8), 1087-1095.

End-point	Index DMD group	Number of on treatment relapses	On-treatment follow-up years	ARR (95% CI)
ARR	Rituximab	3	986.33	0.0030 (0.0006, 0.0089)
	IFN	51	1770.27	0.0288 (0.0215, 0.0379)
	GLA	17	814.15	0.0209 (0.0123, 0.0334)

12-week CDP counts

Group	n	Minimum 3 EDSS scores*	CDP events
RTX	461	321	21
IFN	633	379	37
GLA	289	153	11

*Only patients recording a minimum 3 EDSS scores contributed to the CDP analysis

Appendix 8. Excluded studies with reasons

From randomised controlled trial- and rituximab searches. Studies excluded (161) with reason.

Reference	Reason for exclusion
Afolabi D, Albor C, Zalewski L, Altmann DR, Baker D, Schmierer K. Positive impact of cladribine on quality of life in people with relapsing multiple sclerosis. Multiple Sclerosis Journal 2017;1.	Only analysis of QoL data from register - primary Giovannoni 2010
Alcala C, Gascon F, Perez-Miralles F, Gil-Perotin S, Navarre A, Bosca I, et al. Efficacy and safety of rituximab in relapsing and progressive multiple sclerosis: a hospital-based study. JNeurol 2018;265(7):1690-7.	Mixed population in non-relevant fraction (too far from real population rate)
Alldredge B, Jordan A, Imitola J, Racke MK. Safety and Efficacy of Rituximab: Experience of a Single Multiple Sclerosis Center. ClinNeuropharmacol 2018;41(2):56-9.	Study design is not relevant for effect data. No safety data.
Anonymous. Erratum: Meta-analysis of adverse events in recent randomized clinical trials for dimethyl fumarate, glatiramer acetate, and teriflunomide for the treatment of relapsing forms of multiple sclerosis (International Journal of Neuroscience (2014)). IntJNeurosci 2016;126(1):i.	Erratum
Anonymous. Erratum: oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebo-controlled trial (The Lancet (2016) 387(10023) (1075-1084) (S0140673615013148) (10.1016/S0140-6736(15)01314-8)). Lancet 2017;389(10066):254.	Erratum
Anonymous. Erratum: Use of natalizumab in patients with multiple sclerosis: 2015 update (Canadian Journal of Neurological Sciences (2015) 42 (372-380) DOI: 10.1017/cjn.2015.296). Canadian Journal of Neurological Sciences 2017;44(4):467.	Erratum
Anonymous. MS disease activity in RESTORE: a randomized 24-week natalizumab treatment interruption study.[Erratum for Neurology. 2014 Nov 25;83(22):2099-100; PMID: 25422402]. Neurology 2015;84(8):862.	Erratum
Arnold D, Calabresi P, Kieseier B, Liu S, You X, Fiore D, Hung S. Peginterferon beta-1a improves MRI measures and increases the proportion of patients with no evidence of disease activity in relapsing-remitting multiple sclerosis: 2-year results from the ADVANCE randomized controlled trial. BMC Neurol 2017;17(1):29.	Intervention is not relevant
Arnold D, Fisher E, Brinar V, Cohen J, Coles A, Giovannoni G, Hartung H, Havrdova E, Selmaj K, Stojanovic M, Weiner H, Lake S, Margolin D, Thomas D, Panzara M, Compston D. Superior MRI outcomes with alemtuzumab compared with subcutaneous interferon ?-1a in MS. Neurology 2016;87(14):1464-72.	Data is reported in the core studies (Cohen 2012, CARE MS I, and Coles 2012, CARE MS II) and extracted from those papers
Arnold D, You X, Castrillo-Viguera C. Peginterferon beta-1a reduces the evolution of MRI lesions to black holes in patients with RRMS: a post hoc analysis from the ADVANCE study. JNeurol 2017;264(8):1728-34.	Intervention is not relevant
Arroyo Gonzalez R, Kita M, Crayton H, Havrdova E, Margolin DH, Lake SL, Giovannoni G, Care-Ms I, Investigators II. Alemtuzumab improves quality-of-life outcomes compared with subcutaneous interferon beta-1a in patients with active relapsing-remitting multiple sclerosis. MultScler 2017;23(10):1367-76.	Not relevant outcomes.
Arvin A, Wolinsky J, Kappos L, Morris M, Reder A, Tornatore C, Gershon A, Gershon M, Levin M, Bezuidenhoudt M, Putzki N. Varicella-zoster virus infections in patients treated with fingolimod: risk assessment and consensus recommendations for management. JAMA neurology 2015;72(1):31-9.	Study outcome is not relevant (risk factors and other factors related to Varicella-zoster virus infection)
Baker D, Herrod SS, Alvarez-Gonzalez C, Zalewski L, Albor C, Schmierer K. Both cladribine and alemtuzumab may effect MS via B-cell depletion. Neurology: Neuroimmunology and NeuroInflammation 2017;4(4).	Study outcome is not relevant (lymphocyte phenotyping data)
Bar-Or A, Calabresi PA, Arnold D, Markowitz C, Shafer S, Kasper LH, Waubant E, Gazda S, Fox RJ, Panzara M, Sarkar N, Agarwal S, Smith CH. Rituximab in relapsing-remitting multiple sclerosis: a 72-week, open-label, phase I trial.[Erratum appears in Ann Neurol. 2008 Jun;63(6):803 Note: Arnlod, Douglas [corrected to Arnold, Douglas]]. AnnNeurol 2008;63(3):395-400.	Not listed specifically what type of study this is. If it is a registry study: no description of the register. If it is an RCT: no comparator.
Bar-Or A, Calabresi PAJ, Arnold D, Markowitz C, Shafer S, Kasper LH, Waubant E, Gazda S, Fox RJ, Panzara M, Sarkar N, Agarwal S, Smith CH. Rituximab in relapsing-remitting multiple sclerosis: A 72-week, open-label, phase 1 trial (Annals of Neurology (2007) (399-495)). AnnNeurol 2008;63(6):803.	Erratum
Barra ME, Soni D, Vo KH, Chitnis T, Stankiewicz JM. Experience with long-term rituximab use in a multiple sclerosis clinic. Mult 2016;2:2055217316672100.	Registry study. Only 50-56% RRMS patients
Berenguer-Ruiz L, Sempere AP, Gimenez-Martinez J, Gabaldon-Torres L, Tahoces L, Sanchez-Perez R, Diaz-Marin C. Rescue Therapy Using Rituximab for Multiple Sclerosis. ClinNeuropharmacol 2016;39(4):178-81.	Study design is not relevant for effect data. No safety data.

Beutler E, Sipe JC, Romine JS, Koziol JA, McMillan R, Zyroff J. The treatment of chronic progressive multiple sclerosis with cladribine. ProcNatlAcadSciUSA 1996;93(4):1716-20.	Study population is not relevant
Borets OG, Davydovskaya MV, Demina TL, Lashch NY, Popova NF, Popova EV, Khachanova NV, Khasaeva MV, Shchur SG, Boiko AN. Experience in the Use of the beta-Interferon-1a Biosimilars CinnoVex and Genfaxon-44 at the Moscow City Multiple Sclerosis Center. NeurosciBehavPhysiol 2016:1-5.	Intervention is not relevant
Bourdette D, Yadav V. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. Current Neurology & Neuroscience Reports 2008;8(5):417-8.	Commentary
Boyko A, Bosenko L, Vasilovskiy V, Volkova L, Zakharova M, Kotov S, Lekomtseva E, Negrich T, Parshina E, Patrusheva O, Prokopenko S, Sazonov D, Timchenko P, Trinitatskiy Y, Khabirov F, Khavunka M, Chichanovskaya L, Sherman M, Lin'Kova Y, Zinkina-Orikhan A, Tursunova K. A comparative placebo-controlled clinical study on the efficacy and safety of interferon beta-1A for subcutaneous injections in patients with remitting multiple sclerosis: results of the first year of observations. Zhurnal nevrologii i psihiatrii imeni SS Korsakova Part 2 2017;117(2):107-13.	Study is in a non-usable language
Boyko AN, Alifirova VM. [Efficacy, safety and tolerability of glatiramer acetate injections in dose 40 mg/ml in patients with relapsing-remitting multiple sclerosis]. Zh Nevrol Psikhiatr Im S S Korsakova 2017;117(11):135-9.	Study is in a non-usable language
Boyko AN, Lashch NY, Sharanova SN, Zakharova MN, Trifonova OV, Simaniv TO, Lysogorskaya EV, Guryanova OE, Kotov SV, Iakushina TI, Lizhdvoy VY, Belova YA, Khabirov FA, Babicheva NN, Khaibullin TI, Granatov EV, Averyanova LA, Sazonov DV, Odinak MM, Trinitatsky YV, Tsukurova LA, Sergeeva AI, Ivanov RA, Shustova MS. [Comparative, placebo-controlled clinical study of efficacy and safety of glatiramer acetate 20 mg in patients with relapsing-remitting multiple sclerosis: results of the first year of the study]. Zh Nevrol Psikhiatr Im S S Korsakova 2016;116(10):61-7.	Study is in a non-usable language
Brown BA, Torabi M. Incidence of infusion-associated reactions with rituximab for treating multiple sclerosis: a retrospective analysis of patients treated at a US centre. Drug Safety 2011;34(2):117-23.	Study design is not relevant for effect data. No safety data. Only infusion reactions.
Cadavid D, Wolansky LJ, Skurnick J, Lincoln J, Cheriyan J, Szczepanowski K, et al. Efficacy of treatment of MS with IFNbeta-1b or glatiramer acetate by monthly brain MRI in the BECOME study. Neurology 2009;72(23):1976-83. doi: 10.212/01.wnl.0000345970.73354.17. Epub 2009 Mar 11.	Cannot isolate results for RRMS patients
Calabresi PA, Kieseier BC, Arnold DL, Balcer LJ, Boyko A, Pelletier J, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): A randomised, phase 3, double-blind study. The Lancet Neurology 2014;13(7):657-65.	Intervention not relevant
Chahin S, Balcer L, Miller D, Zhang A, Galetta S. Vision in a phase 3 trial of natalizumab for multiple sclerosis: relation to disability and quality of life. Journal of neuro-ophthalmology 2015;35(1):6-11.	Study outcome is not relevant association/correlation) post-hoc study
Chakravarty EF, Murray ER, Kelman A, Farmer P. Pregnancy outcomes after maternal exposure to rituximab. Blood 2011;117(5):1499-506.	Outcomes for neonates or women who took ritux during pregnancy
Chaudhuri A, Behan PO. Rituximab in relapsing-remitting multiple sclerosis. New England Journal of Medicine 2008;358(24):2646; author reply -7.	Commentary
Cinar B, Kösehasano?ullar G, Yigit P, Ozakbas S. Cognitive dysfunction in patients with multiple sclerosis treated with first-line disease-modifying therapy: a multi-center, controlled study using the BICAMS battery. Neurological sciences 2017;38(2):337-42.	Intervention and control not appropriate
Clanet M, Radue EW, Kappos L, Hartung HP, Hohlfeld R, Sandberg-Wollheim M, et al. A randomized, double-blind, dose-comparison study of weekly interferon beta-1a in relapsing MS. Neurology 2002;59(10):1507-17.	Intervention not relevant
Cocco E, Marrosu MG. Profile of PEGylated interferon beta in the treatment of relapsing-remitting multiple sclerosis. Therapeutics and Clinical Risk Management 2015;11:759-66.	Review
Cohen J, Khatri B, Barkhof F, Comi G, Hartung H, Montalban X, Pelletier J, Stites T, Ritter S, Rosenstiel P, Tomic D, Kappos L. Long-term (up to 4.5 years) treatment with fingolimod in multiple sclerosis: results from the extension of the randomised TRANSFORMS study. J Neurol Neurosurg Psychiatr 2016;87(5):468-75.	Data is reported in the TRANSFORM study. No relevant new data.
Coles A, Cohen J, Fox E, Giovannoni G, Hartung HP, Havrdova E, Schippling S, Selmaj K, Traboulsee A, Compston D, Margolin D, Thangavelu K, Chirieac M, Jody D, Xenopoulos P, Hogan R, Panzara M, Arnold D. Alemtuzumab CARE-MS II 5-year follow-up: efficacy and safety findings. Neurology 2017;89(11):1117-26.	No relevant control group. The control group was previously treated with interferon beta-1a (Rebif®) and now receives Alemtuzumab 12 mg as the intervention
Comi G, Cook S, Rammohan K, Sorensen PS, Vermersch P, Adeniji AK, Dangond F, Giovannoni G. Long-term effects of cladribine tablets on mri activity outcomes in patients with relapsing-remitting multiple sclerosis: The clarity extension study. Therapeutic Advances in Neurological Disorders 2018;11.	No relevant comparator.
Comi G, Freedman MS, Kappos L, Olsson TP, Miller AE, Wolinsky JS, O'Connor PW, Benamor M, Dukovic D, Truffinet P, Leist TP. Pooled safety and tolerability data from four placebo-controlled teriflunomide studies and extensions. Multiple Sclerosis and Related Disorders 2016;5:97-104.	Study population is not relevant. Mixed diagnoses.

Comi G, Stefano N, Freedman M, Barkhof F, Uitdehaag B, Vos M, Marhardt K, Chen L, Issard D, Kappos L. Subcutaneous interferon beta-1a in the treatment of clinically isolated syndromes: 3-year and 5-year results of the phase III dosing frequency-blind multicentre REFLEXION study. Journal of neurology, neurosurgery and psychiatry 2017;88(4):285-94.	Intervention not relevant
Coyle P, Khatri B, Edwards K, Meca-Lallana J, Cavalier S, Rufi P, Benamor M, Brette S, Robinson M, Gold R. Patient-reported outcomes in relapsing forms of MS: real-world, global treatment experience with teriflunomide from the Teri-PRO study. Multiple sclerosis and related disorders 2017;17:107-15.	No relevant control group
Coyle PK, Reder AT, Freedman MS, Fang J, Dangond F. Early MRI results and odds of attaining 'no evidence of disease activity' status in MS patients treated with interferon beta-1a in the EVIDENCE study. Journal of the Neurological Sciences 2017;379:151-6.	Intervention not relevant
Cross AH, Klein RS, Piccio L. Rituximab combination therapy in relapsing multiple sclerosis. Therapeutic Advances in Neurological Disorders 2012;5(6):311-9.	Review
Davis MD, Ashtamker N, Steinerman JR, Knappertz V. Time course of glatiramer acetate efficacy in patients with RRMS in the GALA study. Neurology: Neuroimmunology and NeuroInflammation 2017;4.	Study outcome is not relevant.
de Flon P, Gunnarsson M, Laurell K, Soderstrom L, Birgander R, Lindqvist T, Krauss W, Dring A, Bergman J, Sundstrom P, Svenningsson A. Reduced inflammation in relapsing-remitting multiple sclerosis after therapy switch to rituximab. Neurology 2016;87(2):141-7.	No relevant control group and study population not relevant
de Flon P, Laurell K, Soderstrom L, Gunnarsson M, Svenningsson A. Improved treatment satisfaction after switching therapy to rituximab in relapsing-remitting MS. MultScler 2017;23(9):1249-57.	No relevant control group and study population not relevant
De Stefano N, Curtin F, Stubinski B, Blevins G, Drulovic J, Issard D, et al. Rapid benefits of a new formulation of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis. MultScler 2010;16(7):888-92.	Interferon vs placebo
De Stefano N, Giorgio A, Battaglini M, De Leucio A, Hicking C, Dangond F, Giovannoni G, Sormani MP. Reduced brain atrophy rates are associated with lower risk of disability progression in patients with relapsing multiple sclerosis treated with cladribine tablets. MultScler 2018;24(2):222-6.	Not our outcome (brain atrophy).
Derfuss T, Bergvall N, Sfikas N, Tomic D. Efficacy of fingolimod in patients with highly active relapsing-remitting multiple sclerosis. Current medical research and opinion 2015;31(9):1687-91.	Study population is not relevant
Derfuss T, Ontaneda D, Nicholas J, Meng X, Hawker K. Relapse rates in patients with multiple sclerosis treated with fingolimod: subgroup analyses of pooled data from three phase 3 trials. Multiple sclerosis and related disorders 2016;8:124-30.	Pooled analyses. Original data is included.
Diener HC. Multiple sclerosis: Rituximab for treating relapsing-remitting multiple sclerosis. [German]. Arzneimitteltherapie 2008;26(9):341.	Comment to study by Hauser.
Durelli L, Verdun E, Barbero P, Bergui M, Versino E, Ghezzi A, et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). Lancet 2002;359(9316):1453-60.	Interferon vs interferon
Etemadifar M, Janghorbani M, Shaygannejad V. Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis. Acta Neurol Scand 2006;113(5):283-7.	Interferon vs interferon
Evdoshenko E, Maslyanskiy A, Lapin S, Zaslavsky L, Dobson R, Totolian A, Skoromets A, Bar-Or A. Dynamics of B-Cell Populations in CSF and Blood in Patients Treated with a Combination of Rituximab and Mitoxantrone. Isrn Neurology Print 2013;2013:748127.	Intervention is not relevant
Fernández Ó, Giovannoni G, Fox R, Gold R, Phillips J, Potts J, Okwuokenye M, Marantz J. Efficacy and Safety of Delayed-release Dimethyl Fumarate for Relapsing-remitting Multiple Sclerosis in Prior Interferon Users: an Integrated Analysis of DEFINE and CONFIRM. Clinical therapeutics 2017;39(8):1671-9.	Pooled analyses. Original data is included.
Fox E, Wynn D, Coles A, Palmer J, Margolin D. Alemtuzumab improves neurological functional systems in treatment-naive relapsing-remitting multiple sclerosis patients. Journal of the neurological sciences 2016;363:188-94.	Study outcome is not relevant
Fox R, Gold R, Phillips J, Okwuokenye M, Zhang A, Marantz J. Efficacy and Tolerability of Delayed-release Dimethyl Fumarate in Black, Hispanic, and Asian Patients with Relapsing-Remitting Multiple Sclerosis: post Hoc Integrated Analysis of DEFINE and CONFIRM. Neurology and therapy 2017;6(2):175-87.	Pooled analyses. Original data is included.
Freedman M, Truffinet P, Comi G, Kappos L, Miller A, Olsson T, Benamor M, Chambers S, O'Connor P. A randomized trial of teriflunomide added to glatiramer acetate in relapsing multiple sclerosis. Mult Scler J Exp Transl Clin 2015;1:1-10.	Intervention not relevant
Freedman MS, Leist TP, Comi G, Cree BAC, Coyle PK, Hartung HP, Vermersch P, Damian D, Dangond F. The efficacy of cladribine tablets in CIS patients retrospectively assigned the diagnosis of MS using modern criteria: Results from the ORACLE-MS study. Multiple Sclerosis Journal Experimental, Translational and Clinical 2017;3(4).	Study population not relevant
Gaetano L, Haring DA, Radue EW, Mueller-Lenke N, Thakur A, Tomic D, Kappos L, Sprenger T. Fingolimod effect on gray matter, thalamus, and white matter in patients with multiple sclerosis. Neurology 2018;90(15):e1324-e32.	Study outcome is not relevant
Giovannoni G, Cohen J, Coles A, Hartung H, Havrdova E, Selmaj K, Margolin D, Lake S, Kaup S, Panzara M, Compston D. Alemtuzumab improves preexisting disability in active relapsing-remitting MS patients. Neurology 2016;87(19):1985-92.	New presentation of results. Original data is included.

Giovannoni G, Cook S, Rammohan K, Rieckmann P, Sorensen PS, Vermersch P, Hamlett A, Viglietta V, Greenberg S. Sustained disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets in the CLARITY study: A post-hoc and subgroup analysis. The Lancet Neurology 2011;10(4):329-37.	Study outcome is not relevant
Giovannoni G, Soelberg Sorensen P, Cook S, Rammohan K, Rieckmann P, Comi G, Dangond F, Adeniji AK, Vermersch P. Safety and efficacy of cladribine tablets in patients with relapsing-remitting multiple sclerosis: Results from the randomized extension trial of the CLARITY study. Multiple Sclerosis Journal 2017;1.	No relevant control group.
Giovannoni G, Soelberg Sorensen P, Cook S, Rammohan KW, Rieckmann P, Comi G, Dangond F, Hicking C, Vermersch P. Efficacy of Cladribine Tablets in high disease activity subgroups of patients with relapsing multiple sclerosis: A post hoc analysis of the CLARITY study. MultScler 2018:1352458518771875.	Study outcome is not relevant
Gold R, Arnold D, Bar-Or A, Hutchinson M, Kappos L, Havrdova E, MacManus D, Yousry T, Pozzilli C, Selmaj K, Sweetser M, Zhang R, Yang M, Potts J, Novas M, Miller D, Kurukulasuriya N, Fox R, Phillips T. Long-term effects of delayed-release dimethyl fumarate in multiple sclerosis: interim analysis of ENDORSE, a randomized extension study. Multiple sclerosis (houndmills, basingstoke, england) 2017;23(2):253-65.	No relevant control group
Gold R, Giovannoni G, Phillips JT, Fox RJ, Zhang A, Marantz JL. Sustained Effect of Delayed-Release Dimethyl Fumarate in Newly Diagnosed Patients with Relapsing-Remitting Multiple Sclerosis: 6-Year Interim Results From an Extension of the DEFINE and CONFIRM Studies. Neurol 2016;5(1):45-57.	No relevant control group
Goodin DS, Reder AT, Traboulsee AL, Li DK, Langdon D, Cutter G, Cook S, O'Donnell T, Kremenchutzky M, Oger J, Koelbach R, Pohl C, Wicklein EM. Predictive validity of NEDA in the 16- and 21-year follow-up from the pivotal trial of interferon beta-1b. Multiple sclerosis (Houndmills, Basingstoke, England) 2018:1352458518773511.	Intervention is not relevant
Graves J, Vinayagasundaram U, Mowry EM, Matthews IR, Marino JA, Cheng J, Waubant E. Effects of rituximab on lymphocytes in multiple sclerosis and neuromyelitis optica. Multiple Sclerosis and Related Disorders 2014;3(2):244-52.	Study population is not relevant
Grieb P, Ryba M, Stelmasiak Z, Nowicki J, Solski J, Jakubowska B. Cladribine treatment of multiple sclerosis.[Erratum appears in Lancet 1994 Oct 15;344(8929):1098]. Lancet 1994;344(8921):538.	Letter
Hang Y, Hu X, Zhang J, Liu S, Deykin A, Nestorov I. Analysis of peginterferon ?-1a exposure and Gd-enhanced lesion or T2 lesion response in relapsing-remitting multiple sclerosis patients. J Pharmacokinet Pharmacodyn 2016;43(4):371-83.	Intervention is not relevant
Havrdova E, Arnold DL, Cohen JA, Hartung HP, Fox EJ, Giovannoni G, Schippling S, Selmaj KW, Traboulsee A, Compston DAS, Margolin DH, Thangavelu K, Rodriguez CE, Jody D, Hogan RJ, Xenopoulos P, Panzara MA, Coles AJ, Care-Ms I, Investigators C. Alemtuzumab CARE-MS I 5-year follow-up: Durable efficacy in the absence of continuous MS therapy.[Erratum appears in Neurology. 2018 Apr 17;90(16):755; PMID: 29661899]. Neurology 2017;89(11):1107-16.	No relevant control group
Havrdova E, Giovannoni G, Gold R, Fox R, Kappos L, Phillips J, Okwuokenye M, Marantz J. Effect of delayed-release dimethyl fumarate on no evidence of disease activity in relapsing-remitting multiple sclerosis: integrated analysis of the phase III DEFINE and CONFIRM studies. European journal of neurology 2017;24(5):726-33.	Study outcome is not relevant
Hawker K, O'Connor P, Freedman MS, Calabresi PA, Antel J, Simon J, Hauser S, Waubant E, Vollmer T, Panitch H, Zhang J, Chin P, Smith CH, group Ot. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. AnnNeurol 2009;66(4):460-71.	Study population is not relevant
Hayes, Inc. Ocrelizumab (Ocrevus; Genentech Inc.) for primary progressive and relapsing-remitting multiple sclerosis. Lansdale, PA: HAYES Inc; 2017.	Study population is not relevant
Hu X, Cui Y, White J, Zhu Y, Deykin A, Nestorov I, Hung S. Pharmacokinetics and pharmacodynamics of peginterferon beta-1a in patients with relapsing-remitting multiple sclerosis in the randomized ADVANCE study. British journal of clinical pharmacology 2015;79(3):514-22.	Intervention is not relevant
Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized. Double blind, placebo controlled trial. The IFNB Multiple Sclerosisi Study group	Interferon vs placebo
Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Ann Neurol 1996;39(3):285-94.	Interferon vs placebo
Jeffery D, Cantogno E, Ritter S, Meier D, Radue E, Camu W. The relationship between the rate of brain volume loss during first 24 months and disability progression over 24 and 48 months in relapsing MS. JNeurol 2016;263(2):299-305.	Study outcome is not relevant
Kalincik T, Jokubaitis V, Spelman T, Horakova D, Havrdova E, Trojano M, Lechner-Scott J, Lugaresi A, Prat A, Girard M, Duquette P, Grammond P, Solaro C, Grand'Maison F, Hupperts R, Prevost J, Sola P, Ferraro D, Terzi M, Butler E, Slee M, Kermode A, Fabis-Pedrini M, McCombe P, Barnett M, Shaw C, Hodgkinson S, Butzkueven H. Cladribine versus fingolimod, natalizumab and interferon beta for multiple sclerosis. Multiple sclerosis (Houndmills, Basingstoke, England) 2017:1352458517728812.	Study design is not relevant
Kappos L, Arnold DL, Bar-Or A, Camm J, Derfuss T, Kieseier BC, Sprenger T, Greenough K, Ni PP, Harada T. Safety and efficacy of amiselimod in relapsing multiple sclerosis (MOMENTUM): a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurology 2016;15(11):1148-59.	Intervention is not relevant

