Natalizumab and Tyruko (natalizumab biosimilar) for treating highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy: a systematic review and economic model

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Keywords

Multiple Sclerosis; Systematic Reviews; Network Meta-analysis; Economic model

Abstract

Background

Multiple sclerosis (MS) is an immune-mediated inflammatory disease, causing long-term disability in young adults. Most cases begin as relapsing-remitting MS (RRMS). Some people have a form of RRMS known as highly active RRMS (HARRMS), defined as MS with unchanged or increased disease activity despite prior treatment with at least one disease-modifying therapy (DMT).

Objectives

To appraise the clinical and cost effectiveness of natalizumab (Tysabri) and natalizumab biosimilar (Tyruko) for treating HARRMS compared to other DMT.

Design

Systematic review with network meta-analysis (NMA) and economic model.

Results

We included 42 studies (22, 409 participants): 40 in people with RRMS and two in HARRMS. Six studies also reported data separately for HARRMS. Only four studies evaluated natalizumab or natalizumab biosimilar; none provided data on those with HARRMS. Follow-up ranged from 4 to 36 (median 24) months.

Most interventions reduced relapses (39 studies, 17 interventions) and MRI lesions (19 studies, 11 interventions for Gd+ lesions and 17 studies, 12 interventions for T2 weighted lesions) compared to placebo. Alemtuzumab, ocrelizumab, natalizumab, fingolimod and peginterferon beta 1a reduced disease progression compared to placebo (15 studies, 12 interventions). There were no differences in any adverse events (AEs) (24 studies, 16 interventions), serious AEs (30 studies, 14 interventions) or treatment related AEs (8 studies, no NMA) for any intervention compared to placebo. Fingolimod, glatiramer acetate, interferon beta 1a, interferon beta 1b and peginterferon beta 1a were associated with an increased treatment discontinuation (29 studies, 13 interventions). There was little evidence for a difference in quality of life. There was no evidence of a difference between natalizumab and natalizumab biosimilar for relapse rates (RR 0.65 (95% credible interval (CrI) 0.33, 1.23), Gd+ lesions (HR 1.29 (0.69, 2.37), T2 weighted lesions (HR 1.07 (0.73, 1.57)), any AEs (HR 1.06 (0.77, 1.46) or treatment discontinuation (HR 0.48 (0.13, 1.76)).

Data in HARRMS were available for fingolimod, ocrelizumab, alemtuzumab, cladribine, beta-interferon, AHSCT, and placebo. We also included one study on natalizumab conducted in a population that was close to our definition of HARRMS. All interventions except interferon beta 1a were associated with reduced relapse risk compared to placebo (6 studies; 7 interventions).

Compared with natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC, all treatments had greater net benefit at £20-30,000/QALY, with the only exception being ocrelizumab which had lower net benefits. Costs were generally higher on natalizumab than other treatments, though there was no difference in QALYs with 95% CrI completely overlapping. The results and conclusions were unchanged under all sensitivities. Value of information analysis found that the greatest contributor to decision uncertainty was the effectiveness of treatments.

Conclusions

There is no direct evidence on the effectiveness of natalizumab or its biosimilar in patients with HARRMS. Limited data suggest similar effectiveness in patients with RRMS. The economic model found that natalizumab and natalizumab biosimilar were not cost-effective compared to any of the included comparators in HARRMS, with the only exception being ocrelizumab.

Future work

There is need for studies of natalizumab and natalizumab biosimilar in people with HARRMS.

Study registration

The review was registered at PROSPERO (CRD42024556838).

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List of Abbreviations

Term	Definition
AE	Adverse Event
AHSCT	Autologous Haematopoietic Stem Cell Treatment
AI	Artificial Intelligence
APDDS	Adapted Patient Determined Disease Steps
ARR	Annualised Relapse Rate
AV	Atrioventricular
BCEA	Bayesian Cost-Effectiveness Analysis
BGR	Brookes-Gelman-Rubin
BNF	British National Formulary
CBA	Cost-Benefit Analysis
CC	Complication and Comorbidity
CDP	Confirmed Disease Progression
CE	Cost-Effectiveness
CEA	Cost-Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CEAF	Cost-Effectiveness Acceptability Frontier
CI	Confidence interval
CMA	Cost-Minimisation Analysis
CNS	Central Nervous System
CRD	Centre for Reviews and Dissemination
CrI	Credible Interval
CSF	Cerebrospinal Fluid
CUA	Cost-Utility Analysis
DCP	Disease Control Priorities
DES	Discrete Event Simulation
DESCEM	Discrete Event Simulation for Cost-Effectiveness Modeling
DIC	Deviance Information Criterion
DMD	Disease-Modifying Drug
DMT	Disease-Modifying Therapy
DP	Determiner Phrase
DSU	Decision Support Unit
EAG	External Assessment Group
EED	Economics Evaluations Database
EDSS	Expanded Disability Scale Status
EQ-5D	EuroQol 5 dimensions quality of life index
EBV	Epstein-Barr virus
EVPPI	Expected Value of Partial Perfect Information
FDA	Federal Drugs Agency
GP	Gaussian processes
GAM	Generalised Additive Models
GBP	Great Britain Pound
GBT	Generative Pre-Trained Transformer
HADS	Hospital Anxiety and Depression Scale

Term	Definition
HARRMS	Highly active relapsing remitting multiple sclerosis
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HLA	Human Leukocyte Antigen
HPV	Human Papillomavirus
HR	Hazard Ratio
HRG	Healthcare Resource Group
HRQoL	Health Related Quality of Life
HS	Health State
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ICTRP	International Clinical Trials Registry Platform
IFNB	Interferon beta
IQR	Interquartile range
ISPOR	International Society for Outcomes Research
ITT	Intention to treat
IM	Intramuscular injection
IV	Intravenous
JC	John Cunningham human polyomavirus
LCI	Lower Confidence Interval
MCMC	Markov Chain Monte Carlo
MD	Mean Difference
MLMC	Multilevel Monte Carlo
MPES	Multiparameter evidence synthesis
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NA	Not Applicable
NCT	National Clinical Trial
NHS	National Health Service
NHS EED	NHS Economic Evaluations Database
NI	No information
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMA	Network Meta-Analysis
NR	Not Reported
PCR	Polymerase chain reaction
PICO	Patient, Population or Problem; Intervention; Comparison; Outcome (Cochrane)
PML	Progressive Multifocal Leucoencephalopathy
POCT	Point-Of-Care-Testing
PPMS	Primary Progressive Multiple Sclerosis
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomized Controlled Trial
RES RRMS	Rapidly Evolving Severe Relapse Remitting Multiple Sclerosis

Term	Definition
RR	Rate Ratio
RRMS	Relapse Remitting Multiple Sclerosis
SAD	Sustained Accumulation of Disability
SC	Subcutaneous injection
SD	Standard deviation
SE	Standard error
SF-36	Self-Reported-36 quality of life index
SLR	Systematic Literature Review
SMDM	Society for Medical Decision Making
SOT RRMS	Sub-Optimally Treated Relapse Remitting Multiple Sclerosis
SPMS	Secondary Progressive Multiple Sclerosis
TA	Technology Appraisal
TAG	Technology Assessment Group
TIA	Transient Ischaemic Attack
TSD	Technical Support Document
UCI	Upper confidence interval
UK	United Kingdom
UME	Unrelated Mean Effects
UVB	Ultraviolet B light
VEP	Visually Evoked Potential
VOI	Value-Of-Information
WTP	Willingness-To-Pay
WHO	World Health Organisation

Plain English Summary

What is the problem?

Multiple sclerosis (MS) is a common lifelong condition affecting the brain and spine. It can cause symptoms like vision problems, trouble with balance, movement, thinking, and bladder or bowel control. MS often starts in early adulthood and usually worsens over time, though this varies.

The exact cause of MS is unclear, but factors like genetics, vitamin D levels, inflammation, smoking, and viral infections may increase the risk. Treatments can manage symptoms, slow disease progression, and improve quality of life.

Most people with MS have relapsing-remitting MS (RRMS), marked by relapses—periods when symptoms worsen or new ones appear, lasting weeks or months. Symptoms may improve after a relapse but often leave lasting effects. Some patients, known as having "highly active RRMS (HARRMS)", continue to have relapses despite treatment and may need different medications.

What did we do?

We wanted to know whether a drug called natalizumab (Tysabri) and similar drug known as natalizumab biosimilar (Tyruko) are effective and safe for patients with HARRMS, when compared with other drugs already in use for these patients. We also wanted to know whether using these drugs is a good use of NHS money. We looked at existing research and developed cost models to answer these questions.

What did we find?

No studies were found that specifically evaluated Tysabri or Tyruko in people with HARRMS. However, four studies in people with RRMS showed these drugs seemed equally effective for this group. Evidence from other treatments suggests that drugs effective in general RRMS also work well in HARRMS, so it's reasonable to expect that Tysabri and Tyruko might have similar results for these patients. However, evidence from our cost model suggested that these drugs do not represent good value for money compared to other treatments for MS.

Word count: 271

Scientific Summary

Background

Multiple sclerosis (MS) is a chronic autoimmune condition that affects the central nervous system, usually starting in early adulthood and often causing long-term disability in young adults. Symptoms can vary but commonly include fatigue, muscle weakness, vision problems, and cognitive issues. In the UK, around 130 in every 100,000 people are affected. Most cases (85–90%) begin as relapsing-remitting MS (RRMS), with periods of relapses and remissions, which can later progress to secondary progressive MS (SPMS). A smaller group have primary progressive MS (PPMS) from the start. RRMS can be further categorised based on disease activity. Highly active RRMS (HARRMS), the focus of this appraisal, is broadly defined as MS with unchanged or increased disease activity—clinically or radiologically—despite prior treatment with at least one disease-modifying therapy (DMT). Management typically includes multidisciplinary care and DMTs to reduce relapses and slow progression.

Objectives

The overall aim was to appraise the clinical and cost effectiveness of natalizumab (Tysabri) and natalizumab biosimilar (Tyruko) within their marketing authorisations for treating HARRMS after at least one disease modifying therapy.

Methods

Clinical effectiveness review

We conducted a systematic literature review (SLR) with network meta-analysis (NMA). As we did not expect to find many RCTs in people with HARRMS, we broadened inclusion to people with RRMS. We included RCTs that compared one of the interventions (natalizumab or natalizumab biosimilar) or comparators of interest (glatiramer acetate, interferon beta-1a, interferon beta-1b, peginterferon beta-1a, alemtuzumab, cladribine tablets, fingolimod, ocrelizumab, ofatumumab, ponesimod, and AHSCT) to each other or to placebo.

We searched MEDLINE, EMBASE and trial registries from inception to April 2024. We screened existing relevant technology appraisals, SLRs and submissions from manufacturers of natalizumab and natalizumab biosimilar.