Kappos L, Edan G, Freedman M, Montalbán X, Hartung H, Hemmer B, Fox E, Barkhof F, Schippling S, Schulze A, Pleimes D, Pohl C, Sandbrink R, Suarez G, Wicklein E. The 11-year long-term follow-up study from the randomized BENEFIT CIS trial. Neurology 2016;87(10):978-87.	Intervention is not relevant
Kappos L, Giovannoni G, Gold R, Phillips J, Arnold D, Hotermans C, Zhang A, Viglietta V, Fox R. Time course of clinical and neuroradiological effects of delayed-release dimethyl fumarate in multiple sclerosis. European journal of neurology 2015;22(4):664-71.	Study outcome is not relevant
Kappos L, Havrdova E, Giovannoni G, Khatri B, Gauthier S, Greenberg S, You X, Wang P, Giannattasio G. No evidence of disease activity in patients receiving daclizumab versus intramuscular interferon beta-1a for relapsing-remitting multiple sclerosis in the DECIDE study. Multiple sclerosis (houndmills, basingstoke, england) 2017;23(13):1736-47.	Intervention is not relevant
Kappos L, Kuhle J, Multanen J, Kremenchutzky M, Verdun dCE, Cornelisse P, Lehr L, Casset-Semanaz F, Issard D, Uitdehaag B. Factors influencing long-term outcomes in relapsing-remitting multiple sclerosis: pRISMS-15. J Neurol Neurosurg Psychiatr 2015;86(11):1202-7.	Intervention is not relevant
Kappos L, O'Connor P, Radue E, Polman C, Hohlfeld R, Selmaj K, Ritter S, Schlosshauer R, Rosenstiel P, Zhang-Auberson L, Francis G. Long-term effects of fingolimod in multiple sclerosis: the randomized FREEDOMS extension trial. Neurology 2015;84(15):1582-91.	No relevant control group
Kappos L, Radue EW, Comi G, Montalban X, Butzkueven H, Wiendl H, Giovannoni G, Hartung HP, Derfuss T, Naegelin Y, Sprenger T, Mueller-Lenke N, Griffiths S, Rosenstiel P, Gottschalk R, Zhang Y, Dahlke F, Tomic D. Switching from natalizumab to fingolimod : a randomized, placebo-controlled study in RRMS. Neurology 2015;85(1):29-39.	Study design and outcome are not relevant
Kaufman M, Cree B, Sèze J, Fox R, Gold R, Hartung H, Jeffery D, Kappos L, Montalbán X, Weinstock-Guttman B, Ticho B, Duda P, Pace A, Campagnolo D. Radiologic MS disease activity during natalizumab treatment interruption: findings from RESTORE. JNeurol 2015;262(2):326-36.	Study outcome is not relevant
Khan O, Rieckmann P, Boyko A, Selmaj K, Ashtamker N, Davis M, Kolodny S, Zivadinov R. Efficacy and safety of a three-times-weekly dosing regimen of glatiramer acetate in relapsing-remitting multiple sclerosis patients: 3-year results of the Glatiramer Acetate Low-Frequency Administration open-label extension study. Multiple sclerosis (houndmills, basingstoke, england) 2017;23(6):818-29.	No relevant control group
Khan O, Seraji-Bozorgzad N, Bao F, Razmjou S, Caon C, Santiago C, Latif Z, Aronov R, Zak I, Ashtamker N, Kolodny S, Ford C, Sidi Y. The Relationship Between Brain MR Spectroscopy and Disability in Multiple Sclerosis: 20-Year Data from the U.S. Glatiramer Acetate Extension Study. Journal of neuroimaging 2017;27(1):97-106.	Study outcome is not relevant
Kieseier B, Arnold D, Balcer L, Boyko A, Pelletier J, Liu S, Zhu Y, Seddighzadeh A, Hung S, Deykin A, Sheikh S, Calabresi P. Peginterferon beta-1a in multiple sclerosis: 2-year results from ADVANCE. Multiple sclerosis (houndmills, basingstoke, england) 2015;21(8):1025-35.	Intervention is not relevant
Krueger J, Kircik L, Hougeir F, Friedman A, You X, Lucas N, Greenberg S, Sweetser M, Castro-Borrero W, McCroskery P, Elkins J. Cutaneous Adverse Events in the Randomized, Double-Blind, Active-Comparator DECIDE Study of Daclizumab High-Yield Process Versus Intramuscular Interferon Beta-1a in Relapsing-Remitting Multiple Sclerosis. Adv Ther 2016;33(7):1231-45.	Intervention is not relevant
Lee A, Pike J, Edwards MR, Petrillo J, Waller J, Jones E. Quantifying the Benefits of Dimethyl Fumarate Over beta Interferon and Glatiramer Acetate Therapies on Work Productivity Outcomes in MS Patients. Neurology and Therapy 2017;6(1):79-90.	Study design and outcome is not relevant
Leist TP, Comi G, Cree BAC, Coyle PK, Freedman MS, Hartung HP, Vermersch P, Casset-Semanaz F, Scaramozza M. Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): A phase 3 randomised trial. The Lancet Neurology 2014;13(3):257-67.	Study population is not relevant
Leussink VI, Lehmann HC, Meyer zu Horste G, Hartung HP, Stuve O, Kieseier BC. Rituximab induces clinical stabilization in a patient with fulminant multiple sclerosis not responding to natalizumab. Evidence for disease heterogeneity. JNeurol 2008;255(9):1436-8.	Study design is not relevant
Leussink VI, Warnke C, Tackenberg B, Wiendl H, Kieseier BC. Pegylated interferon beta 1a: A new therapy option for treatment of relapsing-remitting multiple sclerosis. [German]. Nervenarzt 2015;3.	Study is in a non-usable language
Lyseng-Williamson K, Hoy S. Peginterferon beta-1a in relapsing-remitting multiple sclerosis: a guide to its use in the EU. Drugs and therapy perspectives 2015;31(6):190-5.	Narrative review
Malucchi S, Capobianco M, di Sapio A, Re ML, Cavalla P, Bertolotto A. Rituximab suppresses disease activity after natalizumab withdrawal: An exploratory study. Multiple Sclerosis and Demyelinating Disorders 2016;1(1):1-3.	Study population is to low
Marignier R, Durand-Dubief F, du Pasquier R, Vukusic S. Rituximab versus fingolimod after natalizumab in multiple sclerosis: Also consider progressive multifocal leukoencephalopathy risk. AnnNeurol 2016;80(5):791.	Letter
Melendez-Torres GJ, Auguste P, Armoiry X, Maheswaran H, Court R, Madan J, et al. Clinical effectiveness and cost-effectiveness of beta-interferon and glatiramer acetate for treating multiple sclerosis: systematic review and economic evaluation. Health technology assessment (Winchester, England) 2017;21(52):1-352.	We have all trials of interest except one pilot trial Bornstein 1987.
Memon AB, Javed A, Caon C, Srivastawa S, Bao F, Bernitsas E, Chorostecki J, Tselis A, Seraji-Bozorgzad N, Khan O. Long-term safety of rituximab induced peripheral B-cell depletion in autoimmune neurological diseases. PLoS ONE [Electronic Resource] 2018;13(1):e0190425.	Not MS patients

Meng X, Chin PS, Hashmonay R, Zahur Islam M, Cutter G. Effect of switching from intramuscular interferon beta-1a to oral fingolimod on time to relapse in patients with relapsing-remitting multiple sclerosis enrolled in a 1-year extension of TRANSFORMS. Contemporary Clinical Trials 2015;41:69-74.	Post-hoc analyses. Mixes core and extension data
Menge T, Dubey D, Warnke C, Hartung HP, Stuve O. Ocrelizumab for the treatment of relapsing-remitting multiple sclerosis. Expert Rev Neurother 2016;16(10):1131-9.	Review
Miller D, Fox R, Phillips J, Hutchinson M, Havrdova E, Kita M, Wheeler-Kingshott C, Tozer D, MacManus D, Yousry T, Goodsell M, Yang M, Zhang R, Viglietta V, Dawson K. Effects of delayed-release dimethyl fumarate on MRI measures in the phase 3 CONFIRM study. Neurology 2015;84(11):1145-52.	Study outcome is not relevant
Mitsikostas DD, Goodin DS. Comparing the efficacy of disease-modifying therapies in multiple sclerosis. Multiple Sclerosis and Related Disorders 2017;18:109-16.	Review
Mokhber N, Azarpazhooh A, Orouji E, Khorram B, Modares GM, Kakhi S, Khallaghi H, Azarpazhooh M. Therapeutic effect of Avonex, Rebif and Betaferon on quality of life in multiple sclerosis. Psychiatry Clin Neurosci 2015;69(10):649-57.	Intervention is not relevant
Mokhber N, Azarpazhooh A, Orouji E, Rao SM, Khorram B, Sahraian MA, et al. Cognitive dysfunction in patients with multiple sclerosis treated with different types of interferon beta: A randomized clinical trial. Journal of the Neurological Sciences 2014;342(1-2):16-20.	Interferon vs interferon
Montalban X, Comi G, Antel J, O'Connor P, Vera A, Cremer M, Sfikas N, Rosenstiel P, Kappos L. Long-term results from a phase 2 extension study of fingolimod at high and approved dose in relapsing multiple sclerosis. JNeurol 2015;262(12):2627-34.	No relevant control group
Naismith RT, Piccio L, Lyons JA, Lauber J, Tutlam NT, Parks BJ, Trinkaus K, Song SK, Cross AH. Rituximab add-on therapy for breakthrough relapsing multiple sclerosis: a 52-week phase II trial. Neurology 2010;74(23):1860-7.	No relevant control group
Newsome S, Guo S, Altincatal A, Proskorovsky I, Kinter E, Phillips G, You X, Sabatella G. Impact of peginterferon beta-1a and disease factors on quality of life in multiple sclerosis. Multiple sclerosis and related disorders 2015;4(4):350-7.	Intervention is not relevant
Newsome S, Kieseier B, Arnold D, Shang S, Liu S, Hung S, Sabatella G. Subgroup and sensitivity analyses of annualized relapse rate over 2 years in the ADVANCE trial of peginterferon beta-1a in patients with relapsing-remitting multiple sclerosis. JNeurol 2016;263(9):1778-87.	Intervention is not relevant
Newsome SD, Kieseier BC, Liu SF, You XJ, Kinter E, Hung S, Sperling B. Peginterferon beta-1a reduces disability worsening in relapsing-remitting multiple sclerosis: 2-year results from ADVANCE. Therapeutic Advances in Neurological Disorders 2017;10(1):41-50.	Intervention is not relevant
Nielsen AS, Miravalle A, Langer-Gould A, Cooper J, Edwards KR, Kinkel RP. Maximally tolerated versus minimally effective dose: the case of rituximab in multiple sclerosis. MultScler 2012;18(3):377-8.	Letter
Novakovic AM, Thorsted A, Schindler E, Jonsson S, Munafo A, Karlsson MO. Pharmacometric Analysis of the Relationship Between Absolute Lymphocyte Count and Expanded Disability Status Scale and Relapse Rate, Efficacy End Points, in Multiple Sclerosis Trials. Journal of Clinical Pharmacology 2018.	Study outcome is not relevant
O'Connor K, Liddle C. Prospective data collection of off-label use of rituximab in Australian public hospitals. Internal Medicine Journal 2013;43(8):863-70.	Study population is not relevant
O'Connor P, Comi G, Freedman MS, Miller AE, Kappos L, Bouchard JP, Lebrun-Frenay C, Mares J, Benamor M, Thangavelu K, Liang J, Truffinet P, Lawson VJ, Wolinsky JS, Teriflunomide Multiple Sclerosis Oral Trial G, the Mri-Ac in Houston T. Long-term safety and efficacy of teriflunomide: Nine-year follow-up of the randomized TEMSO study.[Erratum appears in Neurology. 2016 Oct 4;87(14):1524; PMID: 27698155]. Neurology 2016;86(10):920-30.	No relevant control group
O'Connor PW, Li D, Freedman MS, Bar-Or A, Rice GP, Confavreux C, et al. A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. Neurology 2006;66(6):894-900.	Mixed population
O'Connor PW, Lublin FD, Wolinsky JS, Confavreux C, Comi G, Freedman MS, et al. Teriflunomide reduces relapse-related neurological sequelae, hospitalizations and steroid use. JNeurol 2013;260(10):2472-80.	Presents processed relapse data from O'Connor 2011. No new raw data.
Panitch H, Goodin DS, Francis G, Chang P, Coyle PK, O'Connor P, et al. Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. Neurology 2002;59(10):1496-506.	Interferon vs interferon
Petereit HF, Rubbert A. Effective suppression of cerebrospinal fluid B cells by rituximab and cyclophosphamide in progressive multiple sclerosis. Archives of Neurology 2005;62(10):1641-2; author reply 2.	Letter
Piccio L, Naismith RT, Trinkaus K, Klein RS, Parks BJ, Lyons JA, Cross AH. Changes in B- and T-lymphocyte and chemokine levels with rituximab treatment in multiple sclerosis. Archives of Neurology 2010;67(6):707-14.	Study outcome is not relevant
Piehl F, Hillert J. Rituximab is an acceptable alternative to ocrelizumab for treating multiple sclerosis - Yes. Multiple Sclerosis Journal 2018;24(9):1157-9.	Commentary
Popova E, Boiko A, Boiko O, Alifirova V, Anishenko L, Belova A, Greshnova I, Dorogov N, Korotkevich N, Laskov V, Magzhanov R, Malkova N, Maslova N, Parshina E, Patrusheva O, Sivertseva S, Spirin N, Stolyarov I, Streknev A, Trushnikova T, Tsukurova L, Fedyanin A, Khabirov F, Chefranova Z, Chichanovskaya L, Sherman M, Shmidt T. Results of a Randomized Open Multicenter Comparative Study of the Tolerability and Safety of Gilenya (fingolimod) in Patients with Remitting Multiple Sclerosis (the GIMN study). NeurosciBehavPhysiol 2017;47(1):102-6.	Translated from Popova 2015. Not relevant comparator (mixture of drugs).

Popova EV, Boyko AN, Boyko OV. [The results of a randomized open multicenter comparative study on the tolerability and safety of gilenya (fingolimod) in patients with remitting multiple sclerosis]. Zh Nevrol Psikhiatr Im S S Korsakova 2015;115(2):45-50.	Russian language.
Radue EW, Sprenger T, Gaetano L, Mueller-Lenke N, Cavalier S, Thangavelu K, Panzara MA, Donaldson JE, Woodward FM, Wuerfel J, Wolinsky JS, Kappos L. Teriflunomide slows BVL in relapsing MS: A reanalysis of the TEMSO MRI data set using SIENA. Neurology neuroimmunology & neuroinflammation 2017;4(5):e390.	Re-analyses of TEMSO study (O'Connor 2011).
Rammohan K, Giovannoni G, Comi G, Cook S, Rieckmann P, Soelberg Sorensen P, Vermersch P, Hamlett A, Kurukulasuriya N, Group CS. Cladribine tablets for relapsing-remitting multiple sclerosis: Efficacy across patient subgroups from the phase III CLARITY study. Multiple Sclerosis and Related Disorders 2012;1(1):49-54.	Study outcome is not relevant
Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Lancet 1998;352(9139):1498-504.	Interferon vs placebo
Romine JS, Sipe JC, Koziol JA, Zyroff J, Beutler E. A double-blind, placebo-controlled, randomized trial of cladribine in relapsing-remitting multiple sclerosis. Proceedings of the Association of American Physicians 1999;111(1):35-44.	Injection of cladribine, only tablets are included.
Ryerson LZ, Green R, Confident G, Pandey K, Richter B, Bacon T, Sammarco C, Laing L, Kalina J, Kister I. Efficacy and tolerability of dimethyl fumarate in White-, African- and Hispanic- Americans with multiple sclerosis. Therapeutic Advances in Neurological Disorders 2016;9(6):454-61.	Study design is not relevant.
Saida T, Itoyama Y, Kikuchi S, Hao Q, Kurosawa T, Ueda K, Auberson L, Tsumiyama I, Nagato K, Kira JI. Long-term efficacy and safety of fingolimod in Japanese patients with relapsing multiple sclerosis: 3-year results of the phase 2 extension study. BMC Neurol2017.	Extension of extension with no proper control groups.
Saida T, Kira J, Ueno Y, Harada N, Hirakata T. Long-term efficacy and safety of intramuscular interferon beta-1a: randomized postmarketing trial of two dosing regimens in Japanese patients with relapsing-remitting multiple sclerosis. Multiple sclerosis and related disorders2016. s. 102-8.	Intervention is not relevant
Saida T, Kira JI, Kishida S, Yamamura T, Ohtsuka N, Dong Q, Tibung JT. Natalizumab for Achieving Relapse-Free, T1 Gadolinium-Enhancing-Lesion-Free, and T2 Lesion-Free Status in Japanese Multiple Sclerosis Patients: A Phase 2 Trial Subanalysis. Neurology and Therapy 2017;6(1):153-9.	Sub analyses of core study, no new data
Saida T, Kira JI, Kishida S, Yamamura T, Ohtsuka N, Ling Y, Torii S, Lucas N, Kuesters G, Steiner D, Tibung JT. Safety and Efficacy of Natalizumab in Japanese Patients with Relapsing-Remitting Multiple Sclerosis: Open-Label Extension Study of a Phase 2 Trial. Neurology and Therapy 2017;6(1):39-55.	Extension study with no proper control group
Schippling S, O'Connor P, Knappertz V, Pohl C, Bogumil T, Suarez G, Cook S, Filippi M, Hartung H, Comi G, Jeffery D, Kappos L, Goodin D, Arnason B. Incidence and course of depression in multiple sclerosis in the multinational BEYOND trial. JNeurol 2016;263(7):1418-26.	Study outcome is not relevant
Scotti B, Disanto G, Sacco R, Guigli M, Zecca C, Gobbi C. Effectiveness and safety of Rituximab in multiple sclerosis: an observational study from Southern Switzerland. PLoS ONE [Electronic Resource] 2018;13(5):e0197415.	Registry study. No comparator mentioned in the method section. In results: use natalizumab as comparator. Also: Only 43 of 82 patients with RRMS
Simon J, Kinkel R, Kollman C, O'Connor P, Fisher E, You X, Hyde R. Ten-year follow-up of the 'minimal MRI lesion' subgroup from the original CHAMPS Multiple Sclerosis Prevention Trial. Multiple sclerosis (houndmills, basingstoke, england) 2015;21(4):415-22.	Intervention is not relevant
Singer B. The role of natalizumab in the treatment of multiple sclerosis: benefits and risks. Therapeutic advances in neurological disorders 2017;10(9):327-36.	Narrative review
Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell LJ, Macdonald JK, Filippini G, Skoetz N, Francis DK, Lopes LC, Guyatt GH, Schmitt J, La Mantia L, Weberschock T, Roos JF, Siebert H, Hershan S, Cameron C, Lunn MP, Tugwell P, Buchbinder R. Adverse effects of biologics: A network meta-analysis and Cochrane overview. Cochrane Database of Systematic Reviews 2011;2011.	Review
Sorensen PS. Multiple sclerosis. Generic glatiramer acetate--a step toward cheaper MS drugs? Nature Reviews Neurology 2016;12(1):5-6.	Commentary article
Sormani M, Stefano N, Francis G, Sprenger T, Chin P, Radue E, Kappos L. Fingolimod effect on brain volume loss independently contributes to its effect on disability. Multiple sclerosis (houndmills, basingstoke, england) 2015;21(7):916-24.	Study objective is not relevant
Stefano N, Tomic D, Radue E, Sprenger T, Meier D, Häring D, Sormani M. Effect of fingolimod on diffuse brain tissue damage in relapsing-remitting multiple sclerosis patients. Multiple sclerosis and related disorders 2016;7:98-101.	Pooled analyses. Original data is included.
Stelmasiak Z, Solski J, Nowicki J, Jakubowska B, Ryba M, Grieb P. Effect of parenteral cladribine on relapse rates in patients with relapsing forms of multiple sclerosis: Results of a 2-year, double-blind, placebo-controlled, crossover study. MultScler 2009;15(6):767-70.	Subcutaneous injection. Inly tablets are included.
Stuve O, Cepok S, Elias B, Saleh A, Hartung HP, Hemmer B, Kieseier BC. Clinical stabilization and effective B-lymphocyte depletion in the cerebrospinal fluid and peripheral blood of a patient with fulminant relapsing-remitting multiple sclerosis. Archives of Neurology 2005;62(10):1620-3.	Study design is not relevant

Tanaka M, Shimizu Y. [Dimethyl Fumarate in Multiple Sclerosis]. Brain & Nerve / Shinkei Kenkyu no Shinpo 2017;69(9):1041-6.	Study is in a non-usable language
Taupin P. Antibodies against CD20 (rituximab) for treating multiple sclerosis: US20100233121. Expert Opinion on Therapeutic Patents 2011;21(1):111-4.	Study objective is not relevant
Tintore M, Sastre-Garriga J. MULTIPLE SCLEROSIS Dimethyl fumarate is coming of age. Nature Reviews Neurology 2016;12(8):436-7.	Commentary article
Tony HP, Burmester G, Schulze-Koops H, Grunke M, Henes J, Kotter I, Haas J, Unger L, Lovric S, Haubitz M, Fischer-Betz R, Chehab G, Rubbert-Roth A, Specker C, Weinerth J, Holle J, Muller-Ladner U, Konig R, Fiehn C, Burgwinkel P, Budde K, Sorensen H, Meurer M, Aringer M, Kieseier B, Erfurt-Berge C, Sticherling M, Veelken R, Ziemann U, Strutz F, von Wussow P, Meier FM, Hunzelmann N, Schmidt E, Bergner R, Schwarting A, Eming R, Hertl M, Stadler R, Schwarz-Eywill M, Wassenberg S, Fleck M, Metzler C, Zettl U, Westphal J, Heitmann S, Herzog AL, Wiendl H, Jakob W, Schmidt E, Freivogel K, Dorner T, investigators G. Safety and clinical outcomes of rituximab therapy in patients with different autoimmune diseases: experience from a national registry (GRAID). Arthritis Research & Therapy 2011;13(3):R75.	Mixture of diseases
Traboulsee A, Li D, Tam R, Zhao G, Riddehough A, Fang J, Dangond F, Kappos L, Prisms, Groups SW. Subcutaneous interferon beta-1a three times weekly and the natural evolution of gadolinium-enhancing lesions into chronic black holes in relapsing and progressive multiple sclerosis: Analysis of PRISMS and SPECTRIMS trials. Mult 2017;3(4):2055217317745340.	Post-hoc analyses. Not our outcomes.
Traboulsee A, Li DKB, Cascione M, Fang J, Dangond F, Miller A. Predictive value of early magnetic resonance imaging measures is differentially affected by the dose of interferon beta-1a given subcutaneously three times a week: An exploratory analysis of the PRISMS study. BMC Neurol 2018;18(68).	Wrong intervention.
Tuohy O, Costelloe L, Hill-Cawthorne G, Bjornson I, Harding K, Robertson N, May K, Button T, Azzopardi L, Kousin-Ezewu O, Fahey MT, Jones J, Compston DAS, Coles A. Alemtuzumab treatment of multiple sclerosis: Long-term safety and efficacy. Journal of Neurology, Neurosurgery and Psychiatry 2015;86(2):208-15.	Not RCT
Vermersch P, Radue EW, Putzki N, Ritter S, Merschhemke M, Freedman MS. A comparison of multiple sclerosis disease activity after discontinuation of fingolimod and placebo. Mult 2017;3(3):2055217317730096.	Compares two included studies. Not our outcome.
Viglietta V, Miller D, Bar-Or A, Phillips J, Arnold D, Selmaj K, Kita M, Hutchinson M, Yang M, Zhang R, Dawson K, Sheikh S, Fox R, Gold R. Efficacy of delayed-release dimethyl fumarate in relapsing-remitting multiple sclerosis: integrated analysis of the phase 3 trials. Ann Clin Transl Neurol 2015;2(2):103-18.	Study outcome is not relevant
Vollmer TL, Sorensen PS, Selmaj K, Zipp F, Havrdova E, Cohen JA, et al. A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. JNeurol 2014;261(4):773-83.	Interferon vs interferon, placebo and lanquinimod
Voskuhl R, Wang H, Wu T, Sicotte N, Nakamura K, Kurth F, Itoh N, Bardens J, Bernard J, Corboy, Jr., Cross A, Dhib-Jalbut S, Ford C, Frohman E, Giesser B, Jacobs D, Kasper L, Lynch S, Parry G, Racke M, Reder A, Rose J, Wingerchuk D, MacKenzie-Graham A, Arnold D, Tseng C, Elashoff R. Estriol combined with glatiramer acetate for women with relapsing-remitting multiple sclerosis: a randomised, placebo-controlled, phase 2 trial. The lancet Neurology 2016;15(1):35-46.	No relevant control group
Wagner S, Adams HP, Sobel DF, Slivka LS, Sipe JC, Romine JS, Koziol JA. New hypointense lesions on MRI in relapsing-remitting multiple sclerosis patients. European Neurology 2000;43(4):194-200.	Injection of cladribine, only tablets are included.
Wallin MT. Rituximab is an acceptable alternative to ocrelizumab for treating multiple sclerosis - No. Multiple Sclerosis Journal 2018;24(9):1159-61.	Commentary
Weinstock-Guttman B, Hagemeier J, Kavak K, Saini V, Patrick K, Ramasamy D, Nadeem M, Carl E, Hojnacki D, Zivadinov R. Randomised natalizumab discontinuation study: taper protocol may prevent disease reactivation. Journal of neurology, neurosurgery and psychiatry 2016;87(9):937-43.	Study outcome is not relevant
White J, Newsome S, Kieseier B, Bermel R, Cui Y, Seddighzadeh A, Hung S, Crossman M, Subramanyam M. Incidence, characterization, and clinical impact analysis of peginterferon beta1a immunogenicity in patients with multiple sclerosis in the ADVANCE trial. Therapeutic advances in neurological disorders 2016;9(4):239-49.	Intervention is not relevant
Wolinsky J, Borresen T, Dietrich D, Wynn D, Sidi Y, Steinerman, Jr., Knappertz V, Kolodny S. 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. Multiple sclerosis and related disorders 2015;4(4):370-6.	Study outcome is not relevant
Xie Q, Li X, Sun J, Yuan B, Li Y, Wang L, Wang M. A meta-analysis to determine the efficacy and tolerability of anti-B-cell monoclonal antibodies in multiple sclerosis. ExpTherMed 2017;13(6):3061-6.	Meta-analyses. Includes included studies from our search.
Ziemssen T, Engelmann U, Jahn S, Leptich A, Kern R, Hassoun L, Thomas K. Rationale, design, and methods of a non-interventional study to establish safety, effectiveness, quality of life, cognition, health-related and work capacity data on Alemtuzumab in multiple sclerosis patients in Germany (TREAT-MS). BMC Neurol 2016;16.	Study design is not relevant.
Zintzaras E, Doxani C, Mprotsis T, Schmid CH, Hadjigeorgiou GM. Network Analysis of Randomized Controlled Trials in Multiple Sclerosis. Clinical Therapeutics 2012;34(4):857-69.e9.	Meta-analyses with many more interventions
Zivadinov R, Dwyer M, Ramasamy D, Davis M, Steinerman, Jr., Khan O. The Effect of Three Times a Week Glatiramer Acetate on Cerebral T1 Hypointense Lesions in Relapsing-Remitting Multiple Sclerosis. Journal of neuroimaging 2015;25(6):989-95.	Study objective is not relevant

Zivadinov R, Medin J, Khan N, Korn JR, Bergsland N, Dwyer MG, Chitnis T, Naismith RT, Alvarez E, Kinkel P, Cohan S, Hunter SF, Silva D, Weinstock-Guttman B. Fingolimod's Impact on MRI Brain Volume Measures in Multiple Sclerosis: Results from MS-MRIUS. Journal of neuroimaging : official journal of the American Society of Neuroimaging 2018.	Study design is not relevant.
Zörner B, Filli L, Reuter K, Kapitza S, Lörincz L, Sutter T, Weller D, Farkas M, Easthope C, Czaplinski A, Weller M, Linnebank M. Prolonged-release fampridine in multiple sclerosis: improved ambulation effected by changes in walking pattern. Multiple sclerosis (houndmills, basingstoke, england) 2016;22(11):1463-75.	Intervention is not relevant.

From registry study searches with comparator. Studies excluded (16) with reason.

Study ID	Reason
Achiron A, Aref H, Inshasi J, Harb M, Alroughani R, Bijarnia M, et al. Effectiveness, safety and health-related quality of life of multiple sclerosis patients treated with fingolimod: Results from a 12-month, real-world, observational PERFORMS study in the Middle East. BMC Neurol 2017;17(150).	Comparator is a mixture of drugs.
Alsop J, Medin J, Cornelissen C, Vormfelde SV, Ziemssen T. Two studies in one: A propensity-score-matched comparison of fingolimod versus interferons and glatiramer acetate using real-world data from the independent German studies, PANGAEA and PEARL. PLoS ONE [Electronic Resource] 2017;12(5):e0173353.	The medication given is combination therapy
Boster A, Nicholas J, Wu N, Yeh WS, Fay M, Edwards M, et al. Comparative Effectiveness Research of Disease-Modifying Therapies for the Management of Multiple Sclerosis: Analysis of a Large Health Insurance Claims Database. Neurology and Therapy 2017;6(1):91-102.	No information about MS diagnosis.
Braune S, Lang M, Bergmann A. Efficacy of fingolimod is superior to injectable disease-modifying therapies in second-line therapy of relapsing remitting multiple sclerosis. Journal of Neurology 2016;263(2):327-33.	Comparator is a mixture of drugs.
Carra A, Onaha P, Luetic G, Burgos M, Crespo E, Deri N, et al. Therapeutic outcome 3 years after switching of immunomodulatory therapies in patients with relapsing-remitting multiple sclerosis in Argentina. European Journal of Neurology 2008;15(4):386-93.	Not our outcome. (Outcome is a comparison between before and after switching therapy)
Castillo-Trivino T, Mowry EM, Gajofatto A, Chabas D, Crabtree-Hartman E, Cree BA, et al. Switching multiple sclerosis patients with breakthrough disease to second-line therapy. PLoS ONE 2011;6.	Clinical effect of switching, not our outcome.
Coyle PK, Cohen BA, Leist T, Markowitz C, Oleen-Burkey M, Schwartz M, et al. Therapy optimization in multiple sclerosis: A prospective observational study of therapy compliance and outcomes. BMC Neurol 2014;14(49).	Method paper only, no outcomes.
Fox RJ, Salter AR, Tyry T, Sun J, You X, Laforet G, et al. Treatment discontinuation and disease progression with injectable disease-modifying therapies: findings from the north american research committee on multiple sclerosis database. International Journal of Ms Care 2013;15(4):194-201.	Not our outcome. Self-reported questionnaire for discontinuation.
Iaffaldano P, Lucisano G, Pozzilli C, Brescia Morra V, Ghezzi A, Millefiorini E, et al. Fingolimod versus interferon beta/glatiramer acetate after natalizumab suspension in multiple sclerosis. Brain 2015;138:3275-86.	Comparator is a mixture of drugs.
Johnson BH, Bonafede MM, Watson C. Platform Therapy Compared with Natalizumab for Multiple Sclerosis: Relapse Rates and Time to Relapse Among Propensity Score-Matched US Patients. CNS Drugs 2015;29(6):503-10.	Comparator is a mixture of drugs.
Jokubaitis VG, Li V, Kalincik T, Izquierdo G, Hodgkinson S, Alroughani R, et al. Fingolimod after natalizumab and the risk of short-term relapse. Neurology 2014;82(14):1204-11.	Switch experience, not our outcome.
Jokubaitis VG, Spelman T, Lechner-Scott J, Barnett M, Shaw C, Vucic S, et al. The Australian Multiple Sclerosis (MS) Immunotherapy Study: A Prospective, Multicentre Study of Drug Utilisation Using the MSBase Platform. PLoS ONE 2013;8.	Baseline information not retrievable for outcome data
Kalincik T, Manouchehrinia A, Sobisek L, Jokubaitis V, Spelman T, Horakova D, et al. Towards personalized therapy for multiple sclerosis: Prediction of individual treatment response. Brain 2017;140(9):2426-43.	Prediction for switching, not our outcome.
Sorensen PS, Koch-Henriksen N, Ravnborg M, Frederiksen JL, Jensen K, Heltberg A, et al. Immunomodulatory treatment of multiple sclerosis in Denmark: A prospective nationwide survey. Multiple Sclerosis 2006;12(3):253-64.	Main objective of the study was to investigate IFNs. The group of GA contained very few patients compared with IFNs. Also: study is over 10 years old.
Spelman T, Kalincik T, Jokubaitis V, Zhang A, Pellegrini F, Wiendl H, et al. Comparative efficacy of first-line natalizumab vs IFN-beta or glatiramer acetate in relapsing MS. Neurology: Clinical Practice 2016;6(2):102-15.	Comparator is a mixture of drugs.
Spelman T, Mekhael L, Burke T, Butzkueven H, Hodgkinson S, Havrdova E, et al. Risk of early relapse following the switch from injectables to oral agents for multiple sclerosis. European Journal of Neurology 2016;23(4):729-36.	Outcomes related to switchers vs stayers, not our outcome.

Appendix 9. Table of ongoing clinical trials

Title	Reg /complete	Sta-tus	Study type /Phase	Follow-up	Re-lapses	Disa-bility	Le-sions	Safety
Alemtuzumab (n=899)								
Phase IIIB-IV long term follow-up study for patients who participated in CAMMS03409 (TOPAZ) **EUCTR2013-003884-71-BE**	2014/NA	On	Interv/3-4	4 years	x	x		x
The Effectiveness of an Additional Course of Alemtuzumab in Relapsing Remitting Multiple Sclerosis Patients After 2 Courses of Alemtuzumab **EUCTR2016-000464-42-DE**	2016/NA	On	Interv/3	1 year	x	x	x	x
Dimethyl fumarate (n=3 430)								
A Study Evaluating the Effectiveness of Tecfidera (Dimethyl Fumarate) on Multiple Sclerosis (MS) Disease Activity and Patient-Reported Outcomes (PROTEC) **NCT01930708**	2013/2019	Act	Interv/4	1 year	x	x		
Study to Assess Resource Utilization and Quality of Life of Patients With RRMS Treated With Tecfidera in Greece (FIDELITY) **NCT03101735**	2017/2021	Act	Obs	1 year				
Monitoring of Patients Followed for a Multiple Sclerosis and Treated by Dimethyl-fumarate (SURV-SEP) **NCT02901106**	2016/2023	Rec	Interv/4	5 years	x	x		
BG00012 Monotherapy Safety and Efficacy Extension Study in Multiple Sclerosis (MS) ENDORSE **NCT00835770**	2009/2020	Act	Interv/3	8 years	x	x	x	x
Fingolimod (n=1 360)								
Fingolimod Versus Dimethyl-fumarate in Multiple Sclerosis (PRAG-MS) **NCT03345940**	2017/2020	Rec	Interv/4	2 years	x	x	x	
Natalizumab (n=41 911)								
Tysabri Observational Program (TOP) **NCT00493298**	2007/2028	Rec	Obs	10 years	x	x		x
Observational Study of Tysabri in Early Relapsing-Remitting Multiple Sclerosis in Anti-JC Virus Antibody Negative Participants (STRIVE) **NCT01485003**	2011/2018	Act	Obs	4 years	x	x	x	
Clinical Disease Activity With Long Term Natalizumab Treatment **NCT02677077**	2015/2018	Act	Obs	4 years	x	x	x	
Tysabri Observational Cohort Study - Multiple Sclerosis (MS) Registries **NCT03399981**	2018/2023	Act	Obs	8 years				x
Difference in Efficacy of Natalizumab Versus Fingolimod for the Treatment of Multiple Sclerosis (BEST-MS) **NCT01981161**	2013/2017	Rec	Obs/4	1 year				
Ocrelizumab (n=4 386)								
A Study of Ocrelizumab in Participants With Relapsing Remitting Multiple Sclerosis (RRMS) Who Have Had a Suboptimal Response to an Adequate Course of Disease-Modifying Treatment (DMT) **NCT02637856**	2015/2019	Rec	Interv/3	2 years	x	x	x	x
A Study to Evaluate the Efficacy and Safety of Ocrelizumab in Patients With Relapsing Remitting Multiple Sclerosis **EUCTR2015-005597-38-GB**	2016/NA	On	Interv/3	2 years	x	x	x	x

Title	Reg /complete	Sta-tus	Study type /Phase	Follow-up	Re-lapses	Disa-bility	Le-sions	Safety
A Study of Ocrelizumab in Participants With Relapsing Remitting Multiple Sclerosis (RRMS) Who Have Had a Suboptimal Response to an Adequate Course of Dis-ease-Modifying Treatment (DMT) **NCT02861014**	2016/2021	Act	Interv/3	4 years	x	x	x	x
Study to Evaluate the Effectiveness and Safety of Oc-relizumab in Participants With Early Stage Relapsing Remitting Multiple Sclerosis (RRMS) **NCT03085810**	2017/2023	Rec	Interv/3	4 years	x	x		
A Study to Evaluate the Effectiveness and Safety of Ocrelizumab in Patients with Multiple Sclerosis Previ-ously Enrolled in A F. Hoffmann-la Roche Sponsored Ocrelizumab Clinical Trial **EUCTR2017-004886-29-DK**	2018/NA	On	Interv/3	2 years	x	x	x	x
Non-interventional Study of Ocrelizumab in Participants With Relapsing or Primary Progressive Multiple Sclero-sis (MuSicalE) **NCT03593590**	2018/2025	Rec	Obs	4 years	x	x		x
Teriflunomide (n=300)								
Teriflunomide Observational Effectiveness Study **NCT02490982**	2015/2019		Obs	2 years		x		
Rituximab and others (n=4 800)								
RItuximab Versus FUmarate in Newly Diagnosed Multi-ple Sclerosis (RIFUND-MS) **NCT02746744**	2016/2021	Rec	Interv/3	2 years	x	x	x	
Traditional Versus Early Aggressive Therapy for Multi-ple Sclerosis Trial (TREAT-MS) **NCT03500328**	2018/2022	Rec	Interv	4 years	x	x	x	x
COMparison Between All immunoTherapies for Multi-ple Sclerosis (COMBAT-MS) **NCT03193866**	2017/2021	Rec	Obs	3 years	x	x		x

Reg, registered; Rec, recruiting; On, ongoing; Act, active; Interv, interventional; Obs, observational

Appendix 10. Table of ECTRIMS abstracts

Reference (6 first authors)	Study type	Follow-up	Relapse	Disability	Lesions	Safety
Alemtuzumab (n=110)						
A. Fält, S. Kågström, S. Safer Demirbüker, J. Hillert, P. Nilsson, C. Dahle, et al. A Swedish nationwide pharmaco-epidemiological study of the long-term safety and effectiveness of alemtuzumab (IMSE 3). Multiple Sclerosis Journal 2018; 24: (S2) 530–737	Obs					x
Cladribine (n=2 434)						
S. Schippling, M.P. Sormani, N. De Stefano, G. Giovannoni, A. Galazka, B. Keller, et al. CLARITY: an analysis of severity and frequency of relapses in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets or placebo. Multiple Sclerosis Journal 2018; 24: (S2) 121–327	RCT	96 weeks	x			
S. Cook, G. Giovannoni, T. Leist, S. Syed, A. Nolting, R. Schick. Updated safety analysis of cladribine tablets in the treatment of patients with multiple sclerosis. Multiple Sclerosis Journal 2018; 24: (S2) 328–529		2 years				x
Dimethyl fumarate (n=247 000)						
K. Smoot, C. Chen, L. Lucas, T. Stuchiner, E. Lucassen, M. Romba, et al. Providence Dimethyl Fumarate Registry: year five results on discontinuation and treatment outcomes. Multiple Sclerosis Journal 2018; 24: (S2) 121–327	Obs	5 years	x			x
S. Urtiaga, M. Cerezo Garcia, V. Galán Sánchez-Seco, J. Sabin Muñoz, I. Moreno Torres, M. Gómez Moreno, et al. Tolerability and safety of Dimethyl fumarate in relapsing multiple sclerosis: a prospective observational post-marketing study. Multiple Sclerosis Journal 2018; 24: (S2) 328–529	Obs					x
S. Safer Demirbüker, S. Kågström, A. Fält, A. Berglund, J. Hillert, P. Nilsson, et al. A Swedish nationwide pharmaco-epidemiological and genetic study of the long-term safety and effectiveness of dimethyl fumarate (IMSE 5). Multiple Sclerosis Journal 2018; 24: (S2) 530–737	Obs					x
J. Hanna, C. Prada, N. Everage, S. Kalari, P. Jayia, P. Singhal, et al. Patients treated with delayed-release dimethyl fumarate have no increased risk of herpes zoster based on clinical trial and post-marketing report data. Multiple Sclerosis Journal 2018; 24: (S2) 530–737	Obs					x
N.J. Everage, C.C. Jones, R. Das, J. Hanna, S. Liu, K. Balashov, et al. Safety and efficacy of delayed-release dimethyl fumarate in multiple sclerosis patients treated in routine medical practice: interim analysis of ESTEEM. Multiple Sclerosis Journal 2018; 24: (S2) 530–737	Obs	5 years	x			x
Fingolimod (n=6 460)						
K. Bencsik, T. Biernacki, J. Füvesi, C. Rózsa, S. Komoly, P. Ács, et a. Interim data from the Hungarian Fingolimod Registry (CFTY720DHU01). Multiple Sclerosis Journal 2018; 24: (S2) 981–1026	Obs	3 years	x	x		
T. Ziemssen, H. Albrecht, J. Haas, L. Klotz, M. Lang, C. Lassek, et al. Treatment effectiveness in relapsing remitting multiple sclerosis patients treated for 5 years with fingolimod in clinical practice: interim results from the observational study PANGAEA. Multiple Sclerosis Journal 2018; 24: (S2) 121–327	Obs	5 years	x	x		
T. Ziemssen, H. Albrecht, J. Haas, L. Klotz, M. Lang, C. Lassek, et al. Safety of fingolimod in RRMS patients treated for up to 5 years in real world: interim results from the non-interventional PANGAEA study. Multiple Sclerosis Journal 2018; 24: (S2) 121–327	Obs	5 years				x
A. Fält, S. Kågström, S. Safer Demirbüker, J. Hillert, P. Nilsson, C. Dahle, et al. A Swedish nationwide pharmaco-epidemiological study of the long-term safety and effectiveness of fingolimod (IMSE 2). Multiple Sclerosis Journal 2018; 24: (S2) 530–737	Obs		x	x		x
C. Lebrun-Frenay, C. Papeix, G. Kobelt, J.M. Visy, M. Coustans, M. Debouverie, et al. Long-term efficacy, safety and tolerability with fingolimod treatment in patients with multiple sclerosis in real-world settings in France: three-year results of the VIRGILE study. Multiple Sclerosis Journal 2018; 24: (S2) 530–737	Obs	3 years	x	x		x

L. Moiola, F. Esposito, M. Di Cristinzi, L. Ferre', G. Sferruzza, M. Romeo, et al. Comparative effectiveness of dimethylfumarate and fingolimod in an Italian monocentric cohort of relapsing remitting multiple sclerosis patients. Multiple Sclerosis Journal 2018; 24: (S2) 8–120	Obs		x	x	x	
J. Lorscheider, S. Schädelin, P. Benkert, C. Lienert, P. Hänni, T. Derfuss, et al. Early versus delayed initiation of fingolimod or dimethyl fumarate in relapsing-remitting multiple sclerosis. Multiple Sclerosis Journal 2018; 24: (S2) 121–327	Obs	1,2 years	x			
M. Guger, C. Enzinger, F. Leutmezer, J. Kraus, S. Kalcher, E. Kvas, et al. Effects of real life use of oral disease-modifying treatments for relapsing-remitting multiple sclerosis in Austria over one year. Multiple Sclerosis Journal 2018; 24: (S2) 121–327	Obs	12 months	x	x		
Glatiramer acetate (2 758)						
O. Fernandez, A. Rodriguez-Antiguedad, R. Cadima, I. Botella. Spanish registry of multiple sclerosis patients on glatiramer acetate 40 mg/ml treatment: real-world results and initial results of first year follow-up. Multiple Sclerosis Journal 2018; 24: (S2) 121–327	Obs	5 years	x	x	x	x
G. Giovannoni, P. Brex, E. Walters, S. Al-Izki, D. Dhiraj, K. Schmierer. Glatiramer acetate slows disability progression - final 10-year results from UK Risk Sharing Scheme. Multiple Sclerosis Journal 2018; 24: (S2) 530–737	Obs	10 years		x		
T. Scott, O. Mokliatchouck, C. Castrillo-Viguera, A. Harrington, M.L. Naylor. Peginterferon beta-1a every 2 weeks demonstrated better clinical outcomes than glatiramer acetate once-daily in patients with RRMS: propensity score matching of phase 3 data from ADVANCE and CONFIRM. Multiple Sclerosis Journal 2018; 24: (S2) 121–327	RCT	2 years	x	x		
Natalizumab (186 777)						
G. Giovannoni, L. Kappos, J. Berger, G. Cutter, R.J. Fox, H. Wiendl, et al. Incidence of natalizumab-associated progressive multifocal leucoencephalopathy and its relationship with the pattern of natalizumab exposure over time. Multiple Sclerosis Journal 2018; 24: (S2) 121–327	Obs					x
N. Schwab, T. Schneider-Hohendorf, I. Meinl, S. Windhagen, L. Klotz, C. Gross, et al. Reduction of the risk of PML in natalizumab treated MS patients in Sweden: an effect of JCV ab index surveillance. Multiple Sclerosis Journal 2018; 24: (S2) 121–327	Obs					x
A. Manouchehrinia, K. McKay, S. Kågström, A. Berglund, J. Lycke, F. Piehl, et al. Long-term effectiveness of natalizumab in multiple sclerosis: a 10-year nationwide prospective cohort study. Multiple Sclerosis Journal 2018; 24: (S2) 328–529	Obs	10 years		x		
S. Kågström, A. Fält, S. Safer Demirbüker, A. Berglund, J. Hillert, P. Nilsson, et al. A Swedish nationwide pharmaco-epidemiological and genetic study of the long-term safety and effectiveness of natalizumab (IMSE 1). Multiple Sclerosis Journal 2018; 24: (S2) 530–737	Obs					x
Rituximab (n=10 952)						
B. Evertsson, K. Fink, A. Finn, F. Piehl, F. Nimer. Low dose rituximab depletes B cells and lowers IgM in blood in MS patients: a study on possible biomarkers to predict treatment response and adverse event profile. Multiple Sclerosis Journal 2018; 24: (S2) 530–737	Obs	7 months				
G. Luna, F. Piehl, T. Frisell. Infection risks among Swedish multiple sclerosis patients treated with rituximab compared to natalizumab, fingolimod, and injectable therapies: a nationwide cohort study. Multiple Sclerosis Journal 2018; 24: (S2) 328–529	Obs					x
E. Alvarez, K. Nair, I. Shelton, N. Zanganeh, S. Sillau, J. Corboy, et al. Evaluating the tolerability and safety profile of switching from rituximab to ocrelizumab: infusion related reactions in relapsing forms of multiple sclerosis. Multiple Sclerosis Journal 2018; 24: (S2) 530–737						x
Teriflunomide (n=7 247)						
R. Zivadinov, M.G. Dwyer, E. Carl, K. Thangavelu, S. Cavalier, N. Bergsland. Evaluating the effect of teriflunomide on whole brain atrophy in the phase 3 TOPIC study. Multiple Sclerosis Journal 2018; 24: (S2) 328–529	RCT	24 months			x	
M. Magyari, M. Buron, Z. Illes, F. Sellebjerg. The Danish experience of teriflunomide treatment in relapsing remitting multiple sclerosis. Multiple Sclerosis Journal 2018; 24: (S2) 328–529	Obs	2 years				x

J. Villafani, J. Peña, V. Gonzalez-Quintanilla, P. Oliva, R. Suarez, D.M. Solar, et al. High persistence rate and sustained efficacy of teriflunomide in relapsing-remitting multiple sclerosis in real-world practice: a 3-year retrospective, multicenter study. Multiple Sclerosis Journal 2018; 24: (S2) 530–737	Obs	3 years	x	x	x	x
S. Safer Demirbüker, S. Kågström, A. Fält, J. Hillert, P. Nilsson, C. Dahle, et al. A Swedish nationwide pharmaco-epidemiological study of the long-term safety and effectiveness of teriflunomid (IMSE 4). Multiple Sclerosis Journal 2018; 24: (S2) 121–327	Obs	2 years		x		x
D.A. Laplaud, L. Barbin, R. Casey, M. Debouverie, S. Vukusic, P. Labauge, et al. Comparative efficacy of teriflunomide versus dimethyl-fumarate on clinical and MRI outcomes: a two years French multicenter observational study. Multiple Sclerosis Journal 2018; 24: (S2) 8–120	Obs	2 years	x	x	x	
M. Buron, M. Magyari, T. Ameri Chalmer, H. Hassanpour-Kalam-Roudy, Z. Illés, Z. Mezei, et al . Comparative effectiveness of teriflunomide and dimethyl fumarate in relapsing remitting multiple sclerosis. A Danish nationwide cohort study. Multiple Sclerosis Journal 2018; 24: (S2) 8–120	Obs	2 years	x	x		x

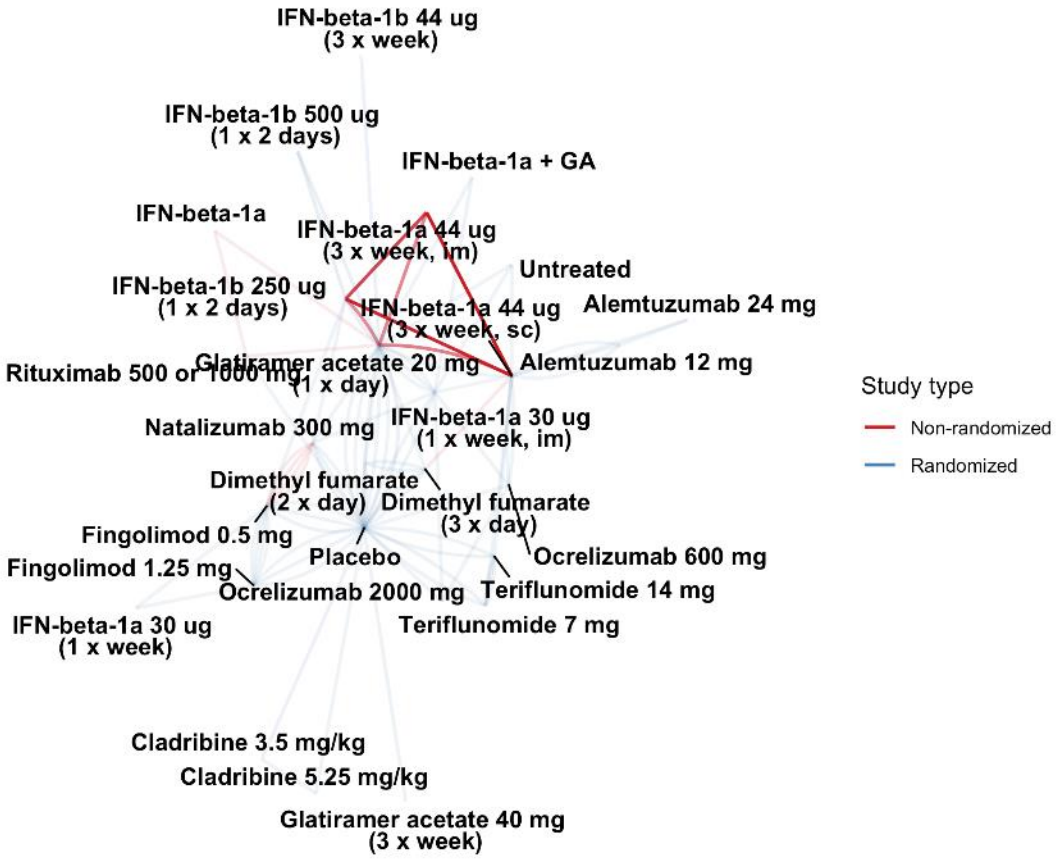
Obs, Observational study; RCT, randomised controlled trial

Appendices – Clinical Effectiveness and safety

Appendix 11. Detailed results for annualised relapse rate

Network evidence for annual relapse rate

The following plot shows the network of evidence used in the analyses of annual relapse rate. Each line represents a direct treatment comparison (blue line= RCT, red line NRS).



Comments to the analyses

Most of the included studies clearly reported how relapses were defined, and all but three of the studies that reported definitions used a version of the McDonald criteria. We judged there to be no meaningful heterogeneity in the methods used to identify relapses for the purpose of evidence synthesis via meta-analysis.

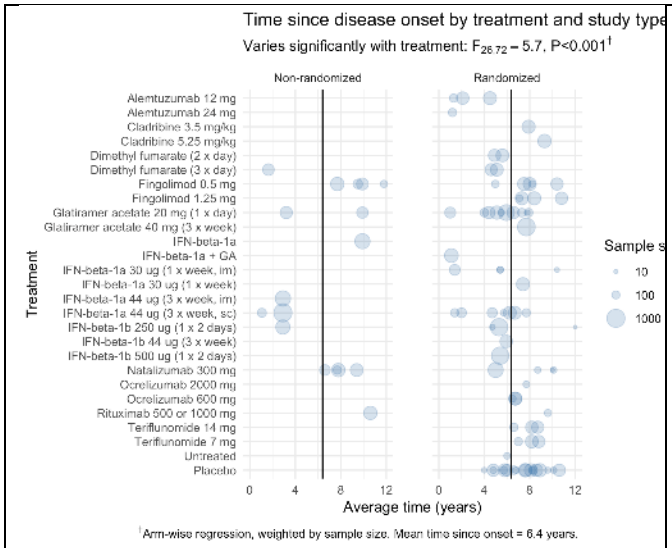
Complete ranking list for all treatments for annualised relapse rate

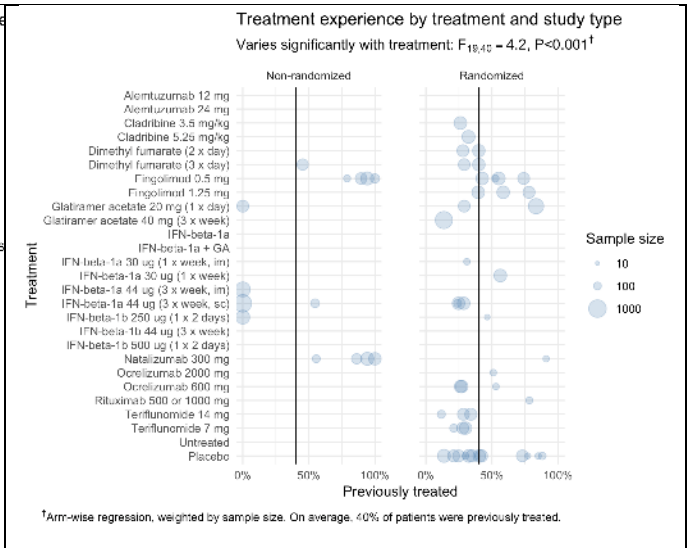
The following table shows treatments, estimates, and their ranks as computed via *P*-scores. The model accounts for possible differences between randomised and non-randomised evidence. Results are shown for all treatments included in the model.

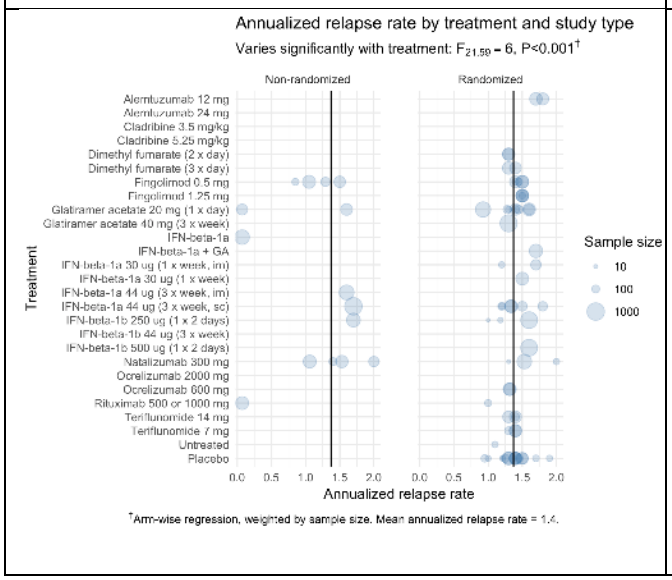
Treatment	Annualised relapse rate	P-score	Rank
Alemtuzumab 24 mg	0.08 (0.05 to 0.14)	0.99	1
Alemtuzumab 12 mg	0.14 (0.10 to 0.20)	0.93	2
Natalizumab 300 mg	0.17 (0.13 to 0.22)	0.88	3
Ocrelizumab 600 mg	0.18 (0.13 to 0.25)	0.85	4
Ocrelizumab 2000 mg	0.17 (0.06 to 0.47)	0.81	5
Cladribine 3.5 mg/kg	0.22 (0.17 to 0.30)	0.75	6
Fingolimod 1.25 mg	0.23 (0.18 to 0.30)	0.72	7
Fingolimod 0.5 mg	0.23 (0.19 to 0.29)	0.72	8
Rituximab 500 or 1000 mg	0.23 (0.12 to 0.44)	0.70	9
Cladribine 5.25 mg/kg	0.24 (0.15 to 0.38)	0.70	10
Dimethyl fumarate (2 x day)	0.27 (0.21 to 0.35)	0.63	11
Dimethyl fumarate (3 x day)	0.27 (0.21 to 0.35)	0.62	12
IFN-beta-1a 44 ug (3 x week, sc)	0.33 (0.26 to 0.43)	0.46	13
Glatiramer acetate 40 mg (3 x week)	0.35 (0.25 to 0.47)	0.42	14
Teriflunomide 14 mg	0.35 (0.27 to 0.44)	0.42	15
IFN-beta-1a + GA	0.36 (0.26 to 0.49)	0.39	16
IFN-beta-1b 500 ug (1 x 2 days)	0.37 (0.29 to 0.47)	0.35	17
Glatiramer acetate 20 mg (1 x day)	0.37 (0.31 to 0.45)	0.35	18
IFN-beta-1b 44 ug (3 x week)	0.38 (0.29 to 0.50)	0.32	19
Teriflunomide 7 mg	0.39 (0.31 to 0.49)	0.31	20
IFN-beta-1b 250 ug (1 x 2 days)	0.41 (0.33 to 0.51)	0.25	21
IFN-beta-1a 30 ug (1 x week)	0.42 (0.29 to 0.61)	0.25	22
IFN-beta-1a 44 ug (3 x week, im)	0.43 (0.29 to 0.65)	0.24	23
IFN-beta-1a 30 ug (1 x week, im)	0.44 (0.33 to 0.57)	0.21	24
IFN-beta-1a	0.56 (0.28 to 1.14)	0.14	25
Placebo	0.53 (0.44 to 0.64)	0.09	26
Untreated	1.06 (0.78 to 1.45)	0.00	27

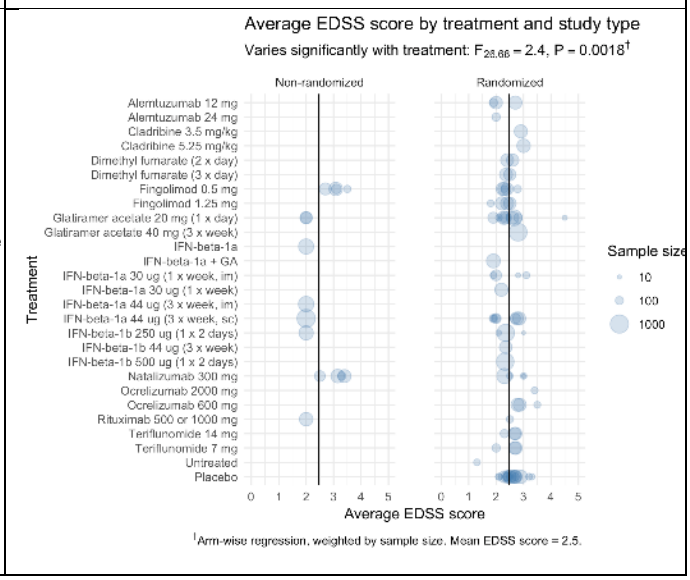
Transitivity assessment for annualised relapse rate

We here present the transitivity assessment of baseline characteristics for time since disease onset by treatment, treatment experience, annualised relapse rate, and average EDSS score.