Title and abstract screening and assessment of full text papers were conducted by two reviewers independently. Data extraction and risk of bias assessment were performed by one reviewer and checked by a second. Risk of bias was assessed with the RoB 2 tool at the outcome level. We extracted and synthesized data on the following outcomes:

- Annualised relapse rate (ARR)
- Disability progression confirmed at 3 and 6 months (CDP3 and CDP6)
- MRI measurements (proportion of participants with gadolinium enhancing (Gd+) or new or enlarging T2 lesions)
- Adverse effects (AEs) of treatment (any AEs, treatment related AEs, serious AEs, AEs leading to treatment discontinuation)
- Health-related quality of life assessed using the EQ-5D or SF-36 scales

For each outcome, we provided a narrative summary of study details, risk of bias, and results. Bayesian random and fixed effects NMA was performed to compare the efficacy and safety of treatment options using the available trial information. Most treatments were not compared in head-to-head RCTs, and NMA allowed for the use of indirect information to make that comparison. We selected the model (random vs fixed effects) that provided the best fit to the data. We presented results as comparisons of each intervention in the network with placebo, mean ranking of each intervention, probability that each intervention would rank first or in specific positions, and a pairwise comparison of each intervention included in the network. Bayesian 95% credible intervals (CrI) were used to represent uncertainty. We used the R package 'multinma' for all analyses.

Cost-effectiveness

We undertook an independent economic assessment using a Discrete Event Simulation (DES) individual patient model. Previous NICE Technology Assessments (TAs) have been criticised as they did not capture treatment sequencing and that they were unable to accurately reflect the course of the condition. Our DES aimed to overcome these limitations by using by modelling of treatment sequences

To design the model, we reviewed models used in previous NICE TAs. These used very similar Markov multistate models based on EDSS severity with transition rates informed by the British Columbia Multiple Sclerosis registry and London Ontario MS databases and treatment effects by individual trials and NMA. Our DES modelled EDSS as an individual attribute, aligning with the structure of the prior models. We also included attributes for age, sex, SPMS status and current treatment. Simulated events were EDSS increase, EDSS decrease, SPMS progression, relapse, SAEs, treatment discontinuation, and death. Patients could switch treatment twice, meaning that up to 4th line therapy was modelled. Patients who progressed SPMS could experience the events EDSS increase, relapse, SAEs, and death.

Event rates were informed by a combination of new analyses conducted by the UK MS Registry and treatment effects of ARR and CDP6 estimated by the NMA. Baseline SAEs and discontinuation came from AFFIRM and ANTELOPE with treatment effects from the NMA. Rates in the SPMS population were informed by the MS Registry analyses as no treatment effects were assumed. Our approach to costs and utilities were aligned with previous TAs. The cost of John Cunningham human polyomavirus (JCV) testing was included for both natalizumab and natalizumab biosimilar as clinical advice was that the manufacturer scheme of paying for JCV testing is not widely available. The economic model was implemented in the R programming language using the DESCEM package and the code was validated by an independent analyst at the consultancy Evidera. The model precited EDSS severity over time was validated by comparison to a Markov model prediction.

The selected base case analysis used the HARRMS population from the MS Registry for baseline rates and the base case selection from the NMA results. Sensitivity analyses were conducted using the All RRMS estimates from the MS Registry, switching to alternative NMA sensitivities, excluding the price of JCV testing for natalizumab-IV and natalizumab-SC (not

the biosimilar), reducing the natalizumab-SC treatment administration costs, and using mortality rates that vary with EDSS. Value of information analysis was used to assess the impact on parameter uncertainty and identify the most influential parameters. The Expected Value of Partial Perfect Information (EVPPI) was estimated for each of the NMA treatment effects, all costs, all utilities, the MS registry baseline rates, the baseline discontinuation rate, and the baseline SAE rate.

Results

We included 42 studies (22, 409 participants): 40 reported data for a general RRMS population and two were conducted in HARRMS. Six studies reported data separately for those with HARRMS. Only four studies evaluated Natalizumab or Natalizumab biosimilar, the technologies of interest for this appraisal; none provided data on those with HARRMS. AHSCT was only evaluated in people with HARRMS.

General RRMS population

All studies were considered to be sufficiently similar for inclusion in the NMAs. The fixed effect model gave the best fit to the data with little evidence of heterogeneity for all outcomes.

ARR (39 studies, 20, 810 participants; 17 interventions)

Follow-up ranged from 4 to 36 (median 24) months. Most interventions were associated with a greater reduction in the risk of relapses compared to placebo (i.e., RR<1 AND 95% CrI excluding 1.00). There was no evidence of a difference between natalizumab and natalizumab biosimilar (RR 0.65 (95% CrI 0.33, 1.23). Seventeen (44%) studies were at low risk of bias, 15 (38%) had some concerns regarding risk of bias, and 7 (18%) were at high risk of bias. Sensitivity analysis restricted to studies at low risk of bias showed similar results.

Disease Progression (23 studies; 12 interventions)

Studies on teriflunomide, ponesimod and ofatumumab did not connect to the network and studies of natalizumab biosimilar and glatiramer acetate SC40 did not report on disease progression, and those on interferon beta 1a SC22 only reported data on CDP3. Fifteen studies (10, 635 participants; 11 interventions) reported CDP3 and fourteen studies (9,306 participants; 10 interventions) reported CDP6. Alemtuzumab, ocrelizumab, natalizumab, fingolimod and peginterferon beta 1a were associated with a lower risk of both CDP3 and CDP6. Six studies were judged at low risk of bias, nine at some concerns and five at high risk of bias.

MRI Outcomes (20 studies; 12 interventions)

Follow-up ranged from 4 to 24 (median 24) months. There were no data on MRI outcomes for studies of ofatumumab, glatiramer acetate (SC40), ponesimod, teriflunomide, and peginterferon beta 1a. Data were only available for T2 lesions for interferon beta 1a (SC22).

Nineteen studies (9, 471 participants; 11 interventions) reported data on Gd+ lesions and seventeen studies (8,883 participants; 12 interventions) on T2 weighted lesions. All interventions were associated with a greater reduction in the risk of developing MRI lesions compared to placebo, with the exception of interferon beta 1a SC44 for T2 weighted lesions. There was no evidence of a difference between natalizumab and natalizumab biosimilar (HR 1.29 (0.69, 2.37) for Gd+ lesions or for T2 weighted lesions (HR 1.07 (0.73, 1.57)).

Adverse events (36 studies)

Follow-up ranged from 6 to 24 months (median 18 months) follow-up. Twenty four studies (9, 471 participants; 16 interventions) reported data on **any adverse events** – data were not available for interferon beta 1a (SC22). Thirty studies (18, 748 participants; 14 interventions) reported data on **SAEs** – data were not available for interferon beta 1a (SC22), cladribine or natalizumab biosimilar. There was no evidence of a difference in the risk of developing any AEs or serious AEs between any of the interventions and placebo. There was no evidence of a difference between natalizumab and natalizumab biosimilar 1.06 (0.77, 1.46) in the risk of any AEs; data were not available for serious AEs. Only eight studies (n=3,361) reported data on **treatment related adverse events**. These did not create a connected network and so an NMA was not possible. There was no evidence of a difference in AEs within any of the studies.

Twenty nine studies (17,892 participants) reported data on **AEs leading to treatment discontinuation**. These did not create a completely connected network – teriflunomide, ponesimod and ofatumumab did not connect to the network and data were not available for interferon beta 1a (SC22). Fingolimod, glatiramer acetate, interferon beta 1a, interferon beta 1b and peginterferon beta 1a were associated with an increased risk of treatment discontinuation compared with placebo. There was no evidence of a difference between natalizumab and natalizumab biosimilar (HR 0.48 (0.13, 1.76)).

Twenty studies were judged at low risk of bias for adverse events, eleven at some concerns and five at high risk of bias.

Quality of life

Only eight studies reported quality of life assessed using the EQ-5D or SF-36 tools. Interventions evaluated were cladribine, fingolimod, peginterferon beta and glatiramer acetate vs placebo and alemtuzumab vs interferon beta 1a. There was little evidence for a difference in quality of life in any of these studies.

HARRMS population

We had data for 6 studies that evaluated fingolimod, ocrelizumab, alemtuzumab, cladribine, beta-interferon, AHSCT, and placebo in people with HARRMS. Three studies were at high risk of bias, one had some concerns, and two were low-risk.

Five studies reported data on ARR. As there were no studies on natalizumab in people with HARRMS, we included one study that compared natalizumab with placebo in a population where participants were required to have had at least one relapse in the previous year and a very high proportion of participants (88%) had previously been treated with a DMT. A connected network for ARR was formed by combining two interferon beta 1a comparators. The network included six studies (2,162 participants) of seven interventions. All interventions except interferon beta 1a, were associated with a reduced ARR compared to placebo, with natalizumab and ocrelizumab ranking highest.

As we only had data on a limited number of interventions in HARRMS, to allow direct comparisons between RRMS and highly active populations, we conducted a sensitivity analysis in RRMS where we restricted the network to the eight interventions in the network for ARR in the highly active population. Results were very similar, although 95% CrI were wider in the highly active population. CDP data were limited and disconnected, but all evaluated interventions reduced progression risk. MRI, QoL and adverse events outcomes were only evaluated in one or two studies and so there was insufficient information on these outcomes to draw conclusions.

Cost-effectiveness

The clinical review found no evidence on autologous haematopoietic stem cell transplantation so this was not included in the economic model. The NMA estimates in all RRMS were used for treatment effects on CDP6, ARR, SAEs, and discontinuation due to AEs, as only limited data were found for HARRMS.

Base case results used 1000 patients and 1000 samples while sensitivities used 100 patients and 100 samples; the lower number were found sufficient for stable results by convergence checks. Validation of EDSS severity over time found less severe trend that was explained by the comparator model mixing RRMS and SPMS patients and not using the latest DMT sequences.

Compared with natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC, all treatments had greater net benefit at £20-30,000/QALY, with the only exception being ocrelizumab. The natalizumabs had close to 0% chance of having highest net benefit at £20-30,000/QALY. Costs were generally higher on natalizumab than other treatments, though there was no difference in QALYs with 95% CrI overlapping. Natalizumab-IV has lower mean net benefit at £20-30,000/QALY than natalizumab biosimilar-IV, although the 95% CrI overlap. Natalizumab-SC has very similar mean net benefit to Natalizumab-IV. The 95% CrI for costs and QALYs on natalizumab biosimilar-IV also overlapped with those for natalizumab-IV suggesting no difference. Natalizumab-SC has very similar costs and QALYs to natalizumab-IV, again with no evidence of a difference.

Conclusions were unchanged under all sensitivities. EVPPI estimates indicated the parameters with greatest impact were the NMA treatment effects on ARR, CDP6, SAEs, and

discontinuation. However, costs, utilities, and MS registry rates, also had substantial impact on the results indicating high parameter uncertainty.

Conclusions

There is no direct evidence on the effectiveness of natalizumab or its biosimilar in patients with highly active disease. Limited data indicate that both treatments show similar effectiveness in patients with RRMS. Comparisons of DMT effectiveness in people with highly active disease and general RRMS suggest that DMTs are at least as effective in the highly active population, although this is based on sparse data. Assuming natalizumab and its biosimilar follow this trend, they may also be effective in this group. However, trials specifically targeting this population are needed to confirm these assumptions.

The economic model used evidence on treatment effects in the general RRMS population and baseline rates in highly active RRMS. Natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC were not cost-effective compared to any of the included comparators in highly active RRMS, with the only exception being ocrelizumab. The greatest decision uncertainty was found in the treatment effects, again supporting the need for trials targeting this population.