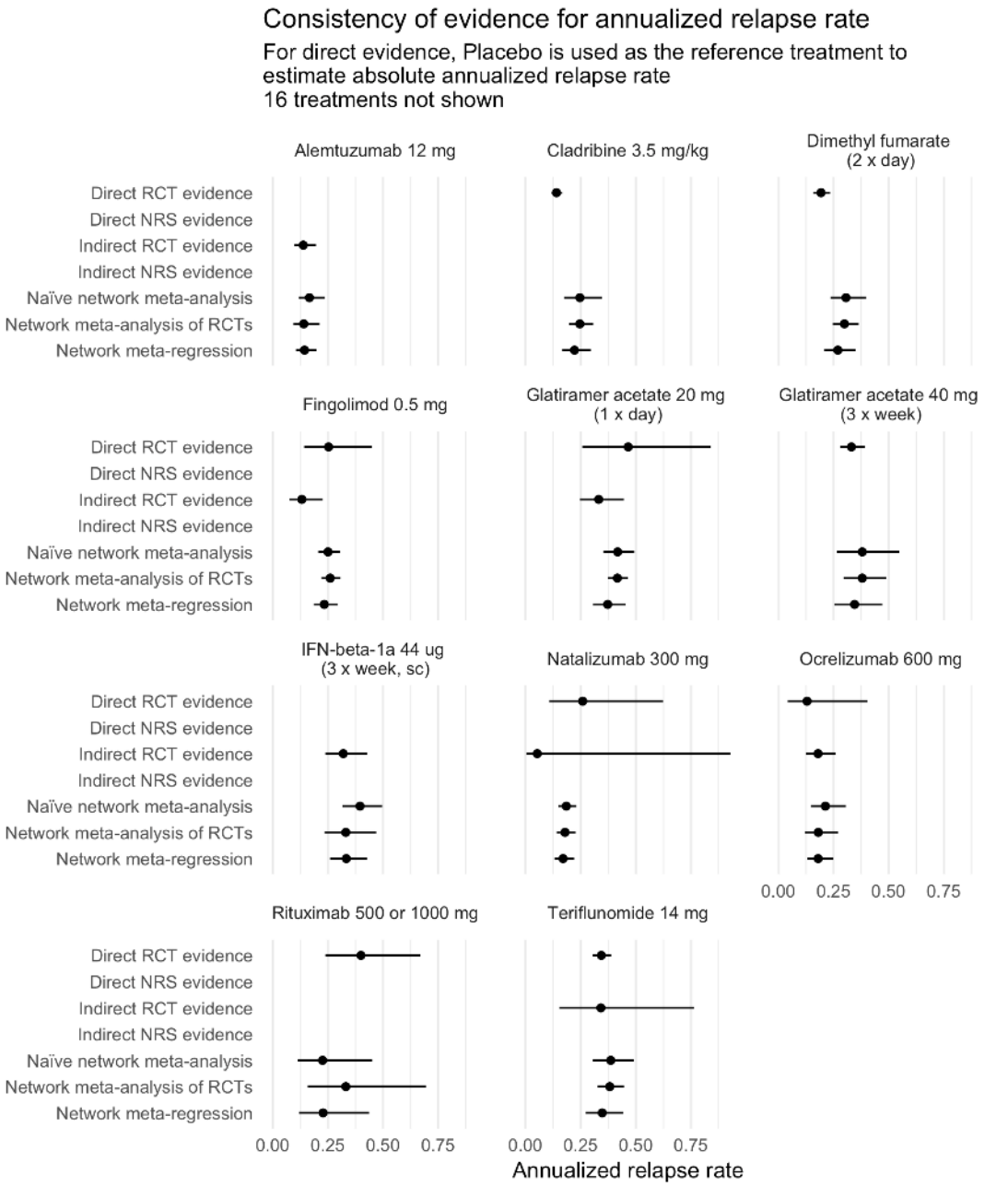






Consistency assessment for annualised relapse rate

The following plot explores inconsistency between the various types of evidence used, and between network meta-analysis and meta-regression estimates. Direct comparisons assume Placebo is the reference treatment.



Means and 95% confidence intervals are shown for: direct RCT evidence (pairwise meta-analyses of RCTs that directly compare treatment and Placebo); indirect RCT evidence (network meta-analysis of RCTs that do not directly compare treatment and Placebo); direct NRS evidence (pairwise meta-analyses of non-randomized studies that directly compare treatment and Placebo); and indirect NRS evidence (network meta-analysis of non-randomized studies that do not directly compare treatment and Placebo). Evidence may be missing for some or all treatments. Naïve network meta-analysis does not account for possible differences between RCT and NRS evidence. Network meta-analysis of RCTs excludes non-randomized evidence. Network meta-regression accounts for possible differences between randomized and nonrandomized evidence.

GRADE assessment

This table describes in more detail the process of grading the network estimate. We used the figure above (inconsistency assessment) for to evaluate the incoherence assessment of the network. We do not show the grading of each loop in the indirect evidence.

	Direct evidence		Indirect evidence		Network assessment				
Comparison vs placebo	**ARR ratio**	**GRADE**	**ARR ratio**	**GRADE**	**Contributing most of direct vs indirect**	**Network meta-regression**	**Incoherence**	**Imprecision**	**Overall GRADE**
Alemtuzumab 12 mg	NA	NA	0.29 (0.19 - 0.44)	LOW (NRS contributing to estimate)	LOW	0.27 (0.19 - 0.40)	No	No	LOW
Cladribine 3.5 mg/kg	0.42 (0.34-0.53)	HIGH	NA	NA	HIGH	0.42 (0.30 - 0.60)	No	No	HIGH
Dimethyl fumarate (2 x day)	0.52 (0.42-0.63)	HIGH	0.39 (0.17 - 0.93)	HIGH	HIGH	0.51 (0.37 - 0.70)	No	No	HIGH
Fingolimod 0.5 mg	0.49 (0.41 - 0.58)	MODERATE (inconsistent)	0.39 (0.25 - 0.59)	MODERATE (inconsistent)	MODERATE	0.44 (0.33 - 0.60)	No	No	MODERATE
GA 20 mg (1 x day)	0.72 (0.64 - 0.81)	HIGH	0.59 (0.39 - 0.88)	LOW (NRS contributing to estimate)	HIGH	0.71 (0.54 - 0.93)	No	Yes	MODERATE (imprecision)
IFN-beta-1a 44 ug (3 x week, sc)	NA	NA	0.68 (0.48 - 0.95)	LOW (NRS contributing to estimate)	LOW	0.63 (0.46 - 0.87)	No	Yes	VERY LOW (imprecision)
Natalizumab 300 mg	0.31 (0.25 - 0.40)	HIGH	0.34 (0.23 - 0.51)	VERY LOW (NRS contributing to estimate, inconsistent)	HIGH	0.32 (0.23 - 0.45)	No	No	HIGH
Ocrelizumab 600 mg	0.20 (0.06-0.67)	VERY LOW (high risk of bias, small study)	0.38 (0.24 - 0.60)	LOW (NRS contributing to estimate)	LOW	0.34 (0.23 - 0.50)	No	No	LOW
Rituximab 500 or 1000 mg	0.57 (0.27-1.20)	VERY LOW (high risk of bias, small study)	0.06 (0.01 - 0.28)	MODERATE (NRS contributing to estimate, but high effect)	MODERATE	0.43 (0.22 - 0.85)	No	Yes	LOW (imprecision)
Teriflunomide 14 mg	0.66 (0.56-0.78)	HIGH	0.74 (0.30 - 1.81)	HIGH	HIGH	0.66 (0.48 - 0.90)	No	Yes	MODERATE (imprecision)

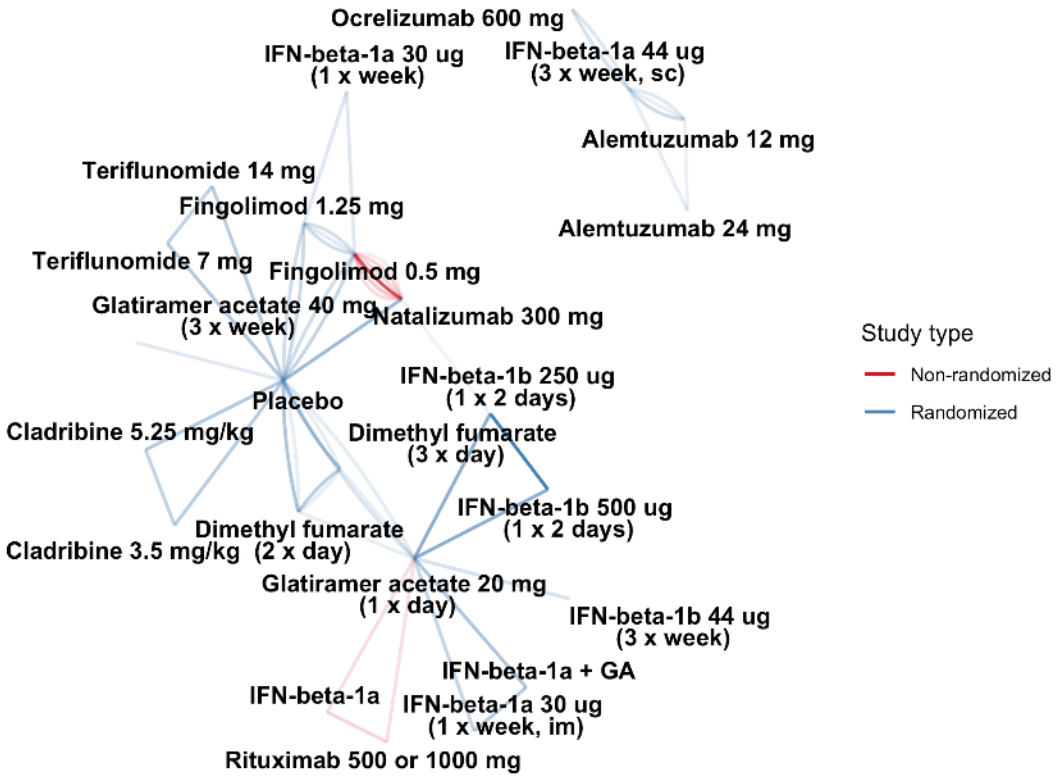
ARR, annualised relapse rate; NA, not available; GA glatiramer acetate; NRS, non-randomised study

Appendix 12. Detailed results for disability progression

Network of evidence for risk of disability progression

The following plot shows the network of evidence used in the analyses of progression of EDSS. Each line represents a direct treatment comparison (blue line= RCT, red line NRS).

Arm-wise data are available for rituximab 500 or 1000 mg (not shown).



There are no studies for this outcome on IFN-beta-1a 44 ug (3 x week, im), Ocrelizumab 2000 mg or Untreated.

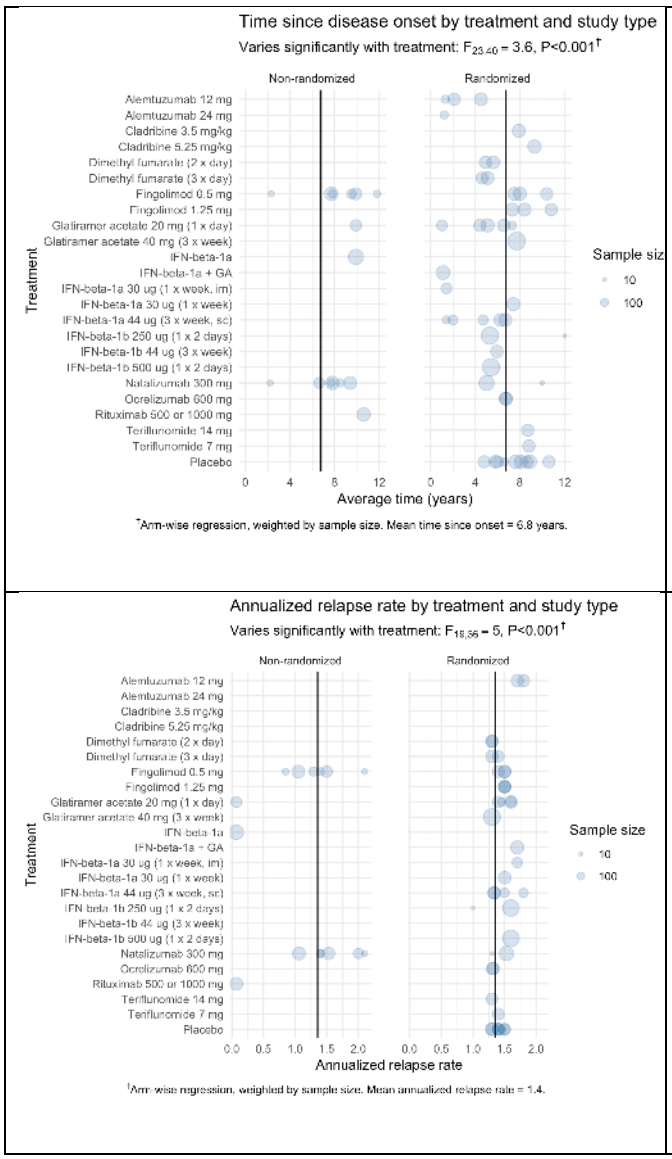
Complete ranking list for all treatments in the network meta-analyses

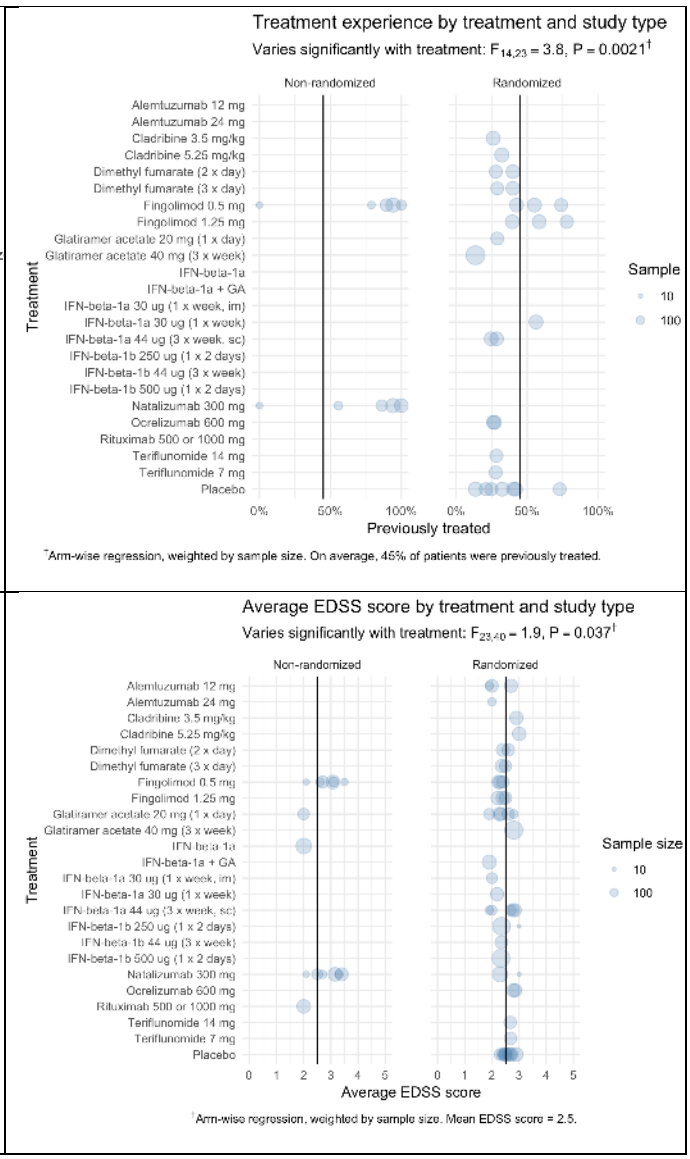
The following table shows treatments, estimates, and their ranks as computed via *P*-scores. The model accounts for possible differences between randomised and non-randomised evidence. Results are shown for all treatments included in the model.

Treatment	Patients progressing per 1000 patients	P-score	Rank
Alemtuzumab 24 mg	66.59 (29.32 to 151.24)	0.87	1
Ocrelizumab 600 mg	86.16 (47.91 to 154.94)	0.77	2
Alemtuzumab 12 mg	87.11 (49.85 to 152.21)	0.77	3
Natalizumab 300 mg	97.50 (66.45 to 143.04)	0.71	4
Dimethyl fumarate (2 x day)	97.86 (65.38 to 146.47)	0.70	5
Rituximab 500 or 1000 mg	87.57 (32.51 to 235.89)	0.70	6
Fingolimod 1.25 mg	107.85 (72.96 to 159.43)	0.61	7
Dimethyl fumarate (3 x day)	108.98 (73.25 to 162.13)	0.60	8
Fingolimod 0.5 mg	111.53 (76.60 to 162.40)	0.58	9
Cladribine 3.5 mg/kg	112.76 (72.82 to 174.60)	0.56	10
Cladribine 5.25 mg/kg	119.16 (77.47 to 183.28)	0.50	11
IFN-beta-1a 30 ug (1 x week, im)	120.69 (73.62 to 197.84)	0.49	12
Teriflunomide 14 mg	120.90 (78.07 to 187.22)	0.49	13
IFN-beta-1a	130.68 (50.48 to 338.28)	0.43	14
Teriflunomide 7 mg	129.88 (84.50 to 199.63)	0.41	15
IFN-beta-1a + GA	131.39 (82.90 to 208.24)	0.40	16
IFN-beta-1a 44 ug (3 x week, sc)	132.76 (78.52 to 224.46)	0.40	17
IFN-beta-1a 30 ug (1 x week)	133.23 (76.31 to 232.60)	0.39	18
Glatiramer acetate 20 mg (1 x day)	133.88 (90.88 to 197.22)	0.38	19
IFN-beta-1b 250 ug (1 x 2 days)	141.28 (91.36 to 218.48)	0.33	20
IFN-beta-1b 500 ug (1 x 2 days)	148.27 (95.92 to 229.21)	0.28	21
Glatiramer acetate 40 mg (3 x week)	157.01 (86.59 to 284.70)	0.26	22
Placebo	161.16 (115.53 to 224.80)	0.19	23
IFN-beta-1b 44 ug (3 x week)	173.00 (99.91 to 299.55)	0.18	24

Transitivity assessment for disability progression

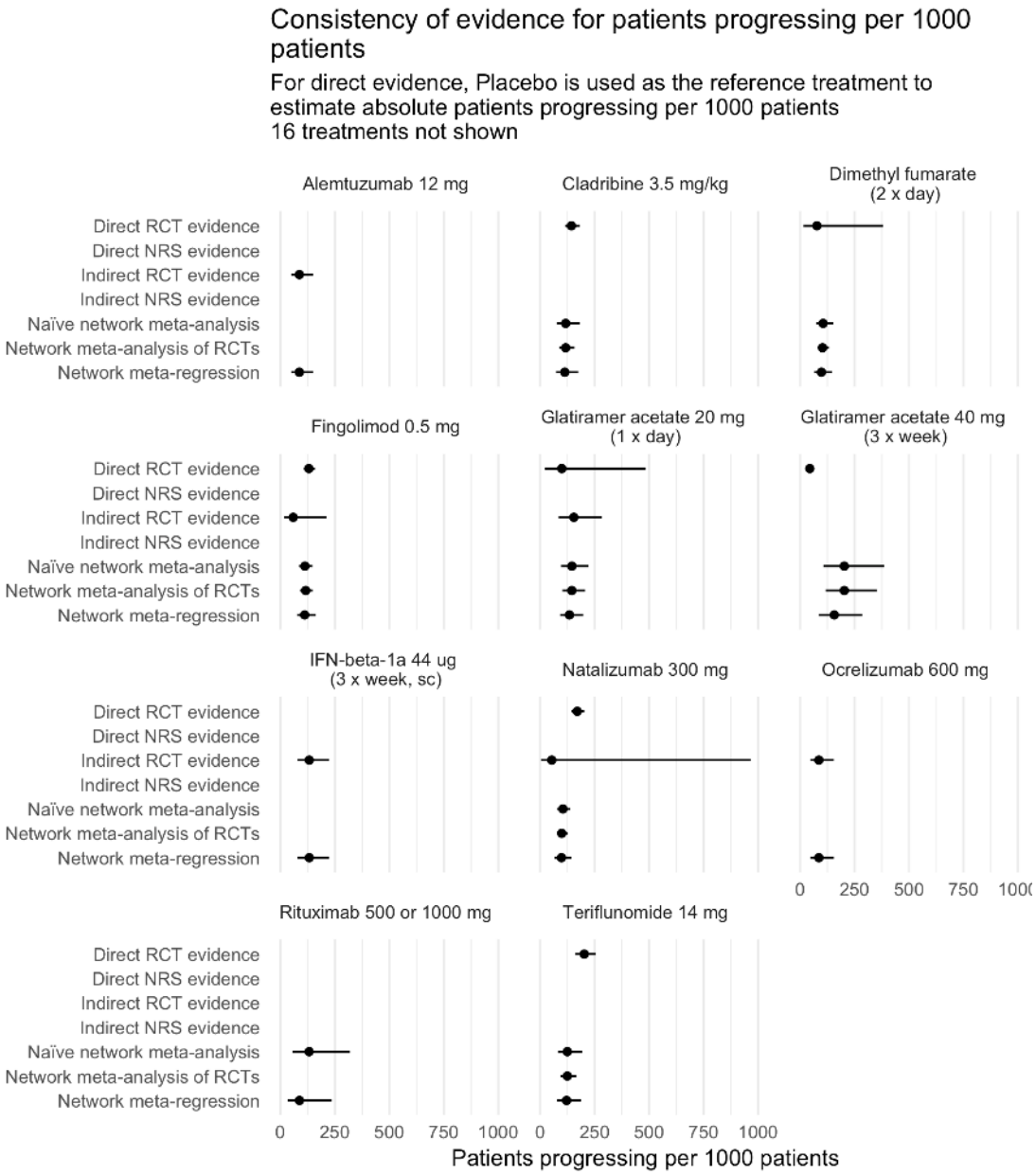
We here present the transitivity assessment of baseline characteristics for time since disease onset by treatment, treatment experience, annualised relapse rate, and average EDSS score.





Consistency assessment for disability progression

The following plot explores inconsistency between the various types of evidence used, and between network meta-analysis and meta-regression estimates. Direct comparisons assume placebo is the reference treatment.



Means and 95% confidence intervals are shown for: direct RCT evidence (pairwise meta-analyses of RCTs that directly compare treatment and Placebo); indirect RCT evidence (network meta-analysis of RCTs that do not directly compare treatment and Placebo); direct NRS evidence (pairwise meta-analyses of non-randomized studies that directly compare treatment and Placebo); and indirect NRS evidence (network meta-analysis of non-randomized studies that do not directly compare treatment and Placebo). Evidence may be missing for some or all treatments. Naïve network meta-analysis does not account for possible differences between RCT and NRS evidence, and excludes the minority of treatments disconnected from the main network. Network meta-analysis of RCTs excludes non-randomized evidence and excludes the minority of treatments disconnected from the main network. Network meta-regression accounts for possible differences between randomized and nonrandomized evidence.

GRADE assessment

This table describes in more detail the process of grading the network estimate. We used the figure above (consistency assessment) to evaluate the incoherence assessment of the network. We do not show the grading of each loop in the indirect evidence.

Comparison vs placebo	Direct evidence		Indirect evidence		Network assessment				Overall GRADE
	Risk of progression	GRADE	Risk of progression	GRADE	Contributing most of direct vs indirect	Network meta-regression	Incoherence	Imprecision	
Alemtuzumab 12 mg	NA	NA	0.48 (0.25 - 0.92)	NA	NA	0.54 (0.28 - 1.04)	NA	NA	NA (Disconnected from the network)
Cladribine 3.5 mg/kg	0.70 (0.52 - 0.93)	HIGH		HIGH	HIGH	0.70 (0.40 - 1.21)	No	Yes	MODERATE (Imprecision)
Dimethyl fumarate (2 x day)	0.61 (0.47 - 0.79)	HIGH		HIGH	HIGH	0.61 (0.36 - 1.02)	No	Yes	MODERATE (Imprecision)
Fingolimod 0.5 mg	0.71 (0.55 - 0.91)	HIGH	0.78 (0.45 - 1.37)	HIGH	HIGH	0.69 (0.42 - 1.14)	No	Yes	MODERATE (Imprecision)
GA 20 mg (1 x day)	0.90 (0.62 - 1.31)	HIGH	0.68 (0.36 - 1.29)	HIGH	HIGH	0.83 (0.50 - 1.38)	No	Yes	MODERATE (Imprecision)
IFN-beta-1a 44 ug (3 x week, sc)	NA		0.75 (0.41 - 1.38)	NA	NA	0.82 (0.44 - 1.53)	NA	NA	NA (Disconnected from the network)
Natalizumab 300 mg	0.59 (0.46 - 0.75)	HIGH	0.74 (0.45 - 1.22)	LOW (Inconsistent, Indirectness)	HIGH	0.60 (0.36 - 1.01)	No	Yes	MODERATE (Imprecision)
Ocrelizumab 600 mg	NA	NA	0.48 (0.24 - 0.96)	NA	NA	0.53 (0.27 - 1.05)	NA	NA	NA (Disconnected from the network)
Rituximab 500 or 1000 mg	NA	NA	0.62 (0.27 - 1.44)	LOW	LOW	0.54 (0.19 - 1.55)	No	Yes	VERY LOW (NRSCT, imprecision)
Teriflunomide 14 mg	0.74 (0.55 - 0.99)	MODERATE		MODERATE (Study high risk of bias)	MODERATE	0.75 (0.43 - 1.30)	No	Yes	LOW (High risk of bias in study, Imprecision)

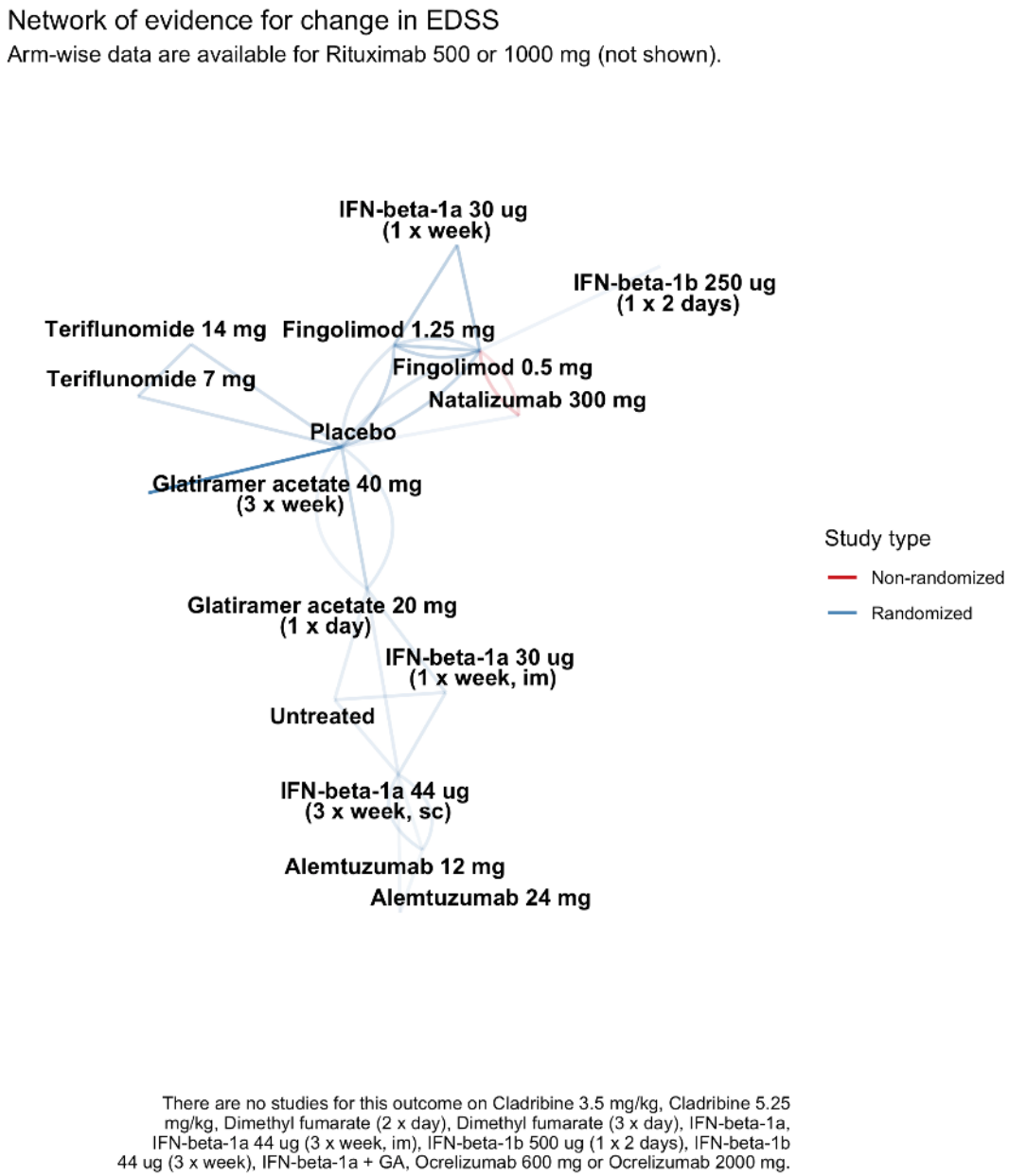
NA, not available; GA glatiramer acetate; NRTC, non-randomised studies

Appendix 13. Detailed results for changes in EDSS

Network evidence for changes in EDSS

The following plot shows the network of evidence used in the analyses of progression of EDSS. Each line represents a direct treatment comparison (blue line= RCT, red line NRS).