Study registration

The review was registered at PROSPERO (CRD42024556838).

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1 Background

Sections of this Chapter have been reproduced from the study's Protocol document, available at the NICE website.[1]

1.1 Multiple sclerosis

Multiple sclerosis (MS) is a chronic, inflammatory, neurological immune mediated inflammatory disease that affects the central nervous system (CNS), which includes the brain and spinal cord.[2] MS usually presents in early adult life and is the most common cause of non-traumatic disabling disease in young adults.[2-4] In MS, the immune system mistakenly attacks the protective covering of nerve fibres called myelin, causing inflammation and damage. This disrupts the normal flow of electrical impulses along the nerves. Inflammation can also lead directly to damage to axons, leading to their degeneration or loss. Axonal loss contributes significantly to the neurological symptoms and disability observed in people with MS.

The symptoms of MS vary widely and can include bladder and bowel dysfunction, cognitive changes, gait disturbance, fatigue, muscle weakness, numbness or tingling, difficulty with coordination and balance, and problems with vision.[2, 3]. It is not clear what causes MS, but a number of theories have been proposed. These include the “outside in” and “inside out” pathways. With the “outside in” model it is hypothesised that an unknown factor triggers the autoimmune response peripherally (outside the Central Nervous System (CNS)), instigating the immune system to begin to invade the CNS, starting the process of demyelination characteristic of MS. The “inside out” model suggest that primary damage of the myelin as the cause of MS, leading to an autoimmune attack which results in further inflammatory demyelination.[5] A number of factors have been associated with the risk of developing MS, these include genetic abnormalities, environmental factors such as vitamin D or ultraviolet B light (UVB) exposure, obesity, smoking and viral infection.[5, 6] More recently a compelling link has been established between Epstein-Barr virus (EBV) and MS – being negative for EBV protects against MS, whereas a history of exposure doubles the risk of developing MS.[6, 7] A number of genes have been found to be associated with MS. The main genetic risk is with the Human Leukocyte Antigen (HLA) HLA-DRB1*15, although genome wide association studies have identified over 200 independent genome-wide significant associations outside the major histocompatibility complex (MHC) and 32 within the MHC region and over 550 candidate risk genes.[8]

MS has a significant impact on individuals' quality of life and imposes a substantial burden on healthcare systems and society as a whole.[3] A recent cross-sectional study of almost 17,000 participants with MS from across 16 countries found that work capacity declined from 82% to 8%, and that quality of life declined from normal population values to less than zero, indicating that the negative aspects of an individual’s life outweigh the positive impacts, as disability became more severe with advancing disease.[3] MS may reduce life expectancy with a recent study estimating life expectancy to be 75.9 years in an MS population compared to 83.4 years in a population matched on sex, age, and region.[9] While

there is currently no cure for MS, treatments are available to help manage symptoms, slow disease progression, and improve quality of life for individuals with MS.

1.2 Epidemiology of MS

MS is estimated to have a global prevalence of over 2.8 million cases (35.6 per 100 000 population), although this may be an underestimate due to the lack of data from large populations including China and India.[10] Incidence and prevalence is increasing in both developed and developing countries.[10]

Estimates of incidence vary across studies, with higher prevalence rates observed in regions further from the equator, particularly in Europe, North America, and parts of Australasia.[4, 6] A 2020 multi-national study reported a pooled incidence rate across 75 studies that provided data as 2.1 per 100 000 persons/year.[10] The prevalence of MS tends to increase with distance from the equator, although there are exceptions to this pattern.[6] The reasons for this geographic variation are not fully understood but may involve a combination of genetic, environmental, and lifestyle factors. Distance from the equator is also associated with UVB exposure which stimulates vitamin D production – low levels of vitamin D have been associated with MS.[6] Migration studies have shown that migrants from low risk countries (e.g. the West Indies) to Europe remain at low risk of developing MS, however children born to migrants in Europe are at high risk.[6] This suggests that environment over-rules genetics, suggesting that prevention should focus on environmental risk factors.

In the United Kingdom (UK), MS is a relatively common neurological condition, with an estimated prevalence of around 130 cases per 100,000 population, with an estimated 7,000 new cases each year.[11] The prevalence of MS in the UK is among the highest in Europe. MS affects people of all ages, but it is most commonly diagnosed in young adults, typically between the ages of 20 and 40. Women are about two to three times more likely to develop MS than men, although in the early 1900s the sex ratio was almost equal.[6] A reason for this change may be the changing prevalence of smoking in women over time – before the first world war very few women smoked. The incidence and prevalence of MS in the UK have been increasing over time, although this trend may be partially attributed to improvements in diagnostic methods and increased awareness of the condition.

1.3 Clinical pathway

1.3.1 Clinical presentation

MS is usually first suspected when a patient presents with what is known as a “clinically isolated syndrome” (CIS), this occurs as result of lesions in the brain or spinal cord and presentation will depend on the location of the lesion. The most frequent presentations include unilateral optic neuritis, brainstem syndromes (e.g. intranuclear ophthalmoplegia, vertigo, hearing loss, facial sensory disturbance) and focal sensory disturbance (e.g. limb paresthesias) although many other presentations exist.[6, 12]

1.3.2 Diagnosis of multiple sclerosis

The diagnosis of multiple sclerosis (MS) is primarily a clinical diagnosis, supported by investigations including imaging and cerebrospinal fluid (CSF) analysis. The key features required for a diagnosis of MS are dissemination in time and space – this involves looking for evidence of disease activity affecting different parts of the CNS across different points in time. Differential diagnosis of MS can be challenging, particularly in the early stages, as many other disorders have similar clinical presentations and paraclinical findings to MS.[13] The 2022 NICE guidelines on the diagnosis and management of MS recommend that people suspected of having MS should be referred for diagnosis by a consultant neurologist or specialist under their supervision.[14]

Diagnostic criteria have evolved over time from the first criteria proposed by Jean-Martin Charcot as early as 1868[15] to the most recently published 2017 McDonald criteria.[16] The McDonald criteria were first developed by an international committee of neurologists and published in 2001.[17] These were updated in 2005, 2010 and most recently in 2017[16] – these are the current criteria recommended for diagnosis of MS by NICE. A 2024 update was announced at the recent ECTRIMS 2024 conference,[18] but these have not yet been published. These are expected to allow for an earlier diagnosis than previous versions of the criteria. Table 1 provides an overview of the 2017 McDonald criteria for diagnosing MS. These follow the principle of aiming to detect evidence of dissemination in time and space.

Table 1 2017 Revised McDonald criteria for diagnosing MS[16]

Number of attacks at clinical presentation	Number of lesions with objective clinical evidence	Additional data needed for diagnosis of MS
≥2	≥2	None
≥2	1 + clear cut historical evidence of a previous attacking involving a lesion in a distinct anatomical location	None
≥2	1	Dissemination in space demonstrated by additional clinical attack implicating a different CNS site *OR* by MRI
1	≥2	Dissemination in time demonstrated by an additional clinical attack *OR* by MRI *OR* demonstration of CSF-specific oligoclonal bands
1	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site OR by MRI AND Dissemination in time demonstrated by an additional clinical attack OR by MRI OR demonstration of CSF-specific oligoclonal bands

Magnetic resonance imaging (MRI) can be used to detect changes in white matter lesions in the brain. It is not sufficiently accurate to be used alone for the diagnosis of MS, but can be helpful in addition to clinical features.[19] CSF analysis involves detection of oligoclonal bands as a surrogate marker of dissemination in space.[20] The presence of oligoclonal bands (bands of immunoglobulin) provides evidence of local immunoglobulin synthesis which occurs most commonly in MS, but can also be found in other conditions and so the finding is not specific for the diagnosis of MS.[21] Findings of elevated CSF protein or significant pleocytosis or the presence of neutrophils is not typical of MS and so suggests an alternative diagnosis. The McDonald 2017 criteria allow for a greater role of MRI and CSF than previous versions, allowing for an earlier diagnosis of MS. This is particularly important as new, earlier aggressive treatments become available for MS; it is important to identify patients with MS so that they can receive treatment as soon as possible, but it is equally important that people are not wrongly diagnosed with MS and given inappropriate treatment with these aggressive treatments.[22] Visually evoked potentials (VEP) have previously been suggested as useful for the diagnosis of MS. These are electrical signals recorded from the brain's occipital lobe in response to visual stimuli, used to assess the integrity of visual pathways, with an abnormal VEP suggesting a second lesion if the clinical presentation did not include the visual pathway. However, these are not included in the current diagnostic criteria due to insufficient evidence.[23]

1.3.3 Measurement of progression

Disease activity and progression are measured using MRI activity, incidence of relapses and short-term (3-6 month) progression in disability.[12] MRI measures of disease activity include the development of new T2 lesions, enlarging T2 lesions, and gadolinium-enhancing lesions. T2 lesions are areas of abnormal signal intensity seen on T2-weighted MRI scans, commonly indicating water content or inflammation in tissues. In MS, T2 lesions often represent areas of demyelination or damage in the brain and spinal cord, providing insights into disease activity and progression. Gadolinium-enhancing lesions are areas of the brain that show increased uptake of gadolinium-based contrast dye during MRI scans, indicating active inflammation. These lesions are used to identify active disease processes, distinguish new lesions from older ones, and to monitor treatment response. Disability is measured using the Expanded Disability Status Scale (EDSS) – this quantifies the accumulation of permanent disability. Scores range from 0 (no disability) to 10 (death) and are measured in incremental units of 0.5 (from EDSS 1). Scores are based on measures of impairment across the eight functional symptoms:[24]

1. Pyramidal Functions: weakness or difficulty in moving limbs
2. Cerebellar Functions: ataxia, loss of coordination, or tremor
3. Brain Stem Functions: problems with speech, swallowing, and nystagmus involuntary eye movement)
4. Sensory Functions: numbness or loss of sensations
5. Bowel and Bladder Functions
6. Visual (or Optic) functions
7. Cerebral (or Mental) Functions

8. Other Functions (neurologic findings)

To provide an accurate and reliable evaluation of confirmed disability progression (CDP), two consecutive examinations should be carried out by the same physician at least 6 months apart. Although EDSS is commonly used it does not capture some important aspects of the impact of MS, particularly on quality of life. It is also prone to bias as it is a subjective measure and so open to investigator bias and is also heavily influenced by mobility.

1.3.4 Classification of MS

MS presents on a continuum from relapsing to progressive disease, with distinctions currently made between different types of disease. Some see this as an artificial distinction as they force cases into distinct boxes, which does not reflect the continuum of illness.[6] Most cases of MS (85-90%) are characterised by relapses followed by periods of remission – known as "relapsing remitting MS" (RRMS). A relapse generally develops over a period of hours to days, then reaches a plateau lasting several weeks, followed by a period of gradual recovery. The nature of the relapse is dependent on the region of the CNS affected by the acute demyelinating lesion, and also by the extent of the inflammation.[4] Although initial relapses can lead to complete recovery, there is often some damage left behind by the relapse, with overall disability increasing slightly after each relapse.[25] As neuronal damage increases, recovery from disability becomes incomplete leading to further disability.[6] RRMS is further subcategorised depending on disease activity and response to treatment. There is a lack of consensus regarding the definitions for the varying subtypes of disease, with different appraisals and studies using slightly different definitions. Table 2 provides an overview of the different subclassification of RRMS, with suggested definitions for each. The population of interest for this appraisal is "highly active disease" (highlighted blue in the table). We provide a very broad definition for this population to encompass most of the variety of different definitions used in existing appraisals and studies.

Table 2 Overview of subclassifications of RRMS[26]

Classification	Definition
Active disease	≥Two clinically significant relapses within the last 2 years. (Any motor relapse, any brainstem relapse, a sensory if it leads to functional impairment, a relapse leading to sphincter dysfunction, optic neuritis, intrusive pain lasting more than 48 hours)
Highly active disease	No consensus definition; previous appraisals for NICE have used different definitions. We will use the following broad definition for this appraisal to encompass the variety of different definitions used in existing trials: *Unchanged or increased clinical or radiological evidence of disease activity despite treatment with at least one Disease Modifying Therapy (DMT)*
Rapidly evolving severe (RES) disease	≥Two disabling relapses in 1 year and MRI changes (one or more gadolinium-enhancing lesions or a significant increase in T2 lesion load compared with a previous MRI). A disabling relapse is defined as any relapse which fulfils one or more of the following criteria: • Affects the patient's social life or occupation, or is otherwise considered disabling by the patient

Classification	Definition
	• Affects the patient's activities of daily living as assessed by an appropriate method • Affects motor or sensory function sufficiently to impair the capacity or reserve to care for themselves or others • Needs treatment/hospital admission.[26]

After 10-15 years RRMS typically develops into "secondary progressive MS" (SPMS), characterised by a gradual progression from discrete relapses to disease that progresses slowly.[23] A smaller proportion have a progressive onset from the start, known as "primary progressive MS" (PPMS). The proportion of patients with PPMS has decreased over time, but this may be an artificial change, caused by patients being more commonly labelled as having RRMS so that they are eligible for some of the newer treatments,[6] or be a result of better ascertainment of relapses leading to more people being identified as having RRMS. PPMS is more common in those presenting in later life (over age 60 years).[4]

1.3.5 Management of MS

Management of MS typically involves a multidisciplinary approach, including medical treatment to manage symptoms and modify disease progression, rehabilitation therapies, and support services to address the physical, cognitive, and emotional challenges associated with the condition. The pathway may vary depending on the subtype of MS, disease severity, individual patient factors, and treatment goals. The MS treatment pathway is dynamic and individualized, requiring ongoing collaboration between patients, healthcare providers, and interdisciplinary teams to optimize outcomes and quality of life for individuals living with MS. NICE guidelines recommend that people with MS should have a comprehensive review of all aspects of their care at least once a year.[12, 14]

Symptomatic management focuses on alleviating symptoms associated with MS, such as fatigue, mobility problems, spasticity, oscillopsia, emotional lability, pain, cognitive and memory problems, ataxia, tremor and dystonia. Symptomatic treatments may include medications, physical therapy, occupational therapy, speech therapy, cognitive rehabilitation, assistive devices, and lifestyle modifications.[14] Acutely, relapses are often treated with corticosteroids and, sometimes, plasma exchange.[27]

Disease-modifying therapies (DMTs) are the cornerstone of treatment for relapsing forms of MS. DMTs aim to reduce the frequency and severity of relapses, delay disability progression, and decrease the number of lesions observed on MRI scans.[12] They work by modifying the course of MS by supressing or modulating immune function. Various DMTs are available, including injectable medications, oral agents, and infusion therapies, each with different mechanisms of action and side effect profiles. Interferon beta-1b was the first DMT to be approved by the Federal Drugs Agency (FDA) in 1993. This was followed by interferon beta-1b and glatiramer acetate. These drugs were generally well tolerated and have a modest impact on the frequency of relapses.[28] Prior to this a variety of immunosuppressive agents

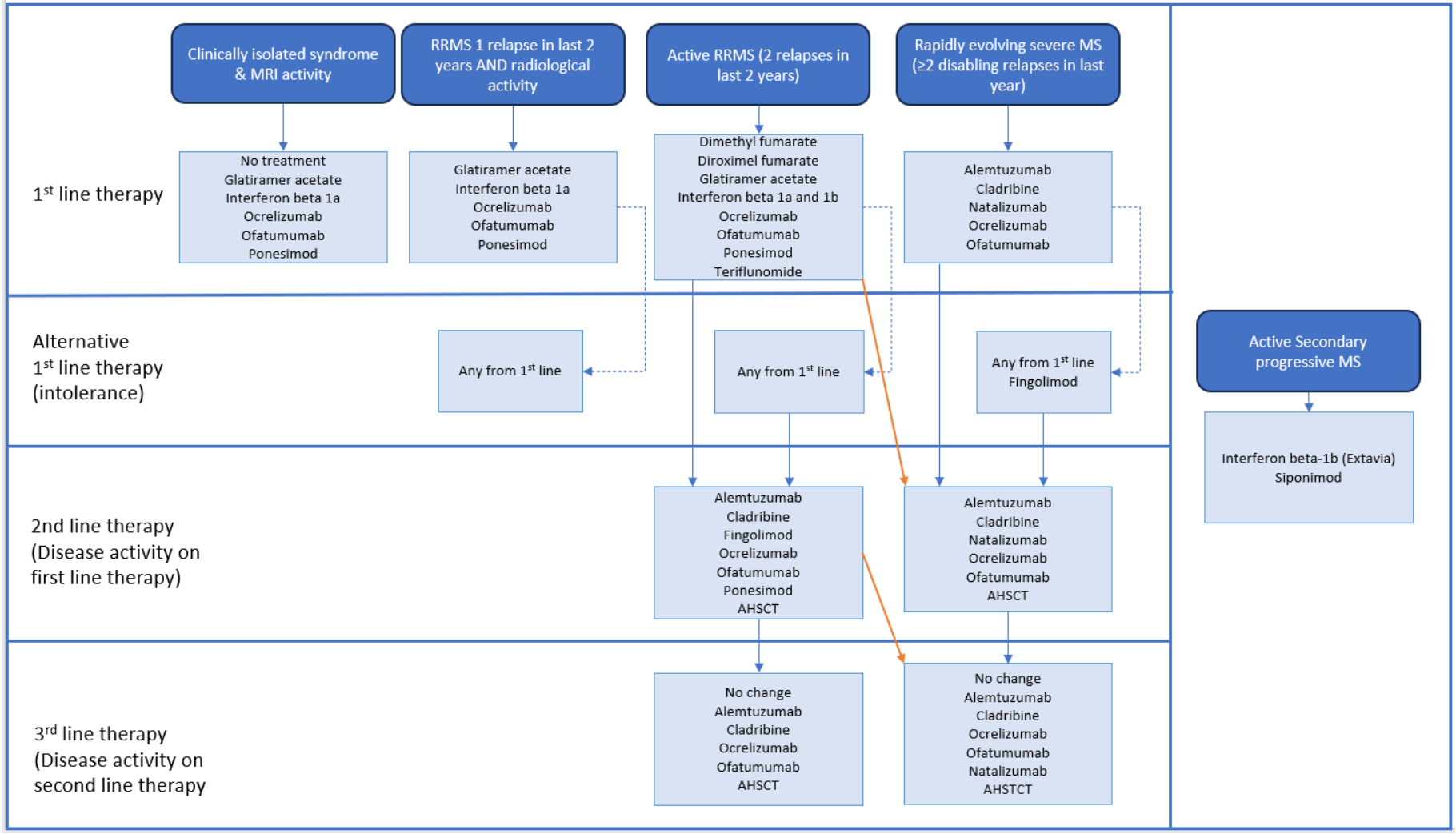
were used to treat MS including azathioprine, methotrexate, mycophenolate mofetil, intravenous immunoglobulin, and corticosteroids.[28]

More recently many MS specific DMTs have become available.[28]
Table 3 provides an overview of the DMTs that have been appraised by NICE. It also highlights which DMTs are included in the scope for this appraisal – interventions and comparators are shown in cells shaded blue in the table, interventions are also highlighted in bold. NHS England have developed a treatment algorithm for DMTs within the NHS. Different treatment options are recommended based on initial presentation.[29] The recommendations for RRMS are summarized in Figure 1. An additional treatment option is *autologous haematopoietic stem cell transplantation*. This involves collecting a patient's healthy stem cells from the blood or bone marrow before treatment, storing this and then giving it back to the patient after treatment. A growing body of evidence suggests that this can induce prolonged remission in patients with RRMS.[28]

Patients who progress to SPMS are managed with Interferon beta-1b (Extavia) or Siponimod if they meet the following starting criteria:

- Patient is able to walk 10 m or more (EDSS less than 7.0)
- >18 years-old
- No contraindications
- Patient has been informed of and agreed to stopping criteria
- For Siponimod, there is also a requirement of active disease (relapses or imagine features of inflammatory activity).[30]

Figure 1 NHS England treatment algorithm for MS DMTs



Orange arrows show treatment pathways for patients with active RRMS who develop RES

AHSCT: autologous haematopoietic stem cell treatment.

Table 3 Overview of DMTs for adults with MS together with details of marketing authorisation and NICE recommendations

Pale blue highlighting shows interventions and comparators included within the scope of this appraisal

Drug name	Mechanism of Action	Administration route and frequency	Marketing authorisation	Related NICE TA	NICE recommendation
Recommended for RRMS					
Glatiramer Acetate	Not fully known	SC injection, once daily or 3 times weekly	Relapsing forms of multiple sclerosis.	TA527[31]	Recommended for treating RRMS
Interferon beta-1a	Not fully known	IM injection, once Weekly or SC injection, 3 times weekly	Relapsing multiple sclerosis. In clinical trials, this was characterised by two or more acute exacerbations (relapses) in the previous three years without evidence of continuous progression between relapses.	TA527[31]	Recommended for treating RRMS
Peginterferon beta-1a	Not fully known	SC injection, every 2 weeks	Relapsing remitting multiple sclerosis.	TA624[32]	Recommended for treating RRMS
Interferon beta-1b (Extavia)	Not fully known	SC injection, every other day	Relapsing remitting multiple sclerosis and two or more relapses within the last two years.	TA527[31]	Recommended for treating RRMS if person has had 2 or more relapses with past 2 years. *Currently not available in the UK*
Recommended for RRMS in specific situations or specific subtypes					
Ocrelizumab	Anti-CD20 mAb	IV infusion, every 6 months	Adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.	TA533[33]	Recommended for active RRMS only if alemtuzumab is contraindicated or otherwise unsuitable
Natalizumab (Tysabri)	α4β1 integrin inhibitor	IV infusion, every 4 weeks can also be given subcutaneously	Highly active RRMS: • Rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1	TA127[34]	Recommended for rapidly evolving severe RRMS