Arm-wise data are available for rituximab 500 or 1000 mg (not shown).



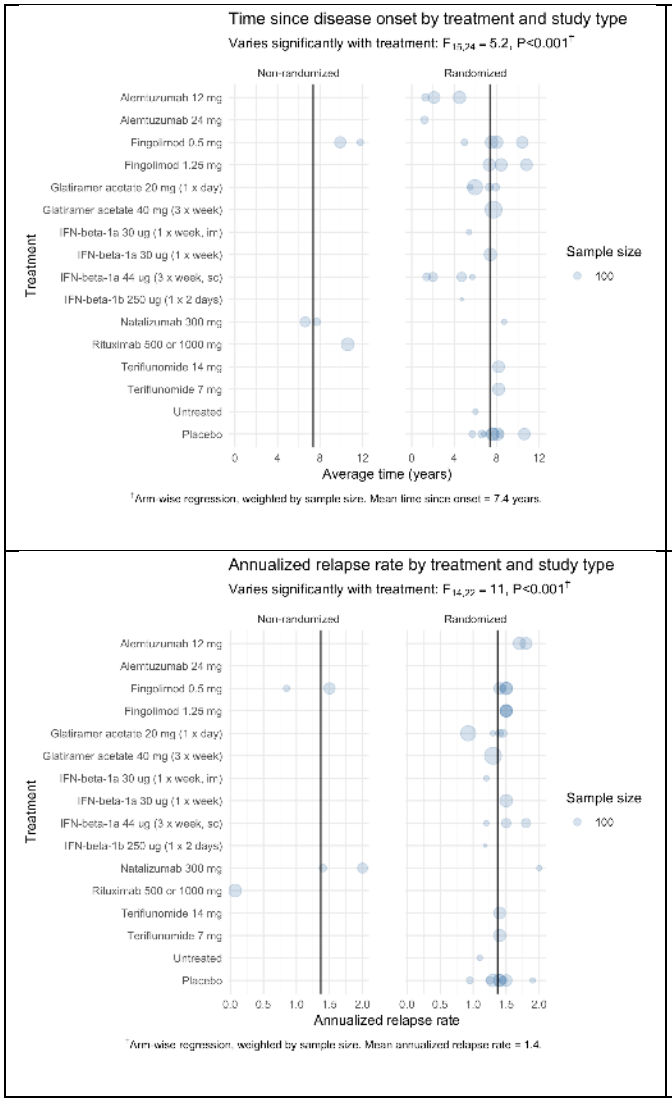
There are no studies for this outcome on Cladribine 3.5 mg/kg, Cladribine 5.25 mg/kg, Dimethyl fumarate (2 x day), Dimethyl fumarate (3 x day), IFN-beta-1a, IFN-beta-1a 44 ug (3 x week, im), IFN-beta-1b 500 ug (1 x 2 days), IFN-beta-1b 44 ug (3 x week), IFN-beta-1a + GA, Ocrelizumab 600 mg or Ocrelizumab 2000 mg.

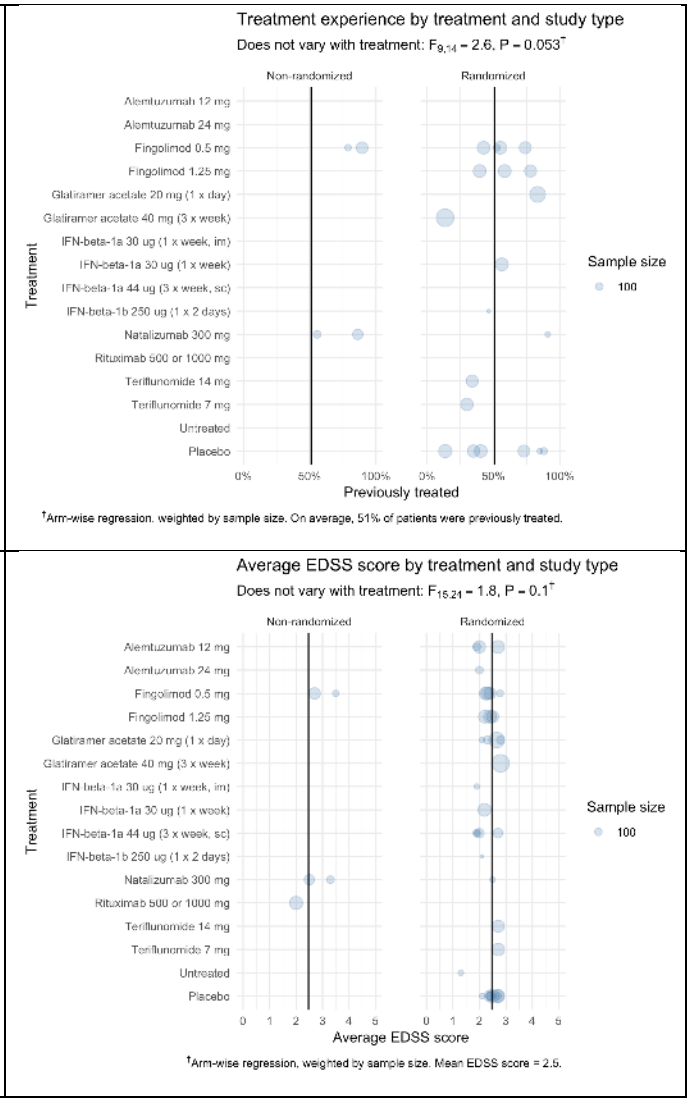
Complete ranking list for all treatments in the network meta-analyses

Treatment	Change in expanded disability status scale (EDSS)	P-score	Rank
Alemtuzumab 24 mg	-0.46 (-0.73 to -0.18)	0.97	1
Natalizumab 300 mg	-0.26 (-0.43 to -0.10)	0.89	2
Alemtuzumab 12 mg	-0.18 (-0.31 to -0.06)	0.82	3
Rituximab 500 or 1000 mg	-0.25 (-0.85 to 0.35)	0.76	4
Fingolimod 1.25 mg	-0.07 (-0.17 to 0.04)	0.68	5
Teriflunomide 14 mg	-0.05 (-0.23 to 0.14)	0.62	6
Glatiramer acetate 40 mg (3 x week)	-0.00 (-0.16 to 0.16)	0.52	7
Fingolimod 0.5 mg	0.01 (-0.08 to 0.10)	0.51	8
IFN-beta-1a 30 ug (1 x week)	0.03 (-0.14 to 0.20)	0.45	9
Teriflunomide 7 mg	0.04 (-0.14 to 0.23)	0.43	10
Glatiramer acetate 20 mg (1 x day)	0.05 (-0.05 to 0.15)	0.41	11
Placebo	0.10 (0.03 to 0.17)	0.29	12
IFN-beta-1a 44 ug (3 x week, sc)	0.13 (0.01 to 0.25)	0.23	13
IFN-beta-1b 250 ug (1 x 2 days)	0.18 (-0.09 to 0.45)	0.21	14
IFN-beta-1a 30 ug (1 x week, im)	0.16 (-0.03 to 0.36)	0.20	15
Untreated	0.46 (0.24 to 0.69)	0.01	16

Transitivity assessment for change in EDSS

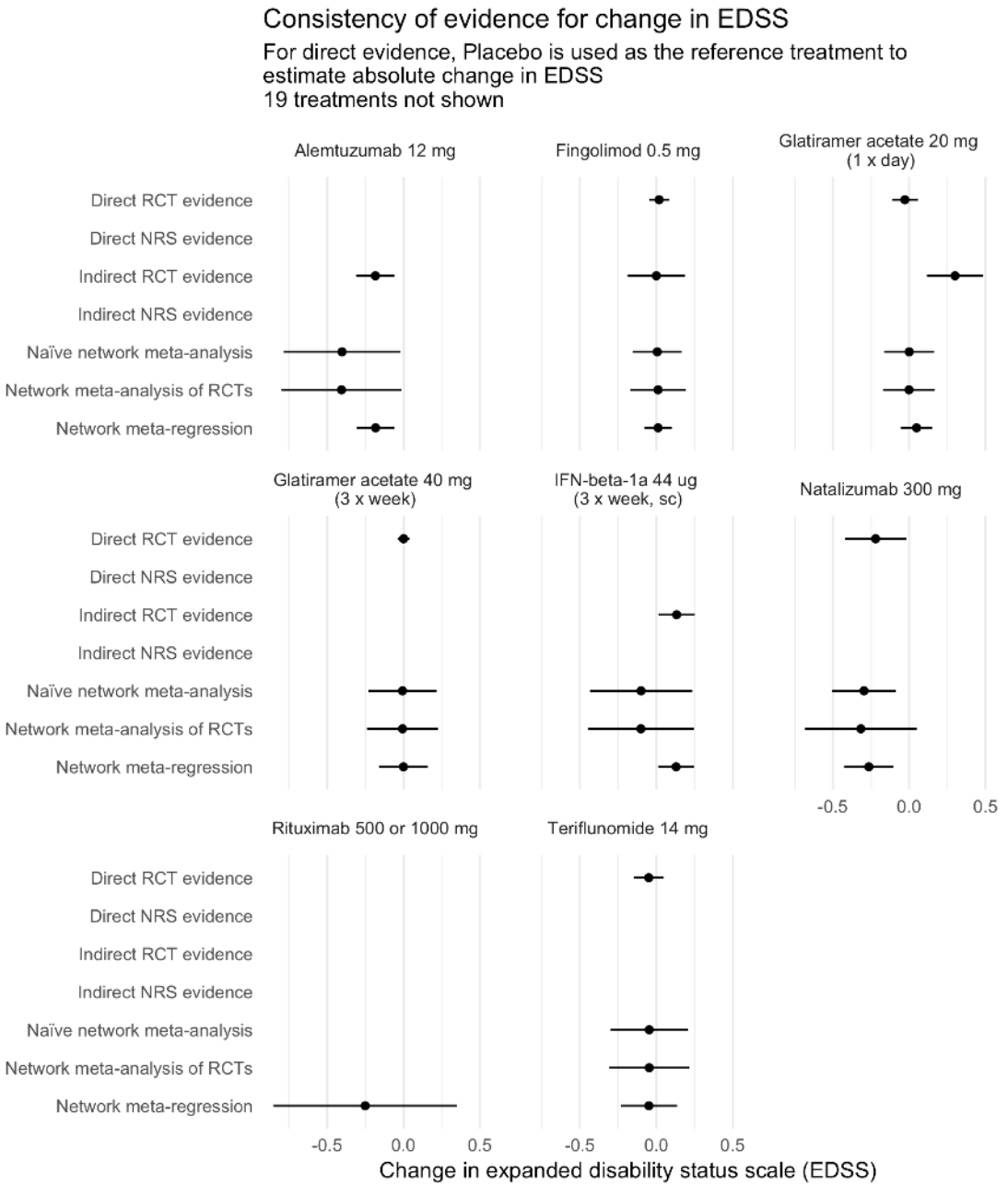
We here present the transitivity assessment of baseline characteristics for time since disease onset by treatment, treatment experience, annualised relapse rate, and average EDSS score.





Consistency assessment for change in EDSS

The following plot explores inconsistency between the various types of evidence used, and between network meta-analysis and meta-regression estimates. Direct comparisons assume placebo is the reference treatment.

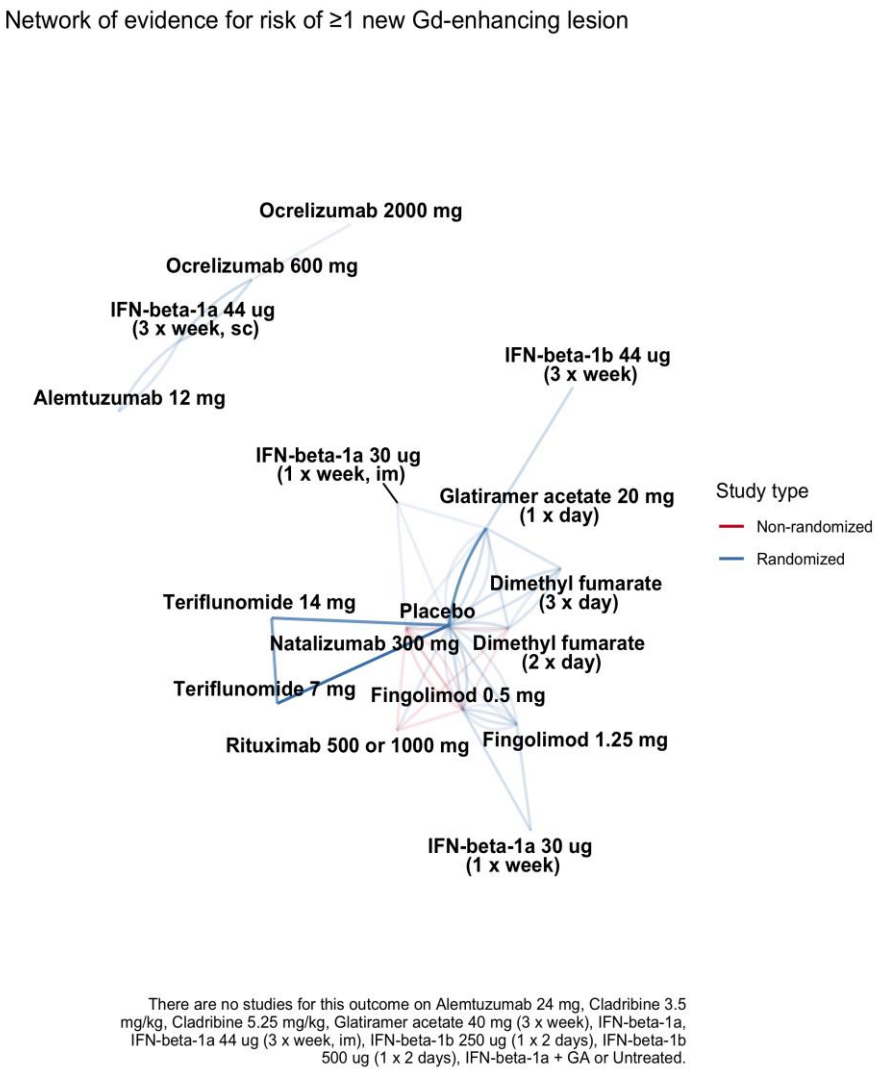


Means and 95% confidence intervals are shown for: direct RCT evidence (pairwise meta-analyses of RCTs that directly compare treatment and Placebo); indirect RCT evidence (network meta-analysis of RCTs that do not directly compare treatment and Placebo); direct NRS evidence (pairwise meta-analyses of non-randomized studies that directly compare treatment and Placebo); and indirect NRS evidence (network meta-analysis of non-randomized studies that do not directly compare treatment and Placebo). Evidence may be missing for some or all treatments. Naïve network meta-analysis does not account for possible differences between RCT and NRS evidence. Network meta-analysis of RCTs excludes non-randomized evidence. Network meta-regression accounts for possible differences between randomized and nonrandomized evidence.

Appendix 14. Detailed results for new MRI lesions (Gd-enhancing lesions)

Network evidence for risk of ≥1 new Gd-enhancing lesion

The following plot shows the network of evidence used in the analyses of progression of EDSS. Each line represents a direct treatment comparison (blue line= RCT, red line NRS).



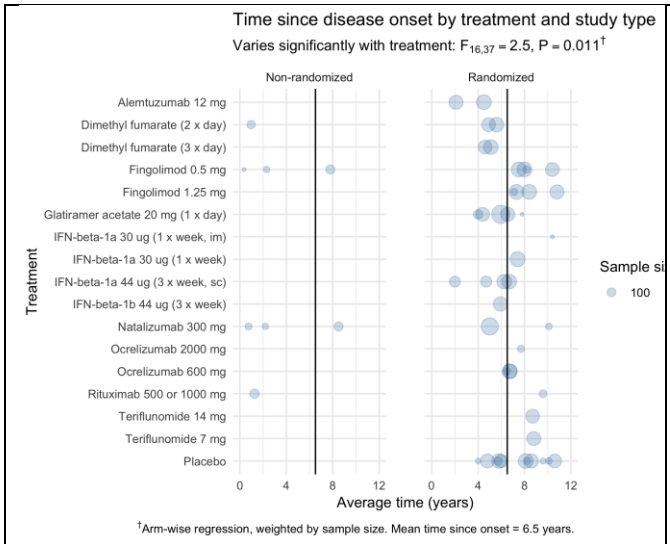
Complete ranking list for all treatments for Gd-enhancing lesions

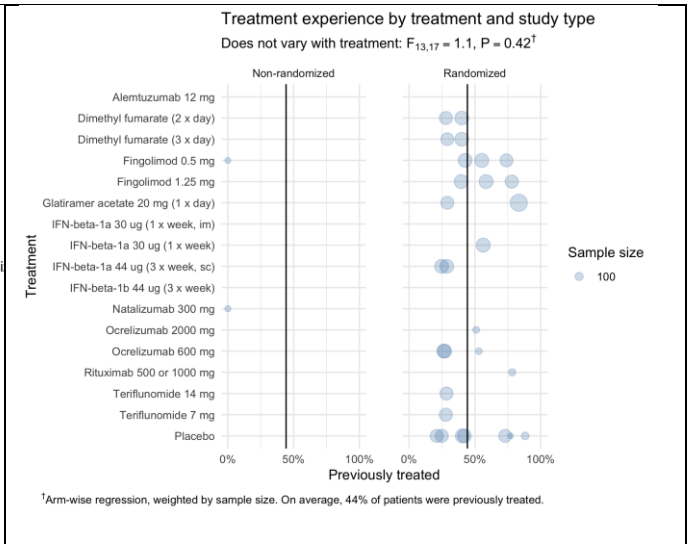
The following table shows treatments, estimates, and their ranks as computed via *P*-scores. The model accounts for possible differences between randomised and nonrandomised evidence. Results are shown for all treatments included in the model.

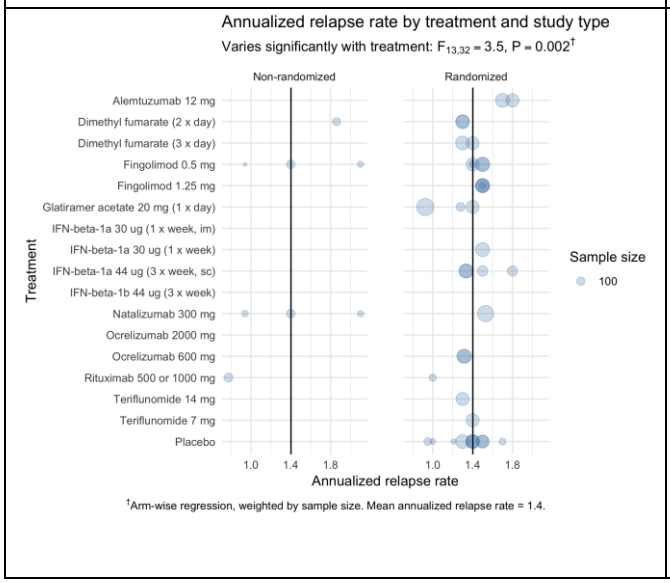
Treatment	Patients with new Gd-enhancing lesions per 1000 patients	P-score	Rank
Natalizumab 300 mg	50.23 (27.30 to 92.42)	0.94	1
Fingolimod 1.25 mg	80.07 (51.85 to 123.66)	0.83	2
Ocrelizumab 2000 mg	75.35 (28.33 to 200.43)	0.81	3
IFN-beta-1a 30 ug (1 x week, im)	56.81 (7.93 to 406.71)	0.81	4
Ocrelizumab 600 mg	100.42 (63.02 to 160.03)	0.73	5
Alemtuzumab 12 mg	103.77 (60.57 to 177.79)	0.71	6
Fingolimod 0.5 mg	117.22 (80.41 to 170.87)	0.65	7
Dimethyl fumarate (2 x day)	146.24 (89.00 to 240.30)	0.53	8
Rituximab 500 or 1000 mg	152.94 (75.91 to 308.14)	0.51	9
IFN-beta-1b 44 ug (3 x week)	173.25 (90.27 to 332.50)	0.45	10
Dimethyl fumarate (3 x day)	187.11 (115.79 to 302.35)	0.41	11
IFN-beta-1a 30 ug (1 x week)	198.63 (107.12 to 368.31)	0.38	12
Teriflunomide 14 mg	280.70 (157.83 to 499.22)	0.21	13
Glatiramer acetate 20 mg (1 x day)	288.14 (205.87 to 403.29)	0.20	14
IFN-beta-1a 44 ug (3 x week, sc)	300.45 (200.93 to 449.25)	0.18	15
Teriflunomide 7 mg	363.20 (205.36 to 642.36)	0.11	16
Placebo	402.31 (314.05 to 515.37)	0.05	17

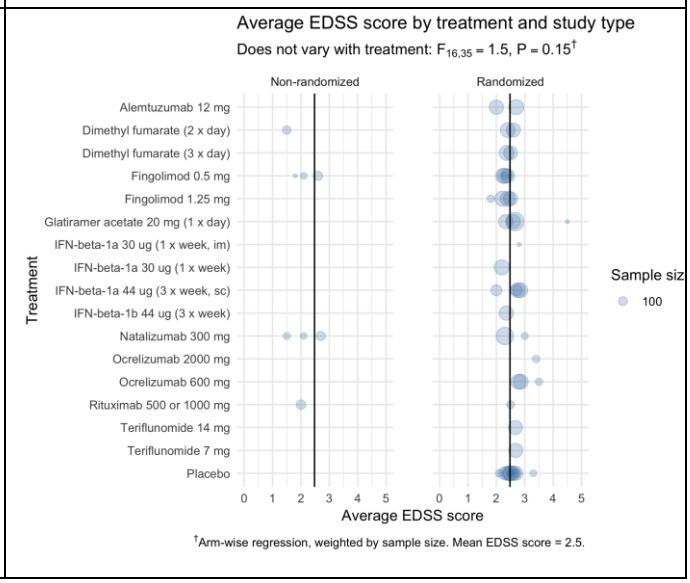
Transitivity assessment for new Gd-enhancing lesions

We here present the transitivity assessment of baseline characteristics for time since disease onset by treatment, treatment experience, annualised relapse rate, and average EDSS score.



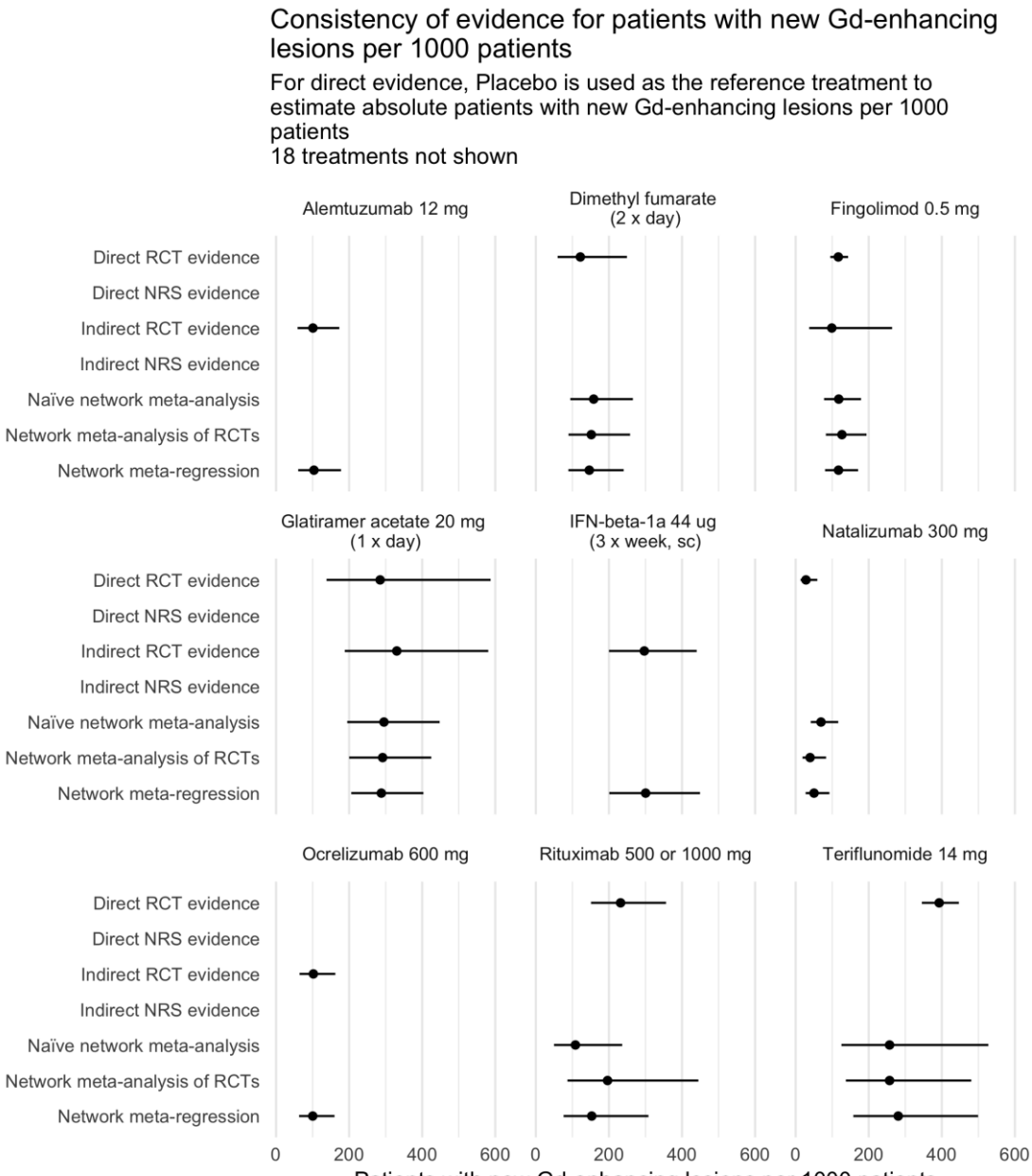






Inconsistency assessment for new Gd-enhancing lesions

The following plot explores inconsistency between the various types of evidence used, and between network meta-analysis and meta-regression estimates. Direct comparisons assume Placebo is the reference treatment.