Drug name	Mechanism of Action	Administration route and frequency	Marketing authorisation	Related NICE TA	NICE recommendation
			or more Gadolinium enhancing lesions on brain Magnetic Resonance Imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI. OR • Highly active disease despite a full and adequate course of treatment with at least one DMT		
Natalizumab biosimilar (Tyruko)	α4β1 integrin inhibitor	IV infusion, every 4 weeks	Highly active RRMS: • Rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain Magnetic Resonance Imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI. OR • Highly active disease despite a full and adequate course of treatment with at least one DMT	NA	Recommended as per Natalizumab (Tysabri) under NICE's biosimilar policy
Diroximel fumarate (Almirall)	Nuclear factor (erythroid derived 2)–like 2 pathway inhibitor	Oral, twice daily	Adult patients with relapsing–remitting multiple sclerosis.	TA794[35] TA320[36]	Recommended for active RRMS only if they do *not* have highly active or rapidly evolving severe relapsing–remitting multiple sclerosis
Dimethyl fumarate	Promotes anti-inflammatory activity and can	Oral, twice daily	Indicated for the treatment of adult patients with relapsing remitting multiple sclerosis	TA320[36]	Recommended for active RRMS, only if:

Drug name	Mechanism of Action	Administration route and frequency	Marketing authorisation	Related NICE TA	NICE recommendation
	inhibit expression of pro-inflammatory cytokines and adhesion molecules				they do not have highly active or rapidly evolving severe relapsing-remitting multiple sclerosis, and the manufacturer provides dimethyl fumarate with the discount agreed in the patient access scheme.
Teriflunomide	Inhibits the enzyme dihydroorotate dehydrogenase (DHODH)	Oral, 14 mg once daily	Approved for the treatment of RRMS in adults and children aged 10 years and older.	NICE TA303[37]	Recommended for active RRMS only if they do not have highly active or rapidly evolving severe RRMS and the manufacturer provides teriflunomide with the discount agreed in the patient access scheme.
Cladribine	Not fully known	Oral, 4-5 days over 2-week treatment courses	Adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features	NICE TA616[38]	Recommended for highly active MS only if the person has rapidly evolving severe RRMS or disease that has responded inadequately to treatment with DMT
Recommended for previously treated RRMS					
Alemtuzumab	Anti-CD52 mAb	IV infusion, once daily	Adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features.	TA312[39]	Recommended for highly active RRMS despite a full and adequate course of treatment with at least 1 disease-modifying therapy OR rapidly evolving severe RRMS

Drug name	Mechanism of Action	Administration route and frequency	Marketing authorisation	Related NICE TA	NICE recommendation
Fingolimod	Sphingosine-1-phosphate inhibitor	Oral, once daily	Indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups: • Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy or • Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI	TA254[40]	Recommended for highly active RRMS if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon
Ofatumumab	Anti-CD20 mAb	SC injection, every 4 weeks	Adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.	TA699[41]	Recommended for previously treated active RRMS, only if alemtuzumab is contraindicated or otherwise unsuitable
Ponesimod	Sphingosine-1-phosphate inhibitor	Oral, once daily	Adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.	TA767[42]	Recommended for previously treated active RRMS
Cladribine	Not fully known	Oral, 4-5 days over 2-week treatment courses	Adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features	NICE TA616[38]	Recommended for highly active MS only if the person has rapidly evolving severe RRMS or disease that has responded inadequately to treatment with DMT
Recommended for SPMS					
Siponimod	Sphingosine 1-phosphate	Oral, once daily	Adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging	TA656[30]	Recommended as an option for treating SPMS with evidence of active disease

Drug name	Mechanism of Action	Administration route and frequency	Marketing authorisation	Related NICE TA	NICE recommendation
	receptor modulator		features of inflammatory activity.		(that is, relapses or imaging features of inflammatory activity)
Interferon beta-1b (Extavia)	Not fully known	SC injection, every other day	Patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.	TA527[31]	Recommended for SPMS with continuing relapses
Recommended for PPMS					
Ocrelizumab	Anti-CD20 mAb	IV infusion, every 6 months	Adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.	TA585[43]	Recommended for treating early PPMS with imaging features characteristic of inflammatory activity
Not recommended					
Interferon beta-1b (Betaferon)	Not fully known	SC injection, every other day	• Patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis. • Patients with relapsing-remitting multiple sclerosis and two or more relapses within the last two years). • Patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.	TA527[31]	**Not recommended**
Ozanimod	Sphingosine 1-phosphate receptor modulator	Oral, once daily	Adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features	TA706[44]	**Not recommended** for treating active RRMS

2 Decision Problem

Sections of this Chapter have been reproduced from the study's Protocol document, available at the NICE website.[1]

2.1 Technologies and population of interest for this appraisal

The technologies of interest for this appraisal are Natalizumab (Tysabri, Biogen) and natalizumab biosimilar (Tyruko, Sandoz). Natalizumab (Tysabri) has a marketing authorization for subcutaneous and intravenous administration, whereas natalizumab biosimilar (Tyruko) has a license for intravenous administration only. Both drugs have been licensed as single disease modifying therapy (DMT) in adults with highly active relapsing remitting multiple sclerosis for the following people:

- People with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain Magnetic Resonance Imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

OR

- People with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy

NICE already recommends natalizumab as a first-line treatment option for people with rapidly evolving severe relapsing–remitting multiple sclerosis (NICE TA127;[34]
Table 3) covering the first part of the population above. This appraisal therefore focuses only **on highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy**. Table 2 provides a summary of how different subtypes are classified.

2.2 Comparators for this appraisal

The comparator for this appraisal is standard care without natalizumab or natalizumab biosimilar. This includes the following interventions:

- Glatiramer acetate
- Interferon beta 1a
- Interferon beta 1b
- Alemtuzumab
- Cladribine tablets
- Fingolimod
- Ocrelizumab. *The NICE scope*[45] *suggested that this should only be if alemtuzumab is contraindicated. However, our clinical advisors suggested that this is not reflective of this drug is used in clinical practice and so we will not apply this restriction for our appraisal.*
- Ofatumumab
- Ponesimod
- Autologous haematopoietic stem cell transplantation

3 Aim and Objectives

Sections of this Chapter have been reproduced from the study's Protocol document, available at the NICE website.[1]

The overall aim of this assessment was to appraise the clinical and cost effectiveness of natalizumab (Tysabri) and natalizumab biosimilar (Tyruko) within their marketing authorisations for treating highly active RRMS after at least one disease modifying therapy.

To address this aim, we completed the following:

1. Systematic literature review (SLR) of treatments for highly active RRMS after at least one disease modifying therapy
2. Network meta-analysis to estimate the clinical effectiveness and safety of treatments for highly active RRMS after at least one disease modifying therapy
3. Economic modelling to assess the cost-effectiveness of treatments for highly active RRMS after at least one disease modifying therapy

4 Assessment of clinical effectiveness

Sections of this Chapter have been reproduced from the study's Protocol document, available at the NICE website.[1]

We conducted an SLR to summarise the effectiveness of treatments for relapsing-remitting multiple sclerosis after at least one disease modifying therapy. The SLR followed the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the NICE Health Technology Evaluations Manual.[46, 47] and is reported according to the PRISMA 2020[48] and PRISMA NMA statements.[49]

4.1 Selection criteria

Studies that met the following criteria were eligible for inclusion:

4.1.1 Participants

The population of interest for this appraisal is people with highly active RRMS who have received at least one previous DMT (see Table 3). As we did not expect to find studies for all interventions of interest in this specific sub-population, inclusion for the SLR was broadened to include all studies in patients with RRMS. RRMS was defined broadly to include studies of "relapsing MS". Studies were included if at least 90% of the participants had RRMS or if data could be extracted for this sub-population of interest.

4.1.2 Interventions

The two interventions of interest for this appraisal are **natalizumab** (300 mg IV infusion, every 4 weeks can also be given subcutaneously – referred to as natalizumab IV300 or natalizumab SC) and **natalizumab biosimilar** 300 mg IV infusion, every 4 weeks. To allow comparison with standard care we also included trials that evaluated the treatments summarised in Table 4. This also shows the intervention label used in tables and figures for each of these specific intervention doses.

Table 4 Overview of eligible comparator interventions

Treatment	Dose	Frequency	Admin-istration	Label in tables and figures
Alemtuzumab	12mg	Month 1 - daily for 5 days in month 1; month 12 - daily for 3 days	IV	Alemtuzumab IV12
Autologous haematopoietic stem cell transplantation				AHSCT
Cladribine	3.5 mg/kg	4-5 days over 2-weeks	Oral	Cladribine O3.5
Fingolimod	0.5 mg	once daily	Oral	Fingolimod O0.5
Glatiramer acetate	20 mg	Daily	SC	Glatiramer acetate SC20
Glatiramer acetate	40 mg	Daily	SC	Glatiramer acetate SC40
Interferon beta 1a (avonex)	30 mcg	Weekly	IM	Interferon beta 1a IM30
Interferon beta 1a (rebif)	22 mcg	3 times weekly	SC	Interferon beta 1a SC44
Interferon beta 1a (rebif)	22 mcg	3 times weekly	SC	Interferon beta 1a SC44
Interferon beta 1b	250 mcg	every other day	SC	Interferon beta 1b IM 2 50

Treatment	Dose	Frequency	Admin-istration	Label in tables and figures
Ocrelizumab	600 mg	every 6 months	IV	Ocrelizumab IV600
Ofatumumab	20 mg	every 4 weeks	SC	Ofatumumab SC20
Peginterferon beta 1a	125 mcg	every 2 weeks	SC	Peginterferon beta 1a S C125
Ponesimod	20 mg	Once daily	Oral	Ponesimod O20

SC: subcutaneous; IV: intravenous; IM: intra-muscular

Studies were required to compare one of the interventions above to an alternative intervention listed above, or to placebo, so that only studies that are informative for the network were included. We excluded studies that only compared different doses, modes of administration, or manufacturers of the same intervention unless these were needed to create a connected network.

4.1.3 Outcomes

Studies that report data on any of the following outcomes were eligible for inclusion:

- Relapse rate
- MRI measurements
- Disability progression
- Disease progression
- Adverse effects of treatment
- Health-related quality of life

4.1.4 Study design

We restricted inclusion to randomised controlled trials; open label extension studies were not eligible. No language or publication restrictions were applied.

4.2 Identification of studies

4.2.1 Literature searches

Studies/reports were identified using bibliographic and non-bibliographic search methods following guidance in the NICE technology appraisal manual.[47]

Bibliographic searching

The following databases were searched:

- MEDLINE (Ovid) 1946 to April 30, 2024
- Embase (Ovid) 1974 to 2024 April 30

The search strategy was written by one researcher and checked by another, taking the following form:

1. Terms for relapsing remitting MS
2. Terms for Interventions listed in section 4.1.2

3. The Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision) supplemented with the Cooper P3 filter[50, 51]
4. 1 and 2 and 3

The bibliographic search strategy was not limited by date of publication or by language. The searches strategies are reported in Appendix 1.

Non-bibliographic search methods

Completed and ongoing trials were identified through searches of the following trials registry resources:

- ClinicalTrials.gov via www.clinicaltrials.gov; and
- World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) via www.who.int/clinical-trials-registry-platform.

For included studies, the study's web page on the trials registry resource was re-checked for data (published results) or linked publications.

Whilst SLRs were not eligible for inclusion, any SLRs published in the last three years (2021-current) and which aligned with our scope, were retained. We checked the studies included in each review to identify any studies not identified by our searches.