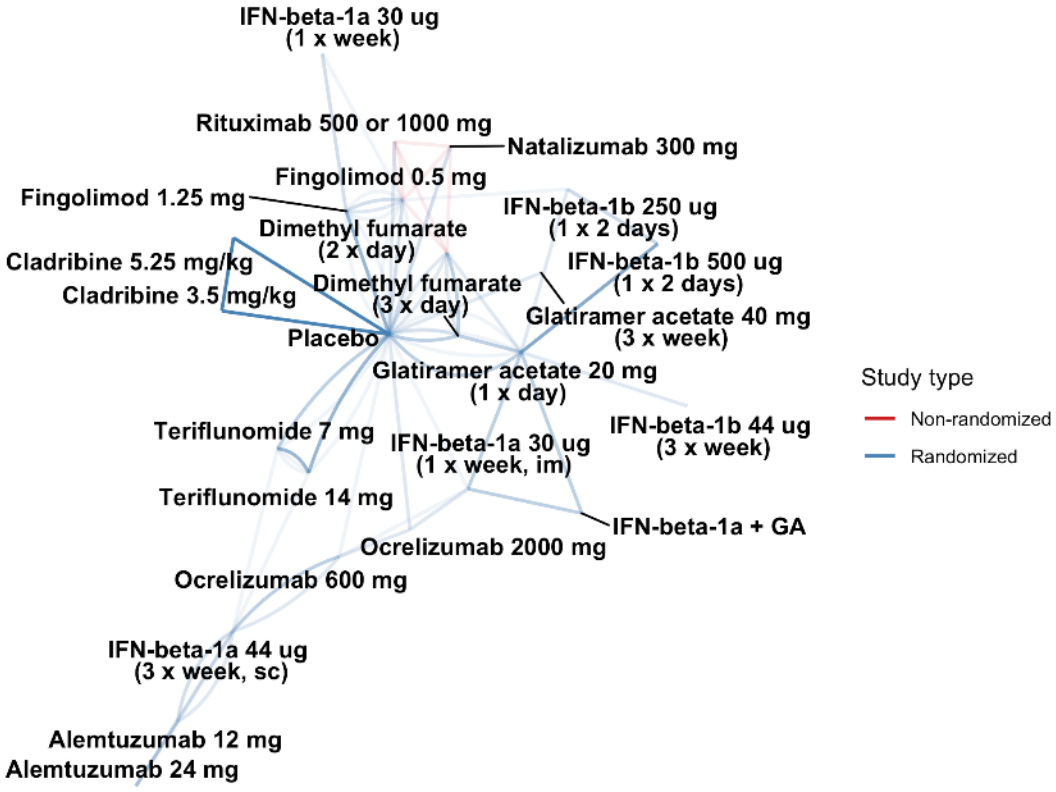


Means and 95% confidence intervals are shown for: direct RCT evidence (pairwise meta-analyses of RCTs that directly compare treatment and Placebo); indirect RCT evidence (network meta-analysis of RCTs that do not directly compare treatment and Placebo); direct NRS evidence (pairwise meta-analyses of non-randomized studies that directly compare treatment and Placebo); and indirect NRS evidence (network meta-analysis of non-randomized studies that do not directly compare treatment and Placebo). Evidence may be missing for some or all treatments. Naïve network meta-analysis does not account for possible differences between RCT and NRS evidence. Network meta-analysis of RCTs excludes non-randomized evidence and excludes the minority of treatments disconnected from the main network. Network meta-regression accounts for possible differences between randomized and nonrandomized evidence.

Appendix 15. Detailed results for mortality risk

Network evidence for mortality risk

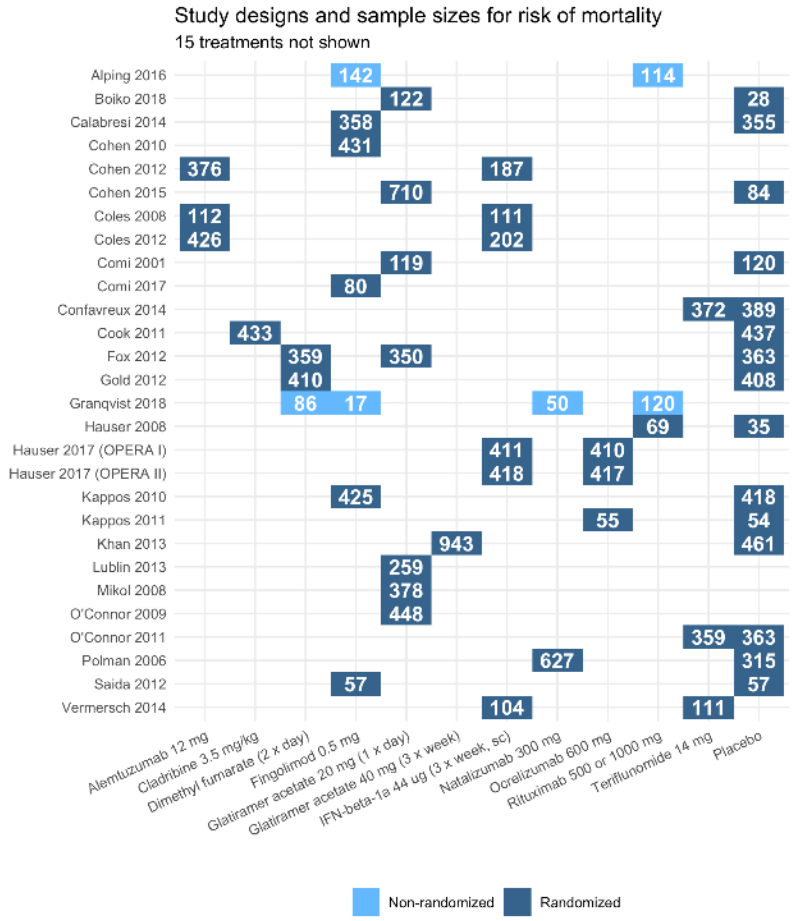
The following plot shows the network of evidence used in the analyses of progression of EDSS. Each line represents a direct treatment comparison (blue line= RCT, red line NRS).



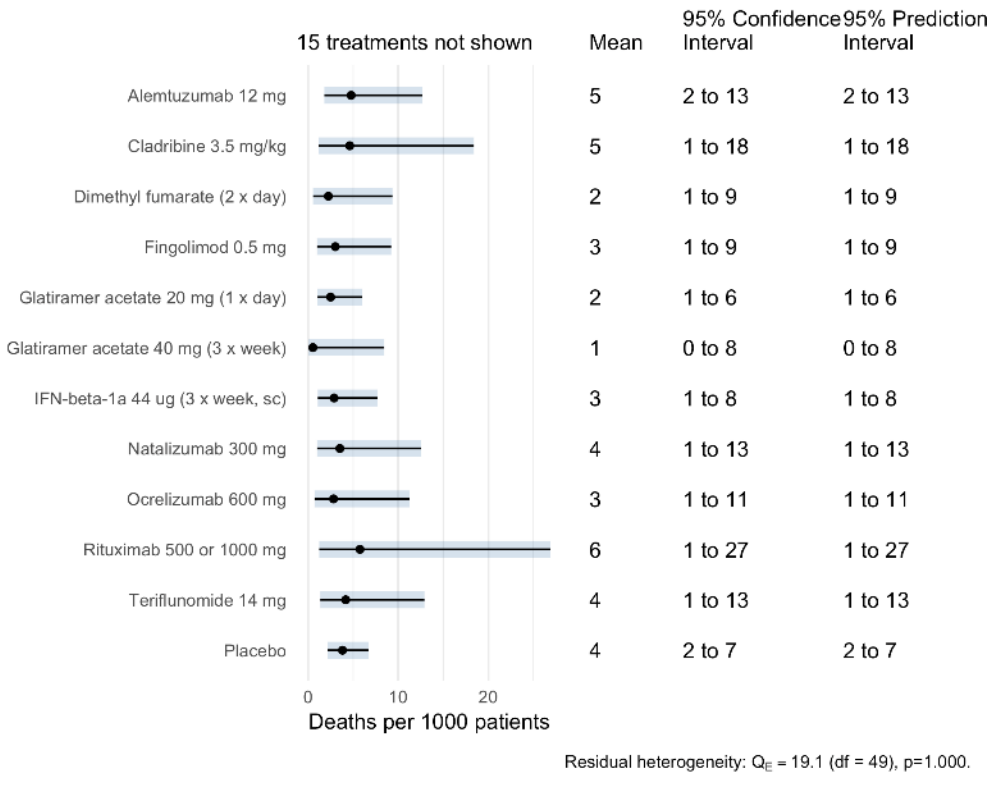
There are no studies for this outcome on IFN-beta-1a, IFN-beta-1a 44 ug (3 x week, im) or Untreated.

Study design, network meta-regression and relative risk of mortality

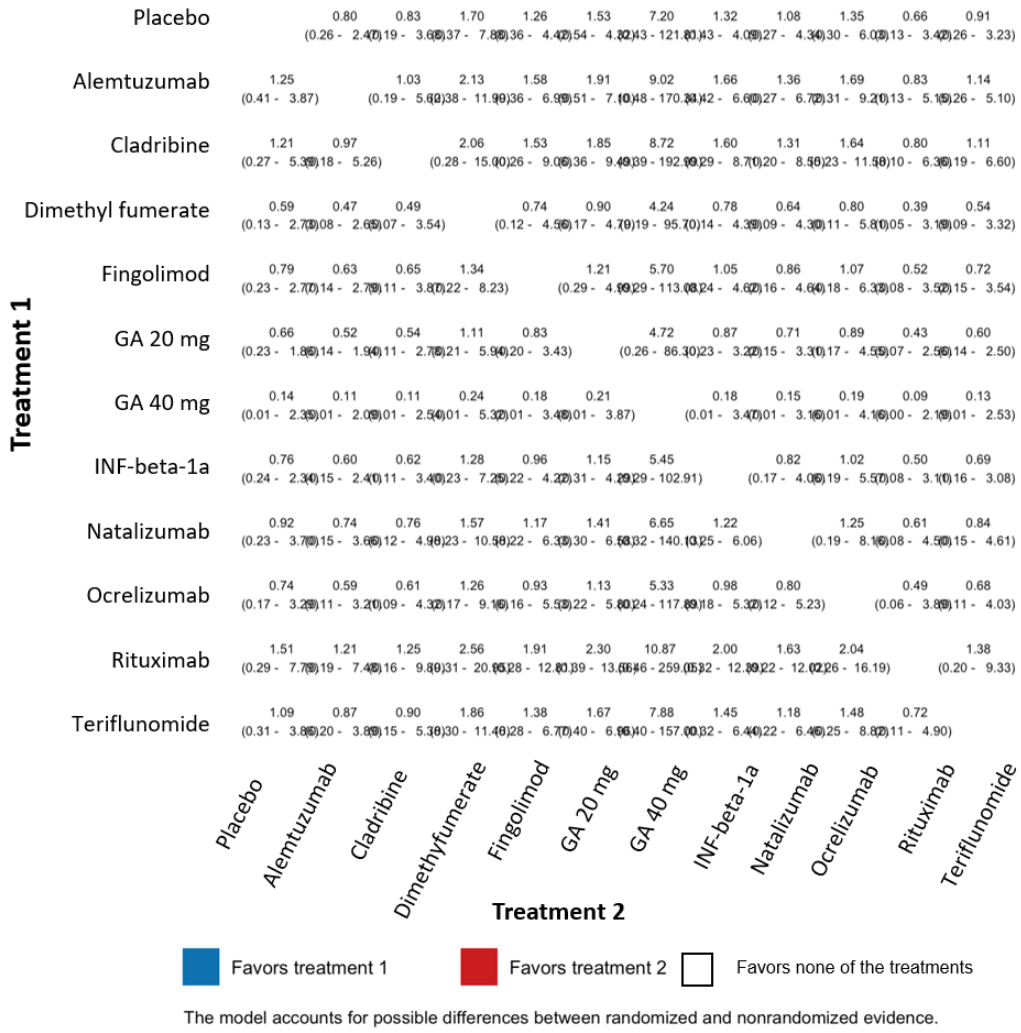
Study design and sample sizes for risk of mortality (15 treatments not shown)



Network meta-regression estimates of deaths per 1000 patients



Effect estimates of relative risk of mortality (95% confidence intervals in parentheses; 15 treatments not shown).



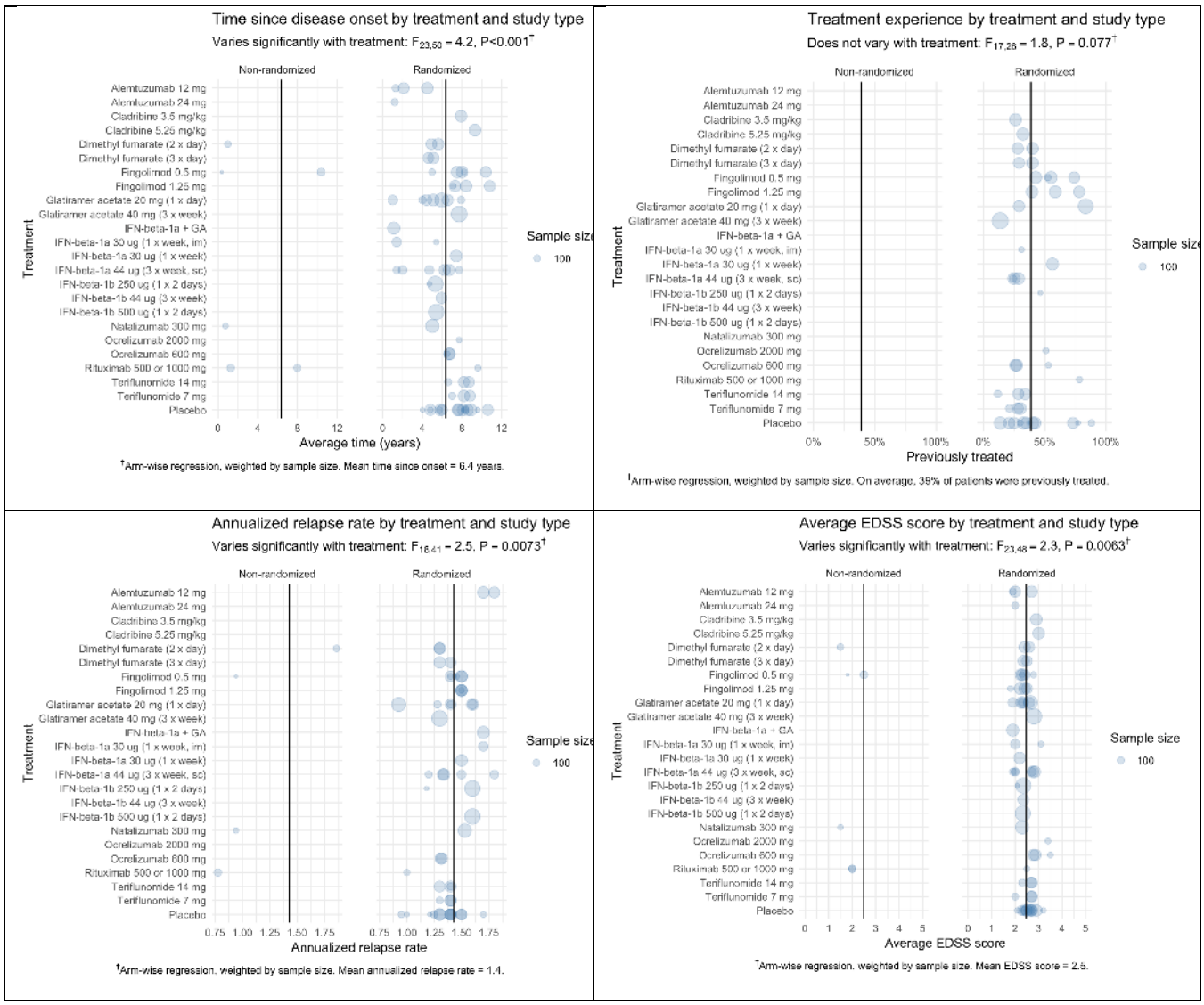
Complete ranking list for all treatments for mortality risk

The following table shows treatments, estimates, and their ranks as computed via *P*-scores. The model accounts for possible differences between randomised and nonrandomised evidence. Results are shown for all treatments included in the model.

Treatment	Deaths per 1000 patients	P-score	Rank
Glatiramer acetate 40 mg (3 x week)	0.53 (0.03 to 8.46)	0.87	1
IFN-beta-1a 30 ug (1 x week)	1.16 (0.07 to 18.47)	0.74	2
IFN-beta-1a + GA	2.00 (0.28 to 14.20)	0.65	3
Dimethyl fumarate (2 x day)	2.25 (0.54 to 9.35)	0.64	4
Glatiramer acetate 20 mg (1 x day)	2.50 (1.04 to 6.00)	0.63	5
Teriflunomide 7 mg	2.47 (0.62 to 9.86)	0.61	6
IFN-beta-1b 250 ug (1 x 2 days)	2.43 (0.34 to 17.13)	0.60	7
Dimethyl fumarate (3 x day)	2.64 (0.66 to 10.55)	0.59	8
IFN-beta-1b 44 ug (3 x week)	2.59 (0.37 to 18.34)	0.58	9
IFN-beta-1a 44 ug (3 x week, sc)	2.88 (1.08 to 7.68)	0.57	10
Ocrelizumab 600 mg	2.82 (0.71 to 11.25)	0.56	11
Fingolimod 0.5 mg	3.02 (0.99 to 9.23)	0.54	12
IFN-beta-1b 500 ug (1 x 2 days)	3.34 (1.08 to 10.33)	0.50	13
Natalizumab 300 mg	3.52 (0.99 to 12.52)	0.48	14
Fingolimod 1.25 mg	3.69 (1.39 to 9.82)	0.46	15
Placebo	3.81 (2.17 to 6.71)	0.44	16
Teriflunomide 14 mg	4.17 (1.35 to 12.90)	0.41	17
Cladribine 5.25 mg/kg	4.39 (1.10 to 17.48)	0.40	18
Cladribine 3.5 mg/kg	4.62 (1.16 to 18.41)	0.38	19
Alemtuzumab 12 mg	4.78 (1.80 to 12.70)	0.35	20
IFN-beta-1a 30 ug (1 x week, im)	5.26 (1.07 to 25.96)	0.35	21
Rituximab 500 or 1000 mg	5.76 (1.23 to 26.90)	0.32	22
Alemtuzumab 24 mg	9.09 (1.29 to 63.96)	0.22	23
Ocrelizumab 2000 mg	18.18 (2.61 to 126.78)	0.09	24

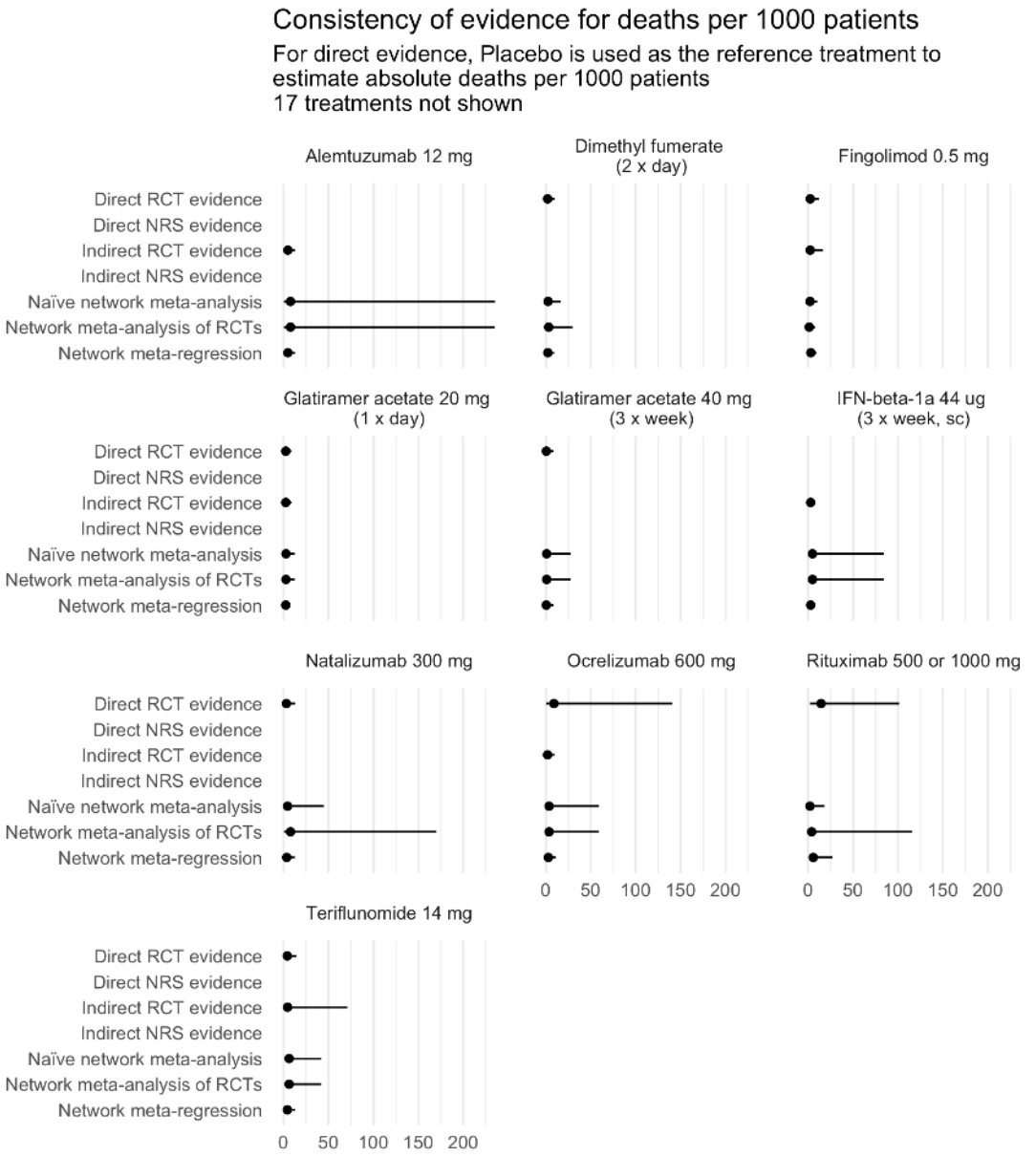
Transitivity assessment for mortality risk

We here present the transitivity assessment of baseline characteristics for time since disease onset by treatment, treatment experience, annualised relapse rate, and average EDSS score.



Consistency assessment for mortality risk

The following plot explores inconsistency between the various types of evidence used, and between network meta-analysis and meta-regression estimates. Direct comparisons assume placebo is the reference treatment.

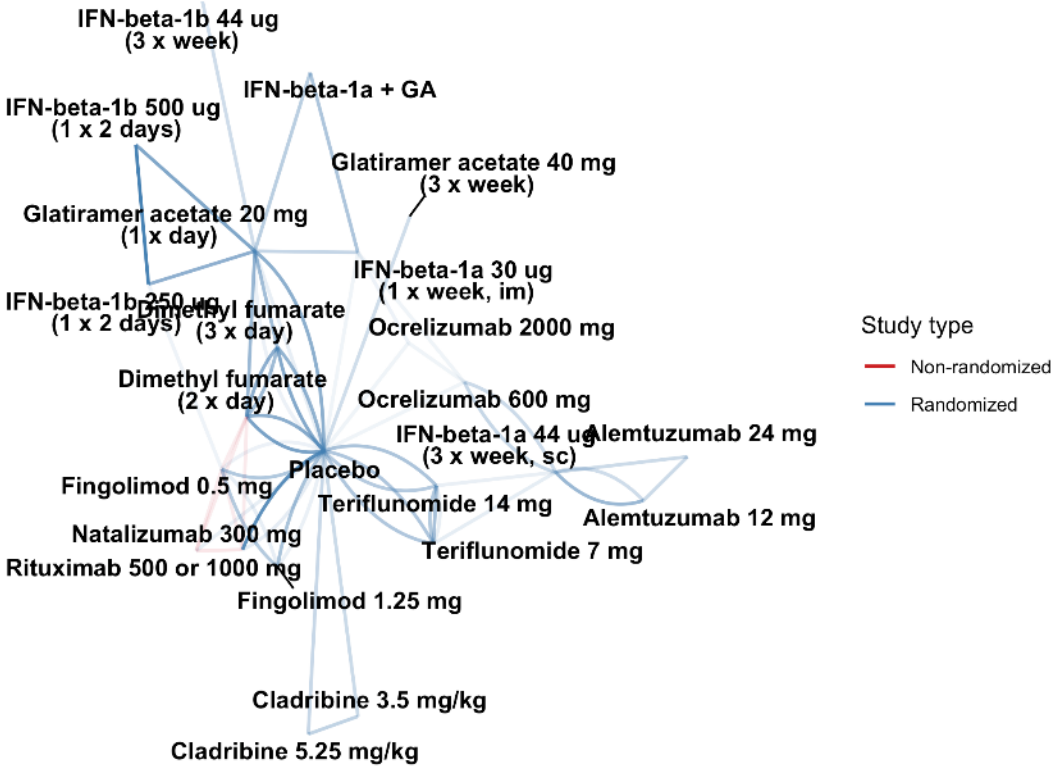


Means and 95% confidence intervals are shown for: direct RCT evidence (pairwise meta-analyses of RCTs that directly compare treatment and Placebo); indirect RCT evidence (network meta-analysis of RCTs that do not directly compare treatment and Placebo); direct NRS evidence (pairwise meta-analyses of non-randomized studies that directly compare treatment and Placebo); and indirect NRS evidence (network meta-analysis of non-randomized studies that do not directly compare treatment and Placebo). Evidence may be missing for some or all treatments. Naïve network meta-analysis does not account for possible differences between RCT and NRS evidence, and excludes the minority of treatments disconnected from the main network. Network meta-analysis of RCTs excludes non-randomized evidence. Network meta-regression includes a fixed effect to account for possible differences between RCT and NRS evidence, but assumes RCT and NRS studies have the same heterogeneity.

Appendix 16. Detailed results for serious adverse events, SAE

Network evidence for patients with ≥1 SAE per 1000 patients

The following plot shows the network of evidence used in the analyses of progression of EDSS. Each line represents a direct treatment comparison (blue line= RCT, red line NRS).



There are no studies for this outcome on IFN-beta-1a, IFN-beta-1a 30 ug (1 x week), IFN-beta-1a 44 ug (3 x week, im) or Untreated.

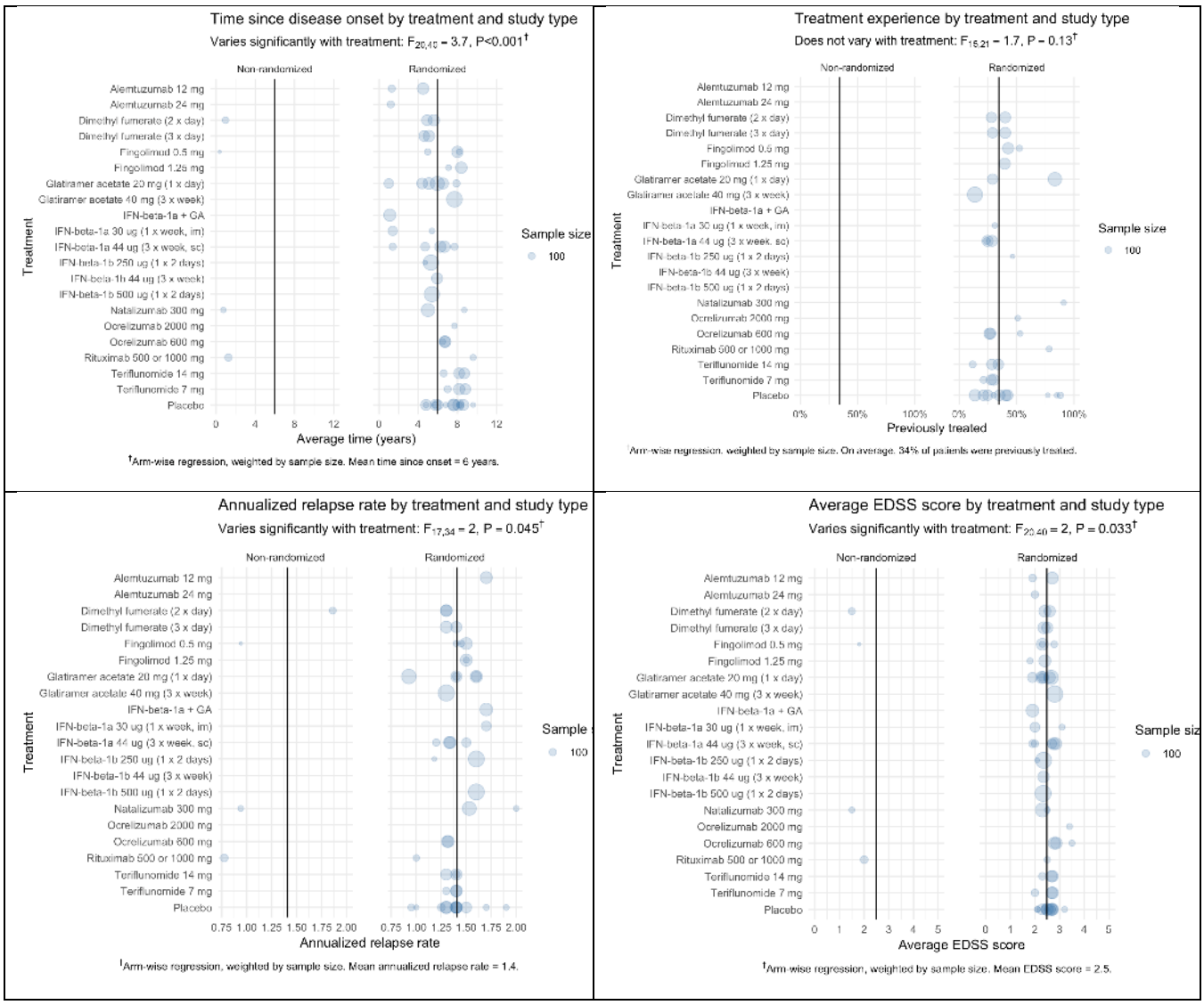
Complete ranking list for all treatments for risk of ≥1 SAE per 1000 patients

The following table shows treatments, estimates, and their ranks as computed via *P*-scores. The model accounts for possible differences between randomised and nonrandomised evidence. Results are shown for all treatments included in the model.

Treatment	Patients with ≥1 SAE per 1000 patients	P-score	Rank
Rituximab 500 or 1000 mg	47.62 (20.65 to 109.80)	0.94	1
IFN-beta-1b 250 ug (1 x 2 days)	83.66 (55.56 to 125.97)	0.77	2
Dimethyl fumarate (3 x day)	89.03 (64.82 to 122.29)	0.73	3
Ocrelizumab 600 mg	89.21 (53.41 to 149.01)	0.69	4
Ocrelizumab 2000 mg	72.55 (15.81 to 332.93)	0.68	5
Fingolimod 0.5 mg	94.99 (63.89 to 141.21)	0.65	6
Glatiramer acetate 20 mg (1 x day)	97.01 (71.70 to 131.25)	0.64	7
Natalizumab 300 mg	98.49 (69.93 to 138.74)	0.62	8
Dimethyl fumarate (2 x day)	98.98 (72.52 to 135.08)	0.62	9
IFN-beta-1b 44 ug (3 x week)	98.58 (56.40 to 172.28)	0.60	10
Glatiramer acetate 40 mg (3 x week)	102.36 (59.92 to 174.84)	0.56	11
Alemtuzumab 12 mg	114.28 (69.97 to 186.66)	0.45	12
IFN-beta-1b 500 ug (1 x 2 days)	116.53 (78.21 to 173.62)	0.42	13
IFN-beta-1a + GA	118.19 (74.55 to 187.38)	0.41	14
IFN-beta-1a 44 ug (3 x week, sc)	118.49 (75.86 to 185.07)	0.41	15
Placebo	120.36 (92.77 to 156.16)	0.38	16
Fingolimod 1.25 mg	123.76 (83.56 to 183.31)	0.36	17
IFN-beta-1a 30 ug (1 x week, im)	126.85 (78.20 to 205.75)	0.34	18
Teriflunomide 14 mg	131.51 (93.73 to 184.51)	0.29	19
Alemtuzumab 24 mg	138.01 (76.63 to 248.54)	0.28	20
Teriflunomide 7 mg	134.00 (96.09 to 186.88)	0.27	21
Cladribine 3.5 mg/kg	145.74 (87.02 to 244.06)	0.22	22
Cladribine 5.25 mg/kg	157.61 (95.28 to 260.71)	0.16	23

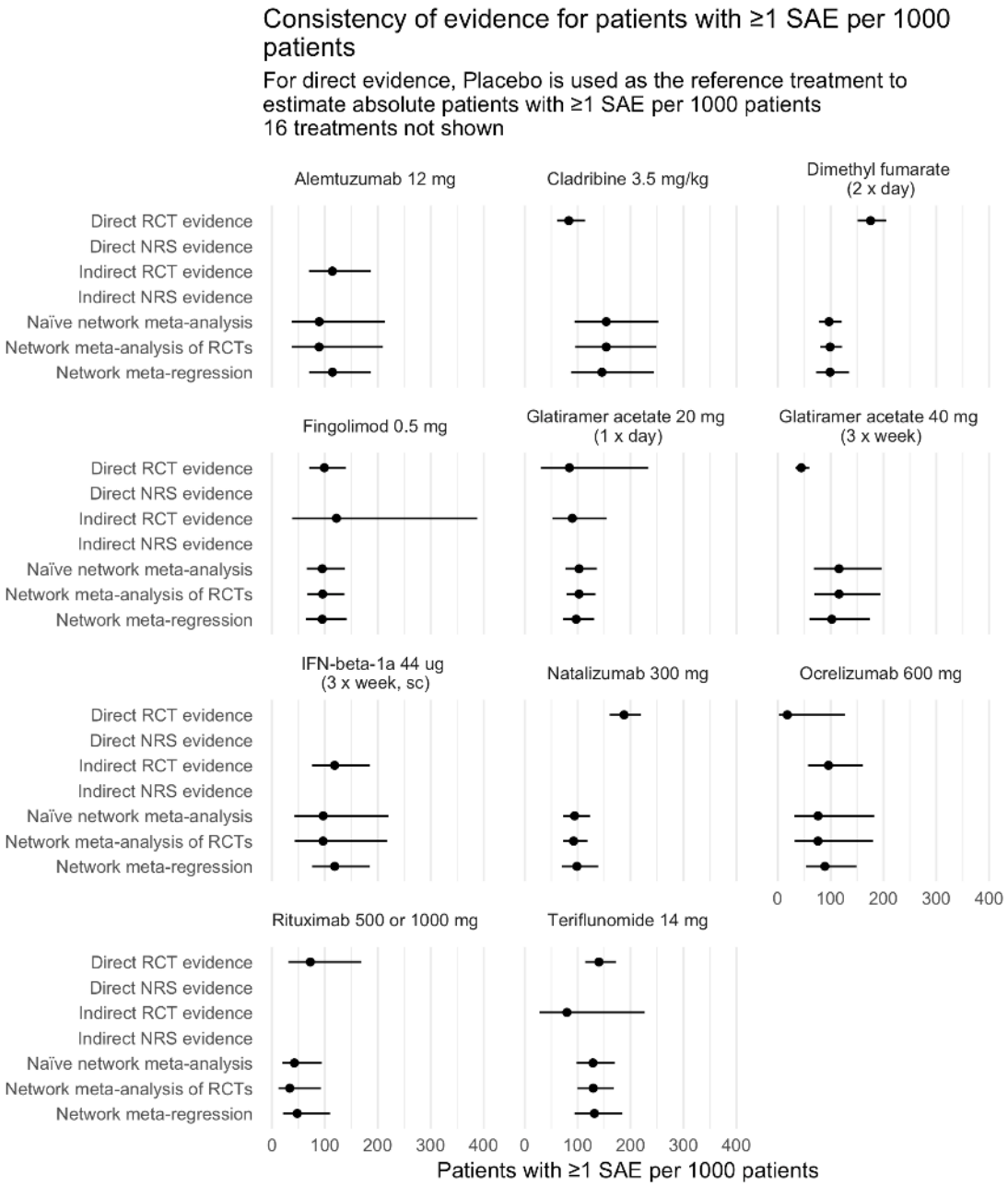
Transitivity assessment for serious adverse events

We here present the transitivity assessment of baseline characteristics for time since disease onset by treatment, treatment experience, annualised relapse rate, and average EDSS score.



Consistency assessment for serious adverse events

The following plot explores inconsistency between the various types of evidence used, and between network meta-analysis and meta-regression estimates. Direct comparisons assume placebo is the reference treatment.

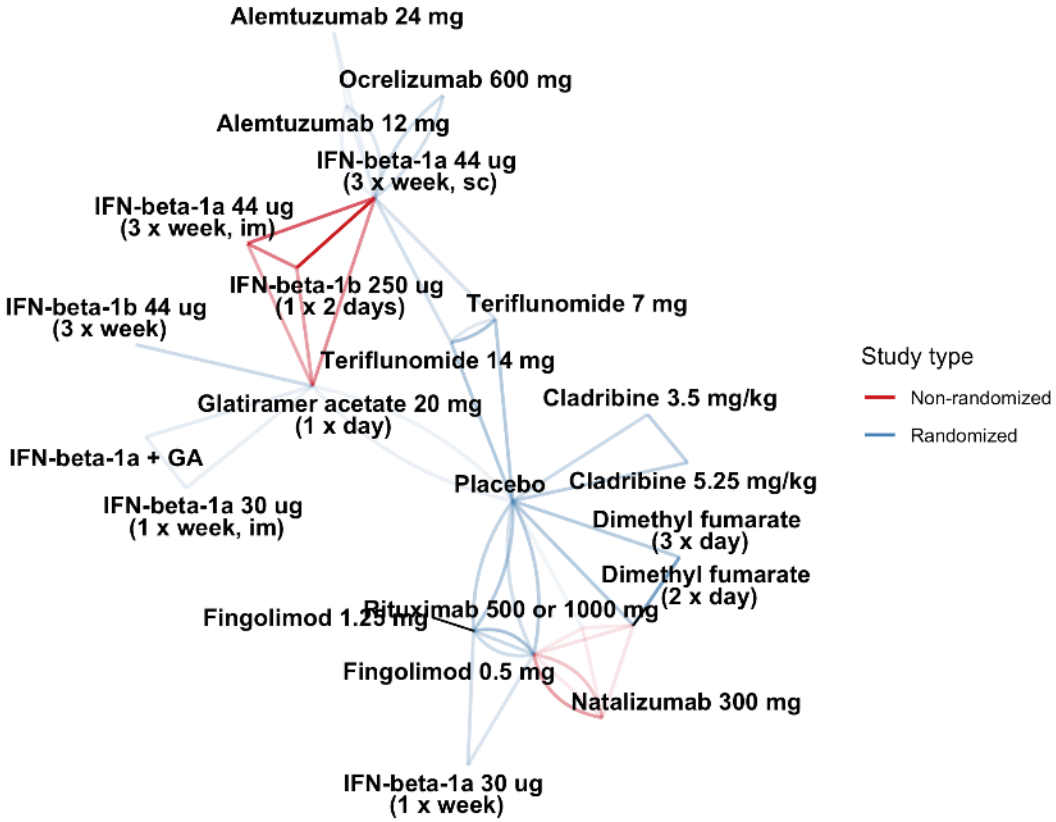


Means and 95% confidence intervals are shown for: direct RCT evidence (pairwise meta-analyses of RCTs that directly compare treatment and Placebo); indirect RCT evidence (network meta-analysis of RCTs that do not directly compare treatment and Placebo); direct NRS evidence (pairwise meta-analyses of non-randomized studies that directly compare treatment and Placebo); and indirect NRS evidence (network meta-analysis of non-randomized studies that do not directly compare treatment and Placebo). Evidence may be missing for some or all treatments. Naïve network meta-analysis does not account for possible differences between RCT and NRS evidence. Network meta-analysis of RCTs excludes non-randomized evidence. Network meta-regression accounts for possible differences between randomized and nonrandomized evidence.

Appendix 17. Detailed results for treatment withdrawal

Network of evidence for treatment withdrawals due to adverse events (AE) per 1000 patients

The following plot shows the network of evidence used in the analyses of progression of EDSS. Each line represents a direct treatment comparison (blue line= RCT, red line NRS).



There are no studies for this outcome on Glatiramer acetate 40 mg (3 x week), IFN-beta-1a, IFN-beta-1b 500 ug (1 x 2 days), Ocrelizumab 2000 mg or Untreated.

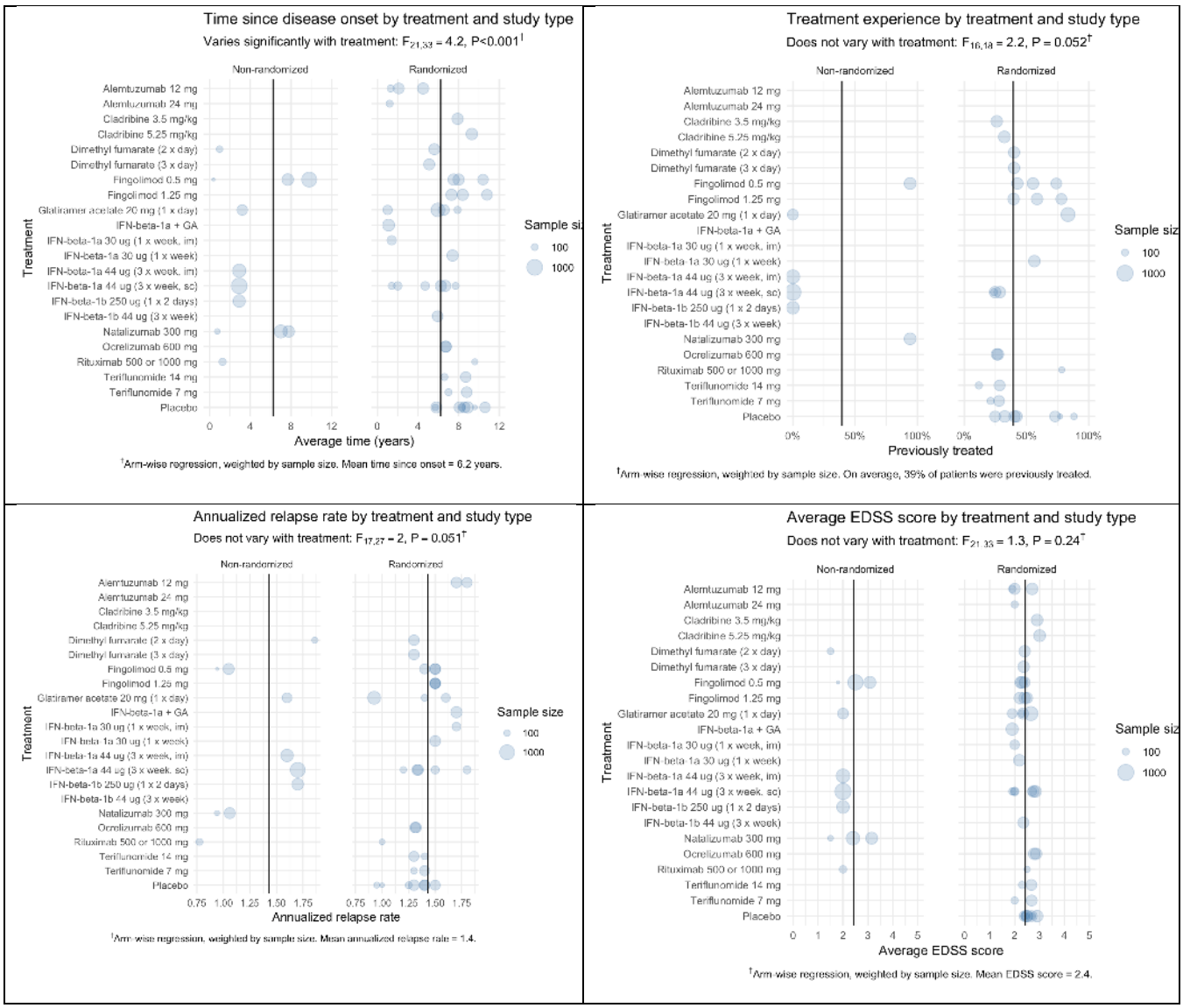
Complete ranking list for all treatments for treatment withdrawal

The following table shows treatments, estimates, and their ranks as computed via *P*-scores. The model accounts for possible differences between randomised and nonrandomised evidence. Results are shown for all treatments included in the model.

Treatment	Withdrawals per 1000 patients	P-score	Rank
Rituximab 500 or 1000 mg	9.58 (2.15 to 42.60)	0.92	1
Alemtuzumab 24 mg	7.58 (0.99 to 58.23)	0.92	2
IFN-beta-1a + GA	19.09 (7.25 to 50.27)	0.83	3
IFN-beta-1a 30 ug (1 x week, im)	19.05 (5.81 to 62.46)	0.81	4
Natalizumab 300 mg	22.68 (11.38 to 45.19)	0.80	5
Alemtuzumab 12 mg	27.06 (14.33 to 51.11)	0.74	6
IFN-beta-1a 30 ug (1 x week)	31.20 (14.31 to 68.02)	0.68	7
Glatiramer acetate 20 mg (1 x day)	34.17 (21.76 to 53.66)	0.66	8
IFN-beta-1a 44 ug (3 x week, im)	36.31 (16.17 to 81.54)	0.61	9
Ocrelizumab 600 mg	41.67 (23.58 to 73.64)	0.55	10
IFN-beta-1b 44 ug (3 x week)	46.01 (22.03 to 96.06)	0.49	11
Placebo	49.73 (35.34 to 69.97)	0.46	12
Cladribine 3.5 mg/kg	49.81 (24.46 to 101.45)	0.45	13
Fingolimod 0.5 mg	51.46 (34.25 to 77.34)	0.44	14
Teriflunomide 7 mg	58.24 (34.83 to 97.37)	0.37	15
Teriflunomide 14 mg	64.58 (39.19 to 106.43)	0.31	16
IFN-beta-1b 250 ug (1 x 2 days)	71.60 (32.56 to 157.42)	0.27	17
Fingolimod 1.25 mg	77.90 (51.23 to 118.45)	0.21	18
IFN-beta-1a 44 ug (3 x week, sc)	78.40 (55.40 to 110.96)	0.20	19
Cladribine 5.25 mg/kg	89.66 (46.81 to 171.76)	0.16	20
Dimethyl fumarate (3 x day)	119.28 (65.21 to 218.20)	0.07	21
Dimethyl fumarate (2 x day)	124.87 (72.56 to 214.92)	0.05	22

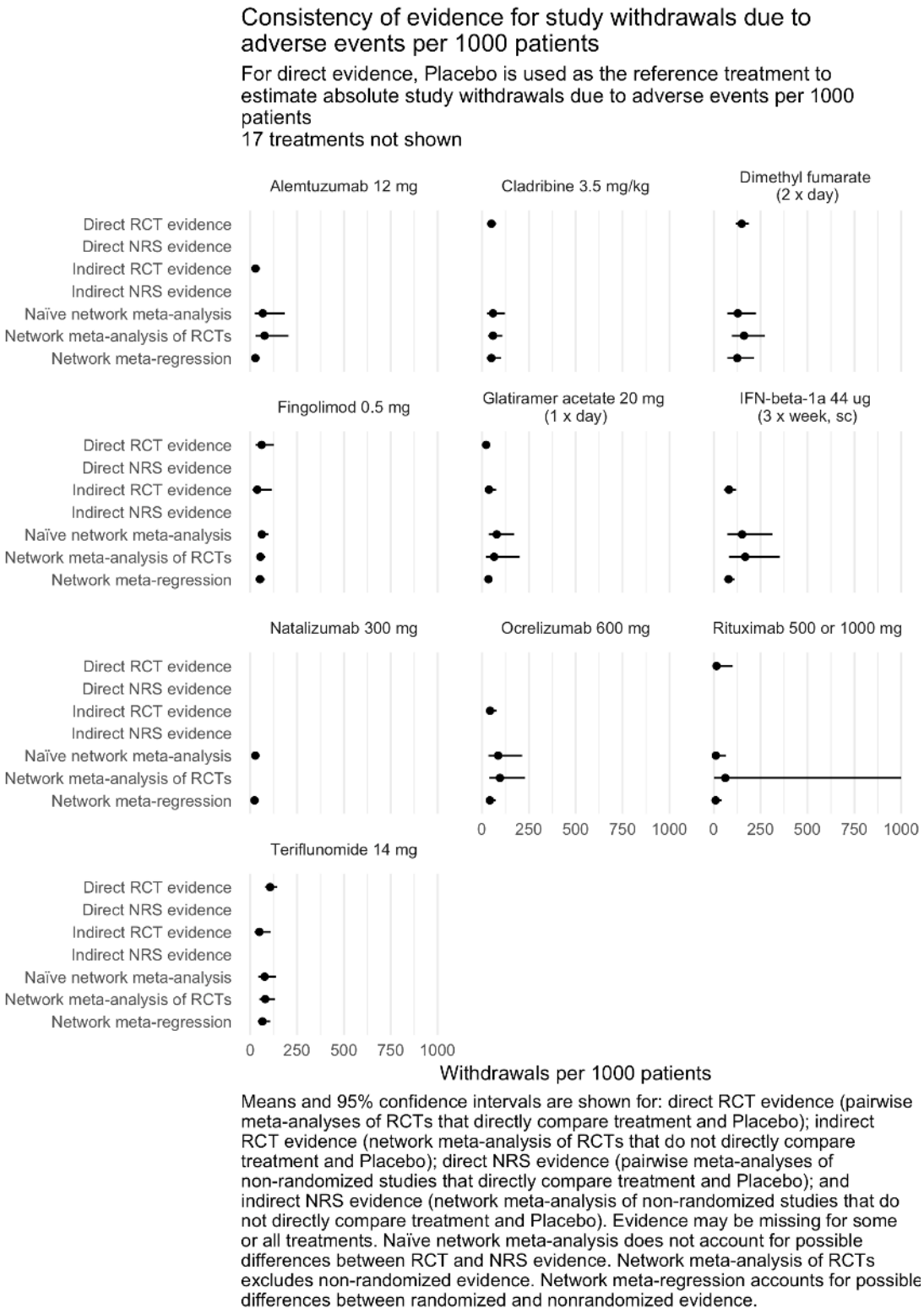
Transitivity assessment for treatment withdrawal

We here present the transitivity assessment of baseline characteristics for time since disease onset by treatment, treatment experience, annualised relapse rate, and average EDSS score.



Consistency assessment for treatment withdrawal

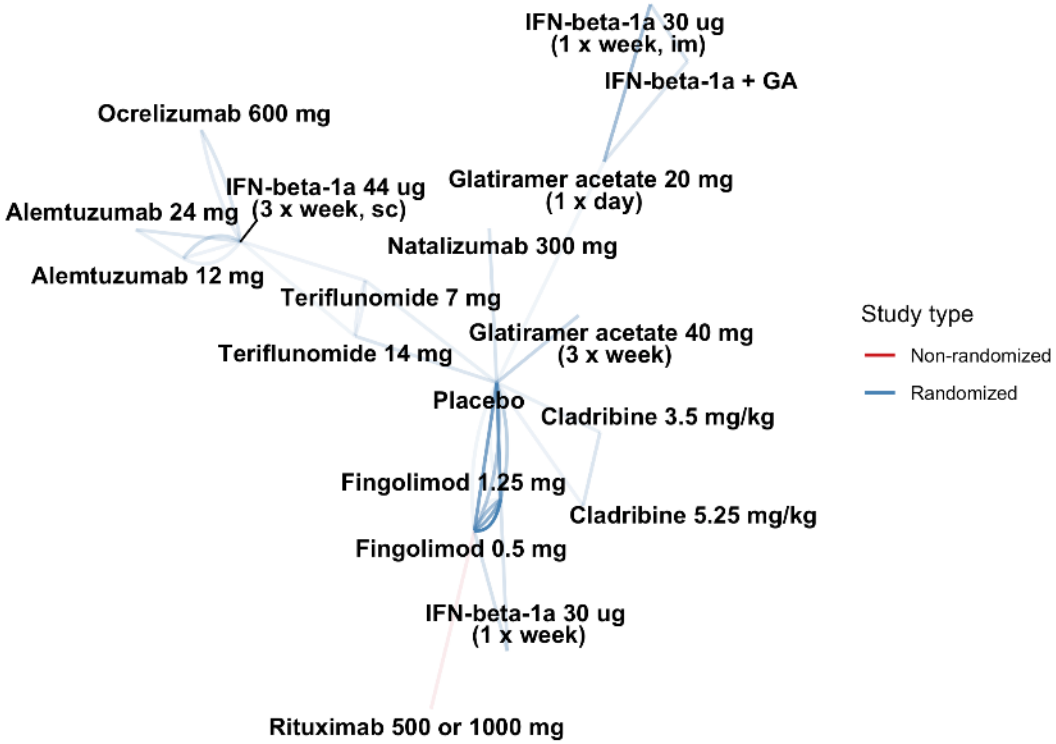
The following plot explores inconsistency between the various types of evidence used, and between network meta-analysis and meta-regression estimates. Direct comparisons assume placebo is the reference treatment.



Appendix 18. Detailed results for risk of cancer

Network of evidence for risk of cancer

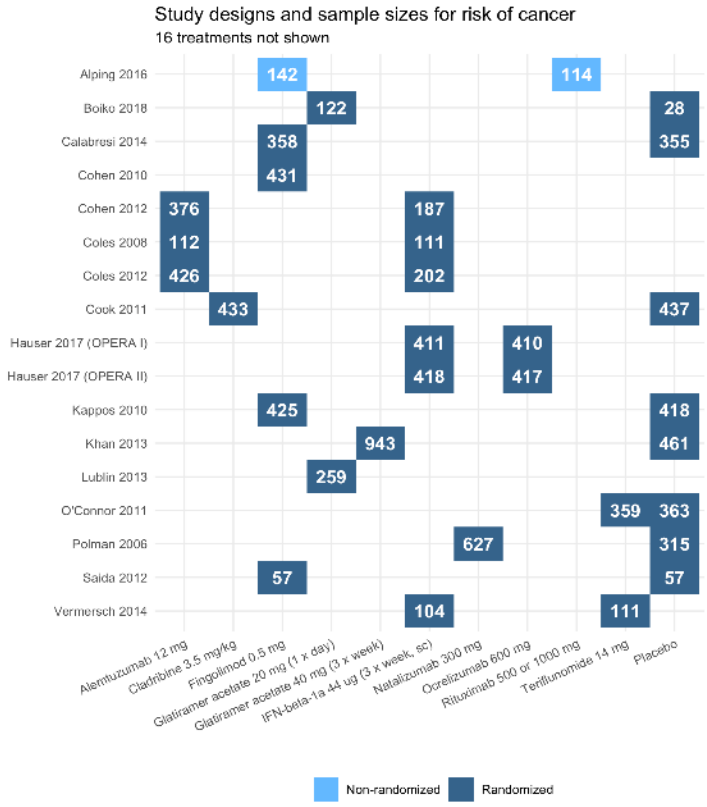
The following plot shows the network of evidence used in the analyses of progression of EDSS. Each line represents a direct treatment comparison (blue line= RCT, red line NRS).



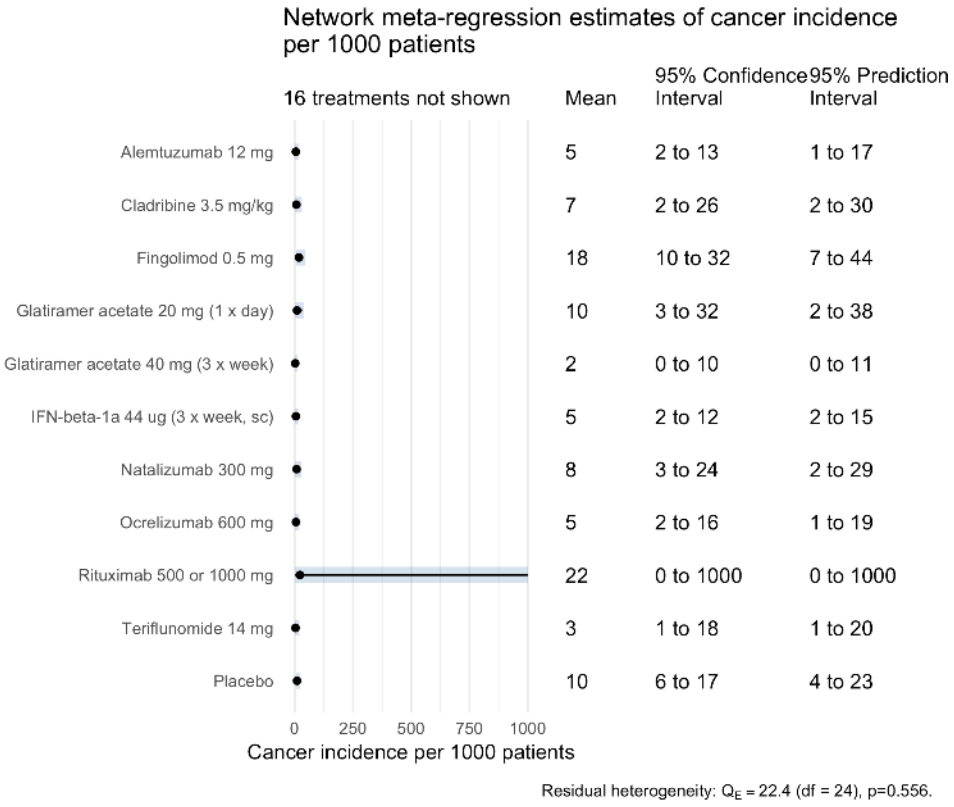
There are no studies for this outcome on Dimethyl fumarate (2 x day), Dimethyl fumarate (3 x day), IFN-beta-1a, IFN-beta-1a 44 ug (3 x week, im), IFN-beta-1b 250 ug (1 x 2 days), IFN-beta-1b 500 ug (1 x 2 days), IFN-beta-1b 44 ug (3 x week), Ocrelizumab 2000 mg or Untreated.