NICE requested submissions from Companies with technologies in scope for this appraisal (See Table 3). We checked the submissions for studies (and study data) which align with our inclusion criteria. Any studies identified through this process were tabulated to show where they contributed to our review or why they were excluded (Appendix 2).

4.2.2 Managing the searches

Search results were exported to EndNote 20 for de-duplication. We compared the studies and study reports from the mapping of TAs to our search results. Search results were exported to Microsoft Access for screening.

4.2.3 Studies included in existing TAs

We reviewed existing TAs of interventions or comparators of interest for this appraisal to determine whether they had included any studies that were not identified by our searches. We also reviewed existing TAs for additional data not available in study reports. Where additional relevant data were found, these were included in the review.

4.3 Review strategy

4.3.1 Title and abstract screening

Titles and abstracts from the literature searches were screened independently by two reviewers using a Microsoft Access database developed specifically for this review. At this stage all records that evaluated one of the interventions of interest in the broad population

of patients with RRMS were retrieved. Full copies of all reports considered potentially relevant were obtained and moved to the inclusion assessment stage. Studies included in existing TAs moved straight to the inclusion assessment stage.

4.3.2 Full text inclusion assessment

Full text studies, including all reports included in existing TAs, were assessed for inclusion against the criteria specified in section 4.1. At this stage of the review process, we moved our review management to a new online systematic review management software – Nested Knowledge (www.nested-knowledge.com). One reviewer assessed studies for inclusion. Where studies were excluded, the reason for exclusion was recorded. For included studies, we recorded basic information for each study including language of report, MS population subtype (e.g. RRMS, SPMS, PPMS, other, mixed), whether data were available for the highly active RRMS sub-population, interventions evaluated, whether outcomes of interest were reported, study design, and study name or trial registry ID. Inclusion assessment and recorded information was checked by a second reviewer. Any disagreements were resolved by consensus or discussion with a third reviewer.

4.3.3 Mapping reports to studies

All reports of studies that met the review inclusion criteria progressed to the mapping stage. This stage linked multiple reports of the same study. The information recorded at the inclusion assessment stage was used to help identify linked reports. We identified a "primary report" for each study, this was the study that reported the most complete trial data and results. Other reports, including NICE technology appraisals that included the primary report, were labelled as secondary reports and were linked within Nested Knowledge. For each linked report we recorded whether data were extracted from the report, and if so, what data were extracted.

4.3.4 Data extraction

Data were extracted using standardised data extraction forms developed in Nested Knowledge (www.nested-knowledge.com). Data extraction forms were piloted on a small sample of papers and adapted as necessary. Data were extracted by one reviewer and checked in detail by a second reviewer. Any disagreements were resolved by consensus or discussion with a third reviewer. Nested knowledge offers some artificial intelligence (AI) features that we used to support data extraction of some baseline data. It incorporates a feature known as "smart tag" recommendations that uses GPT 4, a large language model from OpenAI, to provide automatic highlighting of full texts based on our configured "tags" (fields to extract data to). This was not used to replace human reviewers but as a tool to streamline the data extraction process. Both reviewers read the full text and relevant supplementary materials of all included studies in detail to identify and extract relevant data.

Baseline data

Data were extracted on the following:

- Study phase
- Funding sources (public, industry, mixed)
- Full text or conference abstract
- NCT number
- Study location
- Population
    - Criteria used to diagnose MS
    - Proportion of participants with RRMS
    - RRMS subtype
    - Previous treatment
- Interventions
    - Treatment names
    - Mode of administration
    - Dose
    - Frequency
- Number of participants (eligible, randomised and treated)
- Age
- Sex
- Ethnicity
- EDSS score
- Time from diagnosis of MS to study entry
- Annual relapse rate at baseline

For continuous measures, we extracted mean and standard deviation (SD) in each intervention group – this was reported by the majority of studies. If standard error (SE) was reported instead of the SD, we extracted the SE and sample size (n) and used this to calculate the SD by multiplying the SE by √n. If the SD and SE were not reported we extracted the range or interquartile range, where reported.

If the mean relapse rate was reported over a time period of different than one year, we calculated the mean annual relapse rate by dividing the reported relapse rate by the time period over which the relapse rate was calculated.

Outcome data

Where possible results data were extracted for both the sub-population of interest (highly active RRMS) and for the overall RRMS population. Data were extracted for the time points closest to 12, 24 and 36 months follow-up reported in each study. Where data were only reported graphically, data were extracted from the graphs where possible.

Annualised relapse rate

Studies used different definitions of a relapse, where reported we extracted data on the definition used in each study. We extracted the most appropriate data reported in each

study to calculate the annual relapse rate ratio and 95% confidence interval, based on the following hierarchy:

I. Rate ratios (RR) together with 95% CIs and p-values for comparisons between groups together with details on the methods of analysis, any variables controlled for in the analysis and the test statistic. The reported rate ratios for ARR were converted to the log rate ratio scale (i.e. a log link). The standard error for the log rate ratio was calculated by assuming normality on the log scale and assuming the upper and lower 95% confidence intervals are separated by $2 \times 1.96 \times SE$. If the log rate ratio of an event on arm k relative to arm 1 in trial i is denoted y_{ik} and its standard error se_{ik} ($k \geq 2$) we use the Normal likelihood

$$y_{ik} \sim N(\theta_{ik}, se_{ik}^2)$$

Using the identity link the linear predictor is

$$\theta_{ik} = \delta_{ik}$$

II. Annual relapse rate in each intervention group, together with 95% CIs and p-value for comparisons between groups. For such studies we therefore modeled the absolute log hazard rate for CDP3/6 or log rate for ARR for each arm h_{ik} with standard error hse_{ik}^2, again calculated using $2 \times 1.96 \times SE$, as

$$h_{ik} \sim N(\theta_{ik}, hse_{ik}^2)$$

With link function

$$\theta_{ik} = \mu_i + \delta_{i,bk} I_{k \neq 1}$$

Where μ_i represents the log rate on baseline arm $k = 1$.

III. Annual relapse rate in each intervention group together with number of events per arm for comparisons between groups, together with details on the methods of analysis, any variables controlled for in the analysis and the test statistic. For these studies we used use rates to calculate rate ratio and SE(lnRR) (using rate and number of participants to calculate number of events), as follows,[52] where E represents the number of events:

$$RR = \frac{ARR_1}{ARR_2}$$

$$SE = \sqrt{\frac{1}{E_1} + \frac{1}{E_2}}$$

The calculated rate ratios were also converted to the log rate ratio scale as shown in I.

Disability progression

We extracted data on:

- 3 months confirmed disability progression (CDP3)
- 6 months confirmed disability progression at (CDP6)

These outcomes refer to the proportion of participants who have confirmed disability progression based on their EDSS scores sustained for at least 3 (CDP3) or 6 months (CDP6). Disability progression is usually defined as an increase in EDSS by ⩾1.0 point from the baseline EDSS if the baseline EDSS is ⩽5.5 or an increase of ⩾0.5 points if the baseline EDSS is >5.5.[53] However, studies may use different definitions and so we also extracted the exact definition used in each study.

We extracted data on the following, where reported:

- Hazard ratios for time to CDP3 and time to CDP6 together with 95% CIs and p-values
- Proportion of participants with CDP3 and CPD6.

Reported HRs were treated in the same way as RRs for ARR, as shown in I. When HRs were not reported they were estimated with a hazard rate analysis of event frequencies in relation to time at risk (when follow-up time was available), or from 2x2 tables of event numbers using complementary log-log (cloglog) transformations, assuming proportional hazards,[52] using

$$HR = \frac{E_2 T_1}{E_1 2}$$

Where E is number of events and T is persons-years at risk, and we estimated the SE of the log hazard rate or log rate using[54]

$$SE = \sqrt{\frac{1}{E_1} + \frac{1}{E_2}}$$

Calculated HRs were treated in the same way as calculated RRs for ARR.

MRI outcomes

We only extracted data on the following MRI outcomes, where reported:

- Proportion of participants with gadolinium enhancing (gd+) T1 lesions. We were primarily interested in the total number of lesions.
- Proportion of participants with T2 lesions. We were primarily interested in the those with new or enhancing T2 lesions.

Studies reported slightly different definitions of gd+ lesions and new or enlarging T2 lesions – we extracted details on how these were defined in each study.

We used data on the proportion of participants with lesions in each intervention group and follow-up time to calculate hazard ratios in the same way as it was done for disability progression.

Adverse events

We extracted data on the proportion of participants in each intervention group that experienced the following categories of adverse events (AEs):

- Any AEs
- Treatment related AEs
- Discontinuation due to AEs
- Serious AEs
- Grade 3 or 4 AEs

We used data on the proportion of participants with each type of AEs in each intervention group and follow-up time to calculate hazard ratios in the same way it was done for disability progression. For zero count cells, a continuity correction was applied where a constant (0.5) was added to each cell of the 2x2 table.

We also extracted data on the AEs reported, but did not record the number of participants with each specific AE.

Health-related quality of life

We only extracted data on quality of life measured using the EuroQol 5 dimensions (EQ-5D) or Self-Reported SF-36 scales, but also noted where data were available for other scales. We extracted means/medians together with ranges, standard deviations (SD), standard errors (SE) and/or confidence intervals (CIs) at baseline and follow-up. Summary effect estimates (e.g. mean difference (MD)) together with 95% CIs and p-values for comparisons were extracted.

4.3.5 Quality assessment strategy

The methodological quality of included RCTs was assessed using the updated Cochrane Risk of Bias Tool (RoB-2).[55] This considers the risk of bias across five domains: randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. Domains are rated as “low risk of bias”, “high risk of bias” or “some concerns”. An overall risk of bias assessment is generated based on the “worst” risk of bias in any individual domain i.e. if one domain is judged at high risk of bias the whole study is considered at high risk of bias. Risk of bias assessment was done at the outcome level for the outcomes of ARR, disease progression, MRI outcomes and safety outcomes. Any disagreements were resolved by consensus or discussion with a third reviewer.

4.3.6 Methods of data synthesis

For each population and outcome, we present a narrative summary of included studies. This includes a summary of study characteristics (e.g. sample size, geographical location, publication year) and baseline participant characteristics (proportion of participants that did not have RRMS, age, sex, ethnicity, EDSS scores, annual relapse rate, disease duration, proportion of patients who had received previous DMT treatment) and risk of bias.

Network Meta-Analysis

To compare the efficacy and safety of treatment options using the available trial information, Bayesian Network Meta-Analyses (NMA) was conducted. NMA strengthens inference concerning the relative effect of two treatments by including both direct and indirect comparisons while respecting randomisation. Most treatments were not compared in head-to-head RCTs, and NMA allowed for the use of indirect information to make such comparisons. General details of NMA are given in NICE Decision Support Unit Technical Support Document 2.[56] Interventions with different doses were considered as separate nodes. An exception was made for the analysis for the HARRMS population, where beta-interferons 1a were grouped to create a single node to allow the network to connect. This is similar to the approach of TA767 on posenimod.[42] Table 5 provides an overview of each intervention included in the NMA.