Study design, network meta-regression and relative risk of risk of cancer

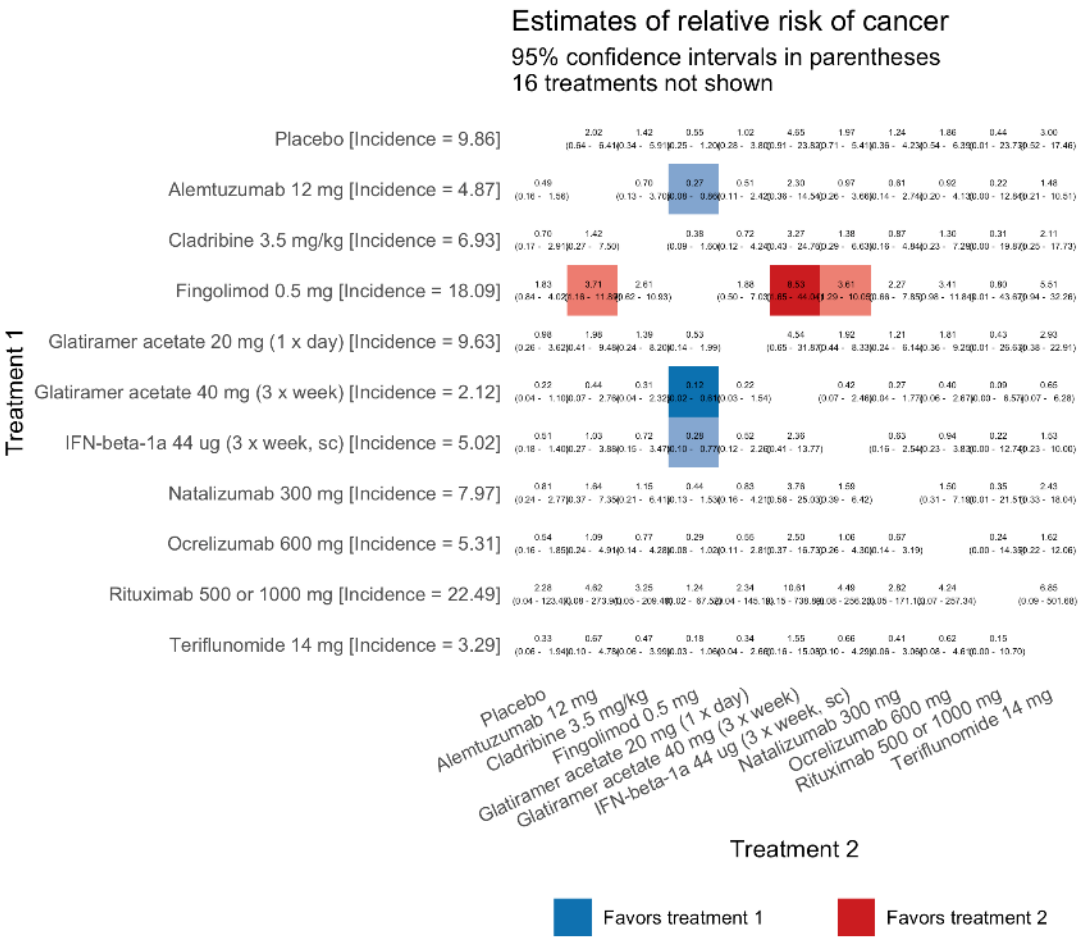
In the network meta-analysis, we included data from 17 studies of which 16 were RCTs. The studies included 27 treatments, 43 study arms, 13 496 patients and 24 367 patient years.



We estimated risk of cancer per 1000 patients, by the end of study follow-up, by network meta-regression:



The effect estimate was the relative effect compared to all other treatments:



The model accounts for possible differences between randomized and nonrandomized evidence.

Ranking list for selected treatments for risk of cancer

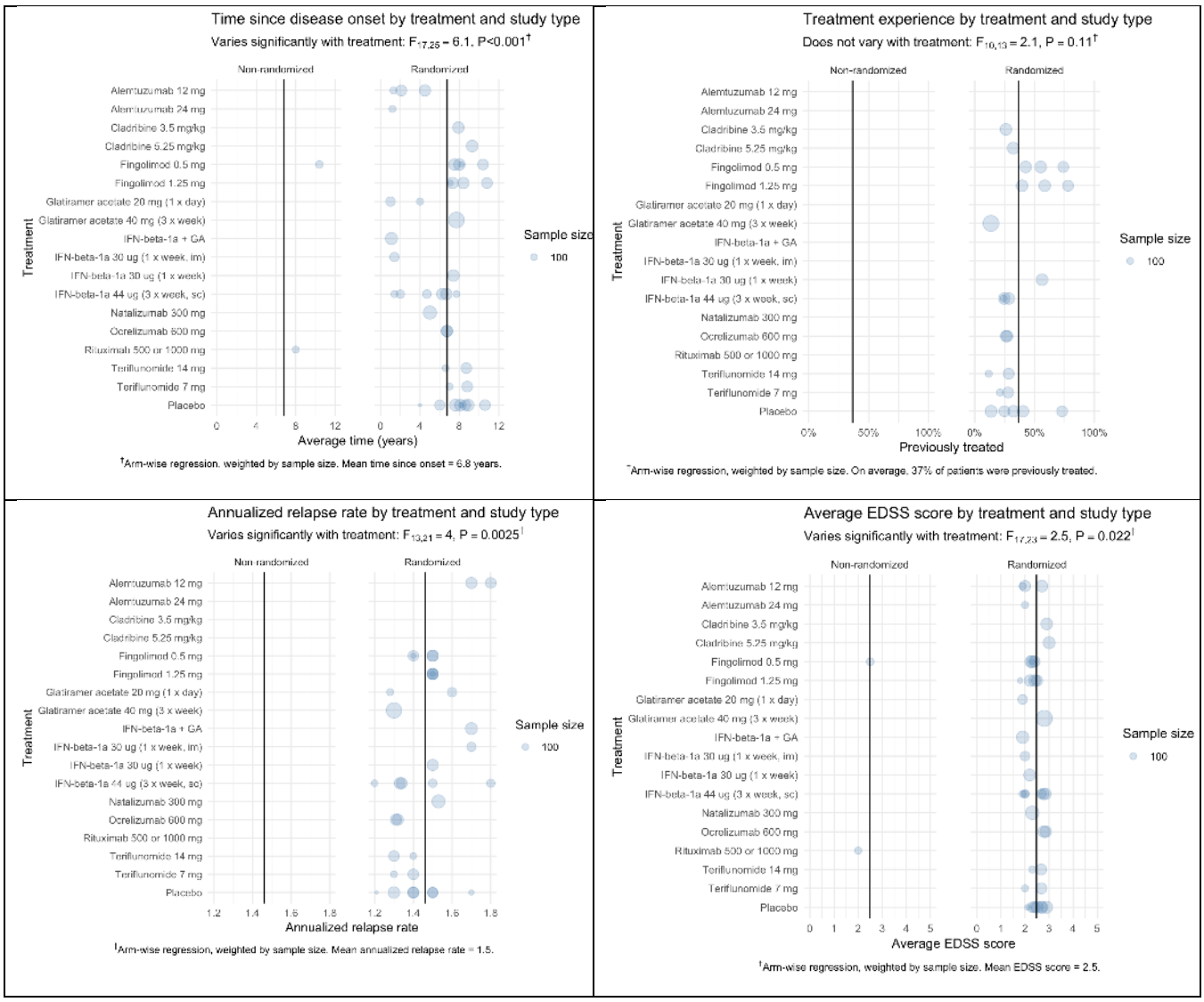
The following table shows treatments, estimates, and their ranks as computed via *P*-scores. The model accounts for possible differences between randomised and nonrandomised evidence. Results are shown for all treatments included in the model.

The reported events from the studies are also listed per 1000 patients.

Treatment	Estimated cancer incidence per 1000 patients	Reported events per 1000 patients*	P-score	Rank
Glatiramer acetate 40 mg (3 x week)	2.12 (0.45 to 9.90)	2	0.82	1
Teriflunomide 14 mg	3.29 (0.62 to 17.53)	2	0.71	5
Alemtuzumab 12 mg	4.87 (1.76 to 13.46)	4	0.62	6
IFN-beta-1a 44 ug (3 x week, sc)	5.02 (2.14 to 11.78)	3	0.62	7
Ocrelizumab 600 mg	5.31 (1.75 to 16.12)	5	0.59	9
Cladribine 3.5 mg/kg	6.93 (1.86 to 25.80)	7	0.50	10
Natalizumab 300 mg	7.97 (2.64 to 24.06)	9	0.45	11
Glatiramer acetate 20 mg (1 x day)	9.63 (2.92 to 31.74)	8	0.38	12
Placebo	9.86 (5.73 to 16.98)	6	0.37	13
Rituximab 500 or 1000 mg	22.49 (0.43 to 1000.00)	0	0.29	15
Fingolimod 0.5 mg	18.09 (10.27 to 31.88)	16	0.16	16
Alemtuzumab 24 mg	27.27 (7.40 to 100.57)	4	0.11	18
* Not estimated from the model				

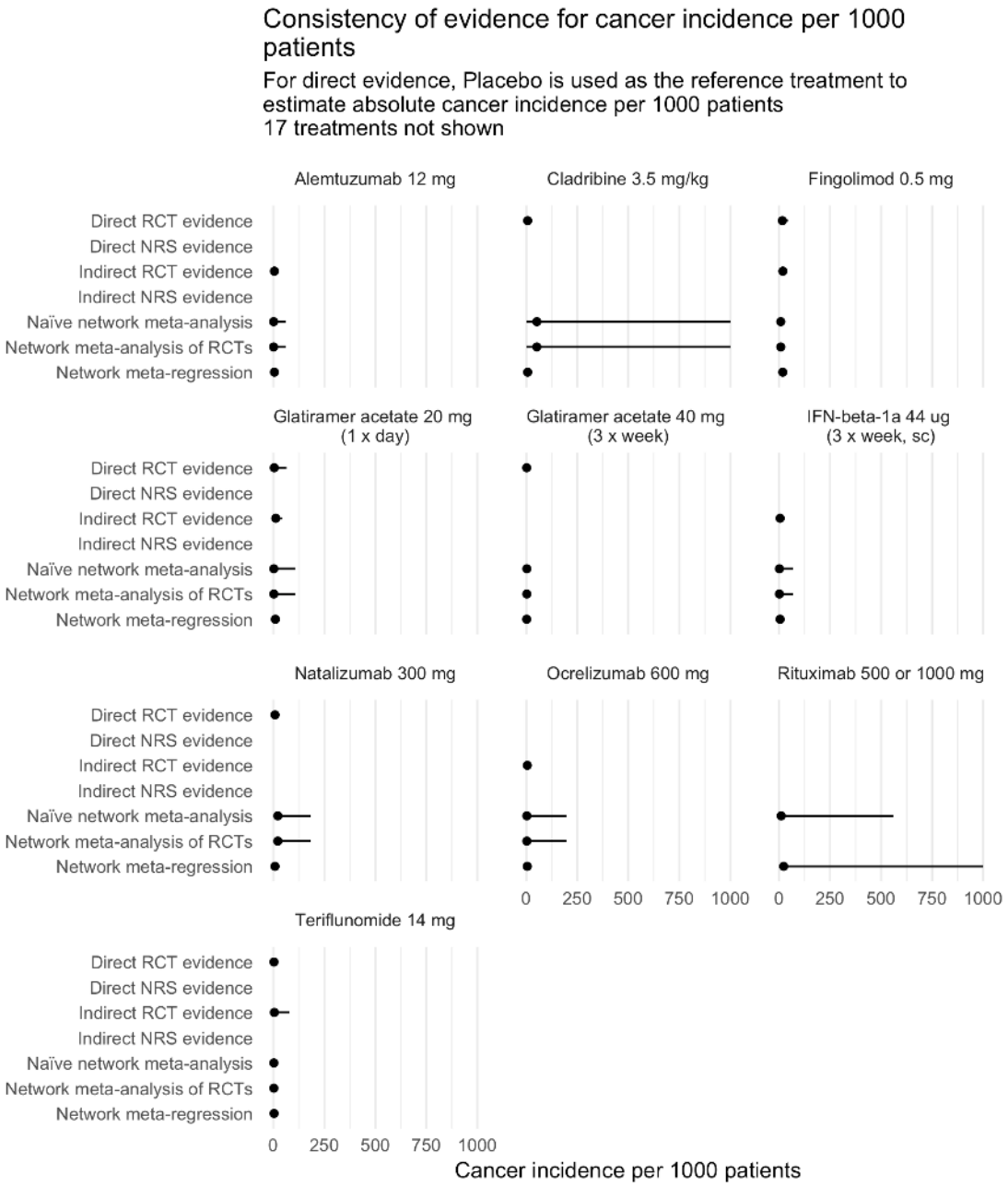
Transitivity assessment for risk of cancer

We here present the transitivity assessment of baseline characteristics for time since disease onset by treatment, treatment experience, annualised relapse rate, and average EDSS score.



Inconsistency assessment for mortality

The following plot explores inconsistency between the various types of evidence used, and between network meta-analysis and meta-regression estimates. Direct comparisons assume placebo is the reference treatment.



Means and 95% confidence intervals are shown for: direct RCT evidence (pairwise meta-analyses of RCTs that directly compare treatment and Placebo); indirect RCT evidence (network meta-analysis of RCTs that do not directly compare treatment and Placebo); direct NRS evidence (pairwise meta-analyses of non-randomized studies that directly compare treatment and Placebo); and indirect NRS evidence (network meta-analysis of non-randomized studies that do not directly compare treatment and Placebo). Evidence may be missing for some or all treatments. Naïve network meta-analysis does not account for possible differences between RCT and NRS evidence. Network meta-analysis of RCTs excludes non-randomized evidence. Network meta-regression accounts for possible differences between randomized and nonrandomized evidence.

Appendices – Methods

Appendix 19. Search strategy

We performed six searches for published studies in a selection of the following databases (see Table):

- 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
- Web of Science
- PubMed (epub ahead of print)
- Epistemonikos
- EUnetHTA POP database (POP = Planned and Ongoing Projects)
- PROSPERO – Centre for Reviews and Dissemination
- WHO ICTRP
- ClinicalTrials.gov

The MEDLINE and Embase search strategy are presented in detail. Information about the other searches will be provided on request.

Table: *Search result*

Name of database	Hits exported to EndNote	Total without duplicates
Search 1: Update based on Couto 2016 (3) Publication type: Systematic Reviews, Health Technology Assessments, Randomised Controlled Trials, Economic Evaluations Year of publication 2015-2018 Search date: 23.05.2018		
Cochrane Library: CDSR Reviews (15), CDSR Protocols (4), Other Reviews (0), Technology Assessments (4), NHS EED [0), Trials (695),	718	637
Centre for Reviews and Dissemination (CRD)	7	7
Embase SR, RCT, Economic eval.	427 253	192 172
MEDLINE: SR, RCT, Economic eval.	273 7	109 3
Epistemonikos	45	10
PubMed (pubmednotmedline/aheadofprint)	104	97
Web of Science	274	274

SveMed+	0	
SBU	1	1
Search 2: Search for medicines not included in Couto 2016 (cladribine & ocrelizumab) Publication type: RCT Year of publication: -2018 Search date: 07.06.2018		
Embase	262	278
Ovid MEDLINE	38	
Web of Science (citation search on included studies)	845	692
Search 3: Search for rituximab use in MS Publication type: all study designs Year of publication: -2018 Search date: 22.05.2018		
Embase	1632	1974
Ovid MEDLINE	358	
Search 4: Search for registry studies of all included medicines Publication type: registry studies Year of publication: -2018 Search date: 12.10.2018		
Embase	298	253
Ovid MEDLINE	33	32
Web of Science	24	24
Search 5: Search in clinical trial registries Year of publication: -2018 Search date: 20.08.2018		
ClinicalTrials.gov	286	246
ICTRP (International Clinical Trials Registry Platform)	269	98
ISRCTN (International Standard Randomised Controlled Trial Number) Registry (including observational and interventional trials)	16	15
PROSPERO (International prospective register of systematic reviews)	7	5
EUnetHTA POP (Planned and Ongoing Projects) database	8	8
Search 6: Search for systematic reviews for adverse effects Year of publication: -2019 Search date: 15.01.2019		
Embase	163	160
Ovid MEDLINE	137	133
Total hits	6485	**5420**

Search strategies

Search 1. Update based on Couto 2016:

Embase 1974 to 2018 May 24, Ovid **MEDLINE**(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to May 23, 2018:

#	**Search**
1	Multiple sclerosis/ or Multiple sclerosis, chronic progressive/ or Multiple sclerosis, relapsing-remitting/ use ppezv [Medline]
2	Multiple sclerosis/ use oemezd [Embase]
3	((multiple or disseminated) adj sclerosis).tw.
4	sclerosis multiplex.tw.
5	((progressive or relapsing or remitting or aggressive or inflammatory or active) adj MS).tw.
6	(SPMS or PPMS or RRMS).tw.
7	MS.ti.
8	or/1-7
9	Fumaric acid dimethyl ester/ use oemezd
10	(dimethyl fumarate* or dimethylfumarate*).tw.
11	Teriflunomide/ use oemezd

12	teriflunomide.tw.
13	Interferon-beta/ use ppezv
14	Beta interferon/ use oemezd
15	(interferon adj1 beta*).tw.
16	Glatiramer/ use oemezd
17	(glatirameracetat* or glatiramer acetat*).tw.
18	Natalizumab/ use oemezd
19	natalizumab.tw.
20	Fingolimod/ use oemezd
21	fingolimod.tw.
22	Alemtuzumab/ use oemezd
23	alemtuzumab.tw.
24	or/9-23
25	8 and 24
26	limit 25 to "reviews (maximizes specificity)"
27	((systematic* or literature) adj2 (review* or overview*)).ti,ab.
28	25 and 27
29	or/26,28
30	limit 29 to yr="1995 -Current" [SR]
31	exp animals/
32	humans/
33	31 not (31 and 32)
34	25 not 33 [not animals]
35	limit 34 to "therapy (maximizes specificity)"
36	randomized controlled trial.pt. use ppezv [RCT-filter]
37	controlled clinical trial.pt. use ppezv
38	randomized.ti,ab. use ppezv
39	placebo.ab. use ppezv
40	clinical trials as topic.sh. use ppezv
41	randomly.ab. use ppezv
42	trial.ti. use ppezv
43	or/36-42
44	34 and 43 [RCT Medline]
45	randomized controlled trial/ use oemezd
46	crossover-procedure/ use oemezd
47	double-blind procedure/ use oemezd
48	single-blind procedure/ use oemezd
49	randomized.ab. use oemezd
50	placebo.ab. use oemezd
51	randomly.ab. use oemezd
52	trial.ti. use oemezd
53	or/45-52
54	34 and 53 [RCT Embase]
55	35 or 44 or 54 [RCT Embase Medline]
56	limit 55 to yr="2013 -Current" [RCT Embase Medline]
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.
58	(quality adjusted life or quality-adjust-life).mp.
59	(qaly* or qald* or qale* or qtime* or qali*).mp.
60	57 or 58 or 59
61	25 and 60
62	limit 61 to yr="2013 -Current"
63	remove duplicates from 56 [RCT 2013 > current]
64	limit 61 to yr="2015 -Current" [QALY]
65	"Cost Benefit Analysis"/ [Filter: Cost effect./-utility]
66	"Cost Effectiveness Analysis"/
67	"Cost Minimization Analysis"/
68	"Cost Utility Analysis"/
69	(cost adj (effectiveness or utility or utilities)).ti,ab.
70	cea.tw.

71	cua.tw.
72	Economic Evaluation/
73	Health economics/
74	(health economic? or economic evaluation?).tw.
75	Pharmacoeconomics/
76	((pharmacoeconomic? or pharmac*) adj economic?).tw.
77	(15D or HRQoL or health-related quality of life instrument).mp.
78	or/60,65-77 [Filter: Cost effect./-utility]
79	25 and 78
80	Cost-Benefit Analysis/
81	(cost adj (effectiveness or utility or utilities)).ti,ab.
82	cea.tw.
83	cua.tw.
84	Economics, Medical/
85	(health economic? or economic evaluation?).tw.
86	Economics, Pharmaceutical/
87	(pharmac* adj economic?).tw.
88	pharmacoeconomic?.tw.
89	(15D or HRQoL or health-related quality of life instrument).mp.
90	or/60,80-89 [Filter: Cost eff./ -utility]
91	25 and 90 [Economic Ev. Medline]
92	79 or 91 [Economic Eval. E and M]
93	remove duplicates from 92
94	limit 93 to yr="2015 -Current" [Economic Eval. Emb and MED]
95	94 use oemezd
96	94 use ppezv
97	limit 56 to yr="2015 -Current" [RCT Embase Medline]
98	(editorial or letter or note).pt.
99	97 not 98
100	remove duplicates from 99
101	100 use oemezd
102	100 use ppezv
103	limit 30 to yr="2015 -Current" [Update SR 20180524]
104	remove duplicates from 103
105	103 use oemezd
106	103 use ppezv

Search 2: Medicines not included in Couto 2016 (cladribine & ocrelizumab):

Embase 1974 to 2018 June 06; Ovid **MEDLINE**(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1	((Randomized Controlled Trial or Controlled Clinical Trial).pt. or Clinical Trials as Topic/ or (randomized or randomised or phase 3 or phase iii).ti,ab. or randomly.ab. or placebo.ab. or trial.ti.) use ppez
2	(randomized controlled trial/ or crossover-procedure/ or double-blind procedure/ or single-blind procedure/ or (randomized or randomised or phase 3 or phase iii).ti,ab. or randomly.ab. or placebo.ab. or trial.ti.) use oemezd
3	(Multiple sclerosis/ or Multiple sclerosis, chronic progressive/ or Multiple sclerosis, relapsing-remitting/ or ((multiple or disseminated) adj sclerosis).tw. or sclerosis multiplex.tw. or ((progressive or relapsing or remitting or aggressive or inflammatory or active) adj MS).tw. or (SPMS or PPMS or RRMS).tw. or MS.ti.) use ppez
4	(Multiple sclerosis/ or ((multiple or disseminated) adj sclerosis).tw. or sclerosis multiplex.tw. or ((progressive or relapsing or remitting or aggressive or inflammatory or active) adj MS).tw. or (SPMS or PPMS or RRMS).tw. or MS.ti.) use oemezd
5	(Cladribine/ or cladribin*.tw,kw,kf. or (chlorodeoxyadenosine or 2-Chloro-2'-deoxyadenosine or 2'-Deoxy-2-chloroadenosine).tw,kw,kf. or (Biodribin* or Hemobine* or Intocel* or Leustat* or Litak* or Litax* or Mavenclad* or Movectro* or Mylinax*).tw,kw,kf. or (RWJ 26251 or RWJ26251).mp.) use ppez
6	(Cladribine/ or cladribin*.tw,kw. or (chlorodeoxyadenosine or 2-Chloro-2'-deoxyadenosine or 2'-Deoxy-2-chloroadenosine).tw,kw. or (Biodribin* or Hemobine* or Intocel* or Leustat* or Litak* or Litax* or Mavenclad* or Movectro* or Mylinax*).tw,kw,tn. or (RWJ 26251 or RWJ26251).mp. or 4291-63-8.rn.) use oemezd

7	((ocrelizumab or Ocrevus*).tw,kw,kf. or (R1594 or PRO70769 or PRO 70769 or rhumab 2H7 or monoclonal antibody 2H7).mp.) use ppez
8	(Ocrelizumab/ or ocrelizumab.tw,kw. or Ocrevus*.tw,kw,tn. or (R1594 or PRO70769 or PRO 70769 or rhumab 2H7 or monoclonal antibody 2H7).mp. or 637334-45-3.rn.) use oemezd
9	1 and 3 and 5 [cladribine MEDLINE]
10	2 and 4 and 6 [cladribine Embase]
11	9 or 10 [cladribine MEDLINE+Embase]
12	remove duplicates from 11 [cladribine MEDLINE+Embase]
13	1 and 3 and 7 [ocrelizumab MEDLINE]
14	2 and 4 and 8 [ocrelizumab Embase]
15	13 or 14 [ocrelizumab MEDLINE+Embase]
16	remove duplicates from 15 [ocrelizumab MEDLINE+Embase]

Search 3. Rituximab use in MS

Embase 1974 to 2018 May 21, Ovid **MEDLINE**(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present, Database Field Guide

1	Multiple sclerosis/ or Multiple sclerosis, chronic progressive/ or Multiple sclerosis, relapsing-remitting/ use ppez
2	Multiple sclerosis/ use oemezd
3	((multiple or disseminated) adj sclerosis).tw.
4	sclerosis multiplex.tw.
5	((progressive or relapsing or remitting or aggressive or inflammatory or active) adj MS).tw.
6	(SPMS or PPMS or RRMS).tw.
7	MS.ti.
8	Rituximab/ use ppez
9	Rituximab/ use oemezd
10	rituximab.tw,kw,kf.
11	(Blitzima or Mabthera or Reditux or Ritemvia or Rituxan or Rituxin or Riximyo or Truxima or Tuxella).tw,kw,kf,tn.
12	(IDEC-C2B8 or IDEC-102).mp.
13	174722-31-7.rn.
14	(or/1-7) and (or/8-13)

Search 4. Registry studies of all included medications

Embase 1974 to 2018 October 12, Ovid **MEDLINE**(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to October 12, 2018

1	Multiple sclerosis/ or Multiple sclerosis, chronic progressive/ or Multiple sclerosis, relapsing-remitting/ use ppez [Medline]
2	Multiple sclerosis/ use oemezd [Embase]
3	((multiple or disseminated) adj sclerosis).tw.
4	sclerosis multiplex.tw.
5	((progressive or relapsing or remitting or aggressive or inflammatory or active) adj MS).tw.
6	(SPMS or PPMS or RRMS).tw.
7	MS.ti.
8	or/1-7
9	Fumaric acid dimethyl ester/ use oemezd
10	(dimethyl fumarate* or dimethylfumarate*).tw.
11	Teriflunomide/ use oemezd
12	teriflunomide.tw.
13	Glatiramer/ use oemezd
14	(glatirameracetat* or glatiramer acetat*).tw.
15	Natalizumab/ use oemezd
16	natalizumab.tw.
17	Fingolimod/ use oemezd
18	fingolimod.tw.
19	Alemtuzumab/ use oemezd
20	alemtuzumab.tw.
21	(Cladribine/ or cladribin*.tw,kw,kf. or (chlorodeoxyadenosine or 2-Chloro-2'-deoxyadenosine or 2'-Deoxy-2-chloroadenosine).tw,kw,kf. or (Biodribin* or Hemobine* or Intocel* or Leustat* or Litak* or Litax* or Mavenclad* or Movectro* or Mylinax*).tw,kw,kf. or (RWJ 26251 or RWJ26251).mp.) use ppez

22	(Cladribine/ or cladribin*.tw,kw. or (chlorodeoxyadenosine or 2-Chloro-2'-deoxyadenosine or 2'-Deoxy-2-chloroadenosine).tw,kw. or (Biodribin* or Hemobine* or Intocel* or Leustat* or Litak* or Litax* or Mavenclad* or Movectro* or Mylinax*).tw,kw,tn. or (RWJ 26251 or RWJ26251).mp. or 4291-63-8.rn.) use oemezd
23	((ocrelizumab or Ocrevus*).tw,kw,kf. or (R1594 or PRO70769 or PRO 70769 or rhumab 2H7 or monoclonal antibody 2H7).mp.) use ppez
24	(Ocrelizumab/ or ocrelizumab.tw,kw. or Ocrevus*.tw,kw,tn. or (R1594 or PRO70769 or PRO 70769 or rhumab 2H7 or monoclonal antibody 2H7).mp. or 637334-45-3.rn.) use oemezd
25	(Rituximab/ or rituximab.tw,kw,kf.) use ppez
26	(Rituximab/ or rituximab.tw,kw,kf.) use oemezd
27	(Blitzima or Mabthera or Reditux or Ritemvia or Rituxan or Rituxin or Riximyo or Truxima or Tuxella).tw,kw,kf,tn.
28	(IDEC-C2B8 or IDEC-102).mp.
29	174722-31-7.rn.
30	or/9-29
31	8 and 30
32	(Registries/ or Medical Record Linkage/ or Medical records systems, computerized/) use ppez or Register/ use oemezd
33	(((registry or registries or register or registers or database* or databank* or repositor*) adj3 multiple sclerosis) or (MS* adj (regist* or database or databank or repositor*)) or (regist* adj2 (stud* or data or analys* or report*)) or register based or panel data or (cohort adj2 (prospective or longitudinal)) or (longitudinal adj1 prospective) or ((real world or real life) adj2 (data or evidence or stud* or result* or outcome*)) or ((real world or real life) adj5 (data* or evidence or research or registry or registries or register or registers))).tw,kw,kf.
34	(((medical or patient) adj2 (register or registers or registry or registries)) or patient-relevant outcome*).tw,kw,kf.
35	or/32-34
36	31 and 35
37	remove duplicates from 36
38	37 use oemezd
39	37 use ppez
40	limit 38 to conference abstract
41	38 not 40 [result without Conference abstract]
42	40 use oemezd [Conference abstracts]

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