Random and fixed effects analyses were performed. For the random-effects models the trial-specific log ratios come from a normal distribution with an estimated heterogeneity variance which is assumed to be the same for all treatment comparisons. For the fixed-effects model the log ratios were assumed to be the same across studies, which is equivalent to setting the between-trial heterogeneity to zero thus assuming homogeneity of the underlying true treatment effects.

Vague priors (Fixed effects model: prior_intercept = normal (0, scale = 10), prior_trt = normal (0, scale = 10), random effects model: prior_intercept = normal (0, scale = 10), prior_trt = normal (0, scale = 10), prior_het = half_normal (scale =2), adapt_delta = 0.99) were used for Bayesian estimation of all treatment effect parameters and for the heterogeneity variance in random effects models, unless the model presented convergence issues. In these cases, informative priors were used and reported together with results in Appendix 4.[57, 58]

Model assessment and selection

Model selection between fixed and random effects was based on the Deviance Information Criterion (DIC), with a difference of 3-5 points considered meaningful.[59, 60] For models with similar DIC we selected the simplest model (lowest effective number of parameters) as this supports interpretability. The total residual deviance, as described in NICE DSU TSD 2,[56] was calculated, and compared to the number of datapoints as an overall assessment of goodness-of-fit.[56] Studies with high residual deviance were qualitatively assessed (e.g., for differences in line of therapy, disease severity, year of publication, concomitant medications).

Network meta-regression

NMA assumes that all effect modifiers are balanced across studies both within (homogeneity) and between (consistency) treatment comparisons. We had intended to assess the impact of effect modifiers using aggregate data network meta-regression, as described in NICE DSU TSD 3[61] for the outcomes ARR and disease progression. However, as

there was little evidence of heterogeneity for ARR and CDP3, and insufficient studies for CDP6, meta-regression was not conducted. Instead, we conducted a sensitivity analysis restricted to studies judged at low risk of bias for ARR, the only outcome with sufficient studies for this to be considered appropriate.

Inconsistency testing

For any networks of evidence with closed loops of direct and indirect evidence we assessed consistency in the final by conducting a node-splitting analysis. Node-splitting models were fitted, where each comparison in the network was split into its direct and indirect components. For each node, we compared the estimates derived from direct and indirect evidence for comparisons against placebo, by calculating the difference in treatment effects and assessing whether the 95% credible intervals (CrIs) overlapped. We also examined the Bayesian p-values from the node-splitting models, which indicate whether there is evidence of inconsistency (i.e., significant differences between direct and indirect evidence).[62]

Model Implementation

Data preparation was conducted in the R programming language.[63] The NMA models were fitted in a Bayesian framework using the R package 'multinma'.[60, 64] Sufficient chains and Markov Chain Monte Carlo (MCMC) samples were used for burn-in and sampling. Convergence was assessed by visual inspection of the trace plots and the Brookes-Gelman-Rubin (BGR) Rhat statistic, which is reported for model parameters.[60]

Populations

We conducted our NMA on all feasible outcomes in the following populations:

1. HARRMS (or studies with at least 90% participants in this group)
2. Any RRMS, including studies with at least 90% of participants with RRMS.

A sensitivity analysis was conducted where a restricted NMA was created for population 2, including only interventions assessed in population 1.

Timepoints

Studies reported outcomes at multiple timepoints. We included all reported time points in the analysis, where studies reported outcomes at multiple time-points we selected the longest follow-up period. Where appropriate data were available, we used hazard ratios to account for differing follow-up periods across the included studies. We had intended to conduct a sensitivity analysis where we would have conducted separate analyses for 12, 24 and 36 months follow-up. However, there were insufficient data on time-points other than 24 months and so this analysis was not considered feasible.

Handling of multi-arm trials

Multi-arm trials were included in the network meta-analysis, and all relevant arms were included in the analyses. These studies were handled automatically using the multinma package in R, which adjusts for correlations within multi-arm studies.

Summary of results

Results were summarised as the mean of the posterior distribution of the treatment effect. The results of the NMA were presented in terms of cross tables with relative treatment effect estimates between all interventions of interest with 95% CrI for all outcomes presented. We also plotted data, including results from the node split models on forest plots to show effects of each intervention included in the network relative to placebo. All results are reported with 95% credible intervals (CrI). The 95% CrI were calculated as the lower 2.5th and upper 97.5th percentile of the MCMC samples. One of the advantages of NMA is that it allows for the ranking of interventions. Based on the results of the NMA, we calculated the probability of each treatment is ranked 1st best, 2nd best, etc. We also presented the mean ranking for each intervention together with 95% CrI, and league tables (RR of HR with 95% CrI) to show comparisons between each pair of included interventions.

The results of the NMA were also used to inform the economic model, as described in Section 6.5.1.

4.4 Protocol changes

The following changes were made to the protocol. These were either to clarify issues that were ambiguous in the original protocol or to focus the review to make this manageable within the resources and time available. Restrictions to outcomes were discussed with and approved by NICE.

4.4.1 Inclusion criteria:

Population: We clarified that RRMS was defined broadly to include studies of patients reported to have “relapsing MS”, and that we were only interested in studies in adults (>18 year olds).

Interventions: We restricted inclusion to studies that evaluated the interventions of interest at modes of administration and doses licensed for use in UK unless they were required to create a connected network.

Outcomes: Due to time and resource constraints, we restricted inclusion to studies that reported on at least one of the following outcomes:

- Relapse rate
- MRI measurements
- Disability progression
- Disease progression
- Adverse effects of treatment

- Health-related quality of life measured using EQ-5D or SF-36

This means that we did not consider the following outcomes:

- Severity of relapses
- Symptoms of multiple sclerosis (such as fatigue, cognition, and visual disturbance)

4.4.2 Literature searches

Rather than screening the existing TAs as a first step, we screened these after we had completed the data extraction for studies identified by bibliographic and non-bibliographic search methods. This was a logistical change to allow us to also determine whether there were any additional data reported in the TAs that were not available in reports of the studies. Additional data could then be included in the review.

4.4.3 Data extraction

We restricted data extraction to the outcomes listed above, focusing specifically on those listed in the methods section of the report. Data extraction was performed in Nested Knowledge instead of Access as initially proposed. We were not aware of this programme at the time the protocol was written – this allowed two reviewers to work remotely on the same database and provided greater efficiencies in the review process.

Due to time and resource constraints, we restricted data extraction and synthesis to the outcomes:

- Annualised Relapse Rate (ARR)
- Disease progression (CDP3 and CDP6)
- MRI outcomes (proportion of participants with Gd+ or new or enhancing T2 lesions)
- Adverse events (any AEs, serious AEs, grade 3-4 AEs, treatment related AEs and discontinuation due to AEs)
- Quality of life

4.4.4 Synthesis and network meta-analysis

Dichotomous data (proportion of participants with MRI lesion sand AE outcomes) were analysed as time to event outcomes, with HR and se(logHR) calculated as shown in 4.3.4. This was done because all outcomes were only expected to occur once per patient, and it allowed us to introduce follow-up time into our calculations.

We had planned to use network meta-regression to investigate heterogeneity in relapse rates and disease progression across studies. However this was not considered to be appropriate for ARR as there was little evidence of heterogeneity, and there were not enough data for other outcomes.

Consistency was evaluated using node splitting and plotting indirect and direct effect estimates against NMA results. Bayesian p-values were also considered. We did not find any inconsistencies, so a comparison of model fit with the Unrelated Mean Effects (UME) model was not done.

We removed the prediction of absolute outcomes from the NMA as absolute outcomes in data from the MS Registry analysis was available to inform the economic model.
We had intended to conduct a sensitivity analysis for the HARRMS population, where treatments that were disconnected would be included through an “any RRMS” study from population 2. Instead, we conducted a sensitivity analysis where a restricted NMA was created for the general RRMS population, including only interventions assessed in people with HARRMS. This restricted NMA in the general RRMA population was plotted together with results from the equivalent network in the HARRM population for comparison. We considered that this would provide a better comparison of whether interventions are similarly effective in the RRMS and HARRMS populations.

5 Results of clinical effectiveness review

Our searches identified 3021 records of which 701 reports were considered potentially relevant after screening titles and abstracts and were retrieved for full text review. We identified two additional relevant studies – one that was published since the searches[65] but for which the trial registry entry was identified by the searches, and one abstract included in a previous systematic review. We were unable to locate a full report of this study and the abstract did not contain sufficient details to include the trial.[66] The flow of studies through the review process is shown in the PRISMA flow diagram in Figure 2.[48]

We included 42 studies (22, 409 participants) reported in 178 reports. This includes two sets of paired studies (OPERA I and OPERA II[67] and ASCLEPIOS I and II[68]) that were reported together in the same set of reports. Table 43 (Appendix 3) provides an overview of each included study,
Table 44 (Appendix 3) summarises reports related to each study and whether additional data were extracted from each report. Studies excluded at the full text assessment stage are summarised in Table 41 (Appendix 2), together with reasons for exclusion. The submissions from the manufacturers for the two drugs of interest for this appraisal (Biogen and Sandos) did not include any relevant studies that we had not identified in our searches – studies included in these submissions, review decision, and reasons for exclusion (where appropriate) are summarised in Table 39 and Table 40 (Appendix 3). We identified a further eight studies that appeared to meet inclusion criteria but are currently ongoing and so results are not yet available. These are summarised in Table 38 (Appendix 2) – interventions being evaluated include stem cell transplantation (4 studies), ocrelizumab, ofatumumab, interferon beta-1a, interferon beta-1b, glatiramer acetate and natalizumab (each in single studies) .

We only identified one small study ofatumumab - APOLITOS[69], and this was conducted in the very specific population of Japanese and Russian participants. We therefore expanded our inclusion criteria to include studies that compared ofatumumab to other interventions not specified in our original inclusion criteria. This lead to the inclusion of an additional 2 studies: ASCLEOPIO I and II[68] that compared ofatumumab to teriflunomide. To create a connected network, we also included the OPTIMUM trial[70] that compared teriflunomide with ponesimod. These three studies are included in our total number of 42 included studies.

Two of the 42 studies included in our review – CARE-MS II[71] and MIST[72] - were restricted to participants with HARRMS. All other studies reported data for the full RRMS population. Six studies (CLARITY[73], FREEDOMS[74], FREEDOMS II[73], OPERA I and II[67], and TRANSFORMS)[75] also reported additional data for a subset of patients with HARRMS. There were no data on natalizumab or natalizumab biosimilar in people with HARRMS.

Table 5 provides an overview of the interventions evaluated by the included studies – different doses of the same interventions were considered as separate interventions.

Twenty studies included a placebo control group, three of these also included an active comparator, and 22 studies included active comparators only. We identified only one study of AHSCT, the MIST study.[76] This study was conducted in patients with HARRMS and compared AHSCT to a DMT. Patients in the DMT group received a DMT of higher efficacy or a different class to the intervention they had been taking at the time of randomisation, based on the judgement of the neurologist - this meant that individual patients received different DMTs.

Only four studies evaluated natalizumab or natalizumab biosimilar, the technologies of interest for this appraisal - ANTELOPE[76], AFFIRM[77], REVEAL[78] and Saida 2017[79]. AFFIRM and Saida 2017 compared natalizumab to placebo, REVEAL compared natalizumab to Fingolimod, and ANTELOPE compared natalizumab to natalizumab biosimilar. All studies of natalizumab evaluated intravenous administration; there were no studies that fulfilled our inclusion criteria of subcutaneous administration. Table 6 provides an overview of the four studies that evaluated natalizumab. All four studies used the McDonald criteria to diagnose MS and were industry funded. Saida 2017 was conducted in Japanese patients, REVEAL did not report on ethnicity but was conducted across 9 countries, and in AFFIRM and ANTELOPE most participants (94-100%) were white. AFFIRM had a follow-up duration of 24 months, follow-up duration was short (24-52 weeks) in the other three studies. A large proportion of patients in the Saida 2017 study had received previous DMT treatment (88%), and participants were required to have had at least one relapse at baseline, meaning participants were close to fulfilling our definition of HARRMS. Half of participants had received previous DMT treatment in REVEAL, while only 9% of those in AFFIRM had received treatment; information on previous treatment was not reported for ANTELOPE. All studies reported on relapse rates and AEs, and all but Saida 2017 reported in the proportion of participant with MRI lesions. AFFIRM was the only study to provide data on disease progression.

Figure 2 PRISMA Flow diagram

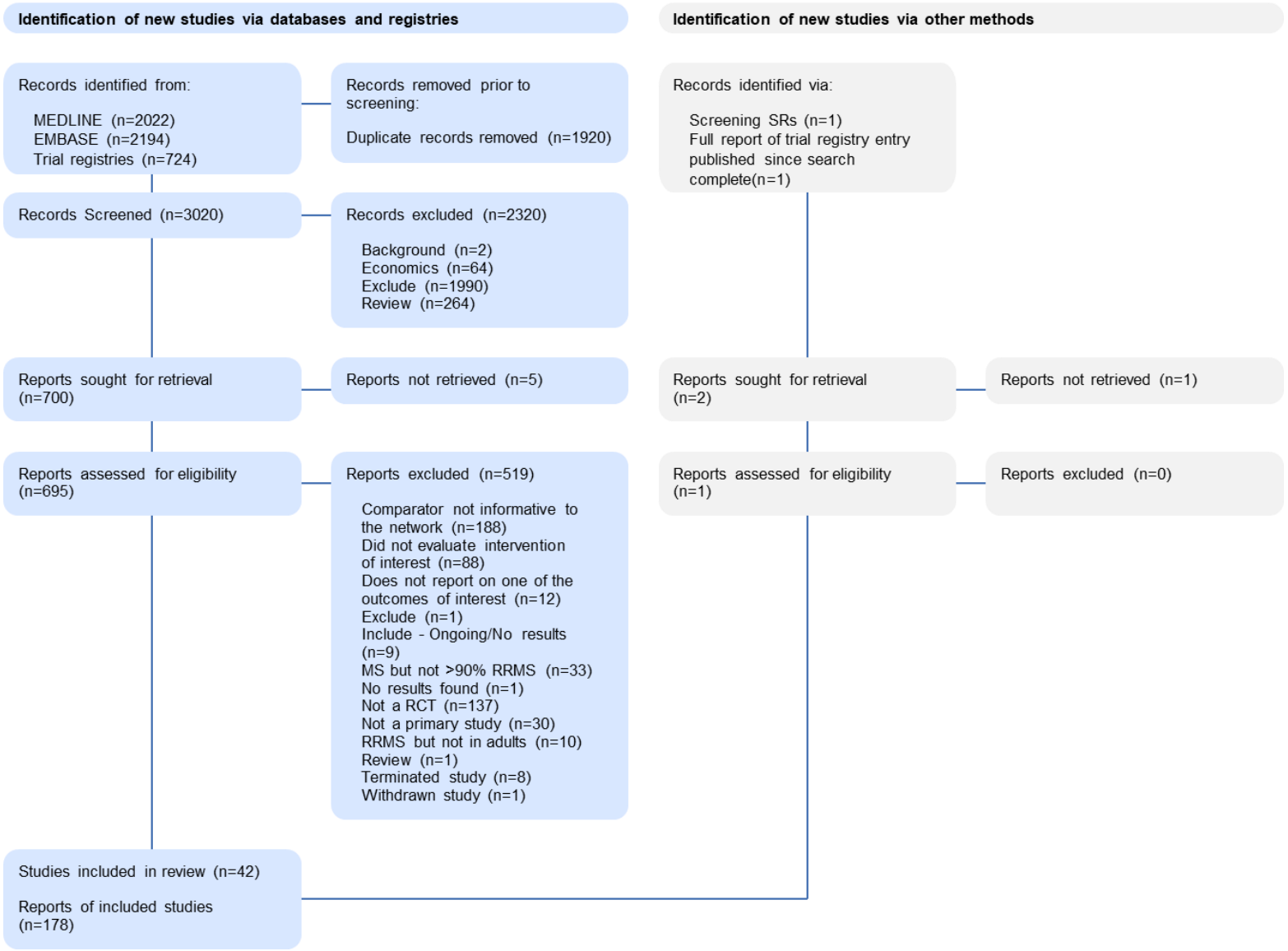


Table 5 Overview of interventions evaluated in each of the included studies

Study Name	Population	Intervention																		
		Placebo	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1a SC22	Interferon beta 1b SC250	Peginterferon beta 1a SC125	Glatiramer acetate SC20	Glatiramer acetate S420	Fingolimod O0.5	Ponesimod O20	Ocrelizumab IV600	Alemtuzumab IV12	Natalizumab IV300	Natalizumab biosimilar	Ofatumumab SC20	Cladribine O3.5	Teriflunomide O14	AHSCT
ADVANCE[80]	RRMS	x					x												
AFFIRM[77]	RRMS	x												x					
ANTELOPE[76]	RRMS													x	x				
APOLITOS[69]	RRMS	x														x			
ASCLEPIOS I[68]	RRMS															x		x	
ASCLEPIOS II[68]	RRMS															x		x	
ASSESS[81]	RRMS							x		x									
BEYOND[82]	RRMS					x		x											
Calabrese 2012[83]	RRMS	x		x				x											
CAMMS223[84]	RRMS			x									x						
CARE-MS I[85]	RRMS			x									x						
CARE-MS II[71]	HA			x									x						
CLARITY[86]	RRMS + HA		x														x		
CombiRx[87]	RRMS		x					x											
CONFIDENCE[88]	RRMS							x	x										
CONFIRM[89]	RRMS	x						x											
Copolymer 1 Multiple Sclerosis Study Group[90]	RRMS	x						x											
Etemedifar 2006[91]	RRMS		x	x		x													
European/ Canadian	RRMS	x						x											

Study Name	Population	Intervention																		
		Placebo	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1a SC22	Interferon beta 1b SC250	Peginterferon beta 1a SC125	Glatiramer acetate SC20	Glatiramer acetate S420	Fingolimod O0.5	Ponesimod O20	Ocrelizumab IV600	Alemtuzumab IV12	Natalizumab IV300	Natalizumab biosimilar	Ofatumumab SC20	Cladribine O3.5	Teriflunomide O14	AHSCT
glatiramer acetate study group[92]																			
EVIDENCE[93]	RRMS		x	x															
FREEDOMS[74]	RRMS + HA	x								x									
FREEDOMS II[73]	RRMS + HA	x								x									
GALA[94]	RRMS	x							x										
GATE[95]	RRMS	x						x											
GOLDEN[96]	RRMS					x				x									
IFNB Multiple Sclerosis Study Group[97]	RRMS	x				x													
IMPROVE[98]	RRMS	x		x															
INCOMIN[99]	RRMS		x			x													
Kappos 2011[100]	RRMS	x	x									x							
MIST[72]	HA																		x
OPERA I[67]	RRMS + HA			x								x							
OPERA II[67]	RRMS + HA			x								x							
OPTIMUM[70]	RRMS										x							x	
PEGINTEGRITY[65]	RRMS	x					x												
Ponesimod Phase II study Group[101]	RRMS	x									x								
PRISMS[102]	RRMS	x		x	x														
REGARD[103]	RRMS			x				x											
REVEAL[78]	RRMS									x				x					

Study Name	Population	Intervention																		
		Placebo	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1a SC22	Interferon beta 1b SC250	Peginterferon beta 1a SC125	Glatiramer acetate SC20	Glatiramer acetate S420	Fingolimod O0.5	Ponesimod O20	Ocrelizumab IV600	Alemtuzumab IV12	Natalizumab IV300	Natalizumab biosimilar	Ofatumumab SC20	Cladribine O3.5	Teriflunomide O14	AHSCT
Saida 2012[104]	RRMS	x								x										
Saida 2017[79]	RRMS	x												x						
The Multiple Sclerosis Collaborative Research Group	RRMS	x	x																	
TRANSFORMS[75]	RRMS + HA		x							x										

RRMS: Relapsing remitting MS; HA: highly active

Table 6 Overview of study details and baseline characteristics for studies that evaluated natalizumab or its biosimilar

Study Name	Interventions evaluated	Number enrolled	Duration (median follow-up)	Study Location	Age	% Female	Years from diagnosis	EDSS	Relapse rate	% treated	Outcomes reported
AFFIRM[77]	Natalizumab Placebo	943	2 years	99 sites in Europe, North America, and New Zealand	36.0	70	NR	2.3	1.5	9	ARR, CDP3, CDP6, MRI Gd+, MRI T2, any AEs, SAEs, AEs leading to treatment discontinuation
ANTELOPE[76]	Natalizumab Natalizumab biosimilar	265	48 weeks	48 sites in 7 countries	36.7	61	5.3	3.3	1.4	NR	ARR, MRI Gd+, MRI T2, any AEs, treatment related AEs, AEs leading to treatment discontinuation
REVEAL[78]	Natalizumab Fingolimod O0.5	111	52 weeks	43 sites in nine countries.	36.6	69	4.8	NR	1.9	50	ARR, MRI Gd+, MRI T2, SAEs, treatment related AEs, AEs leading to treatment discontinuation
Saida 2017[79]	Natalizumab Placebo	94	24 weeks	25 sites in Japan	36.4	70	5.5	2.2	2.0	88	ARR, any AEs, SAEs, AEs leading to treatment discontinuation

Table 7 Risk of bias for studies in the general RRMS population

Study	Outcome	Domain					Overall	Rationale
		1	2	3	4	5		
ADVANCE[80]	ARR; CDP; AE; QoL	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
AFFIRM[77]	ARR; MRI	Low	Low	Low	Low	Low	**Low**	No concerns for any domains; protocol not available but ARR and MRI specified as outcomes in trial registry entry
	CDP					Some concerns	**Some concerns**	Outcome not specified in trial registry entry
	QoL			High		Low	**High**	Outcome data only available for 85% participants
ANTELOPE[76]	ARR; MRI; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
APOLITOS[69]	ARR; AE	Some concerns	Low	Low	Low	Low	**Some concerns**	Insufficient information on randomisation and allocation concealment; no evidence of baseline imbalance; protocol not available
ASCLEPIOS I[68]	ARR; CDP; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
ASCLEPIOS II[68]	ARR; CDP; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
ASSESS[81]	ARR; MRI; AE	Low	High	High	Low	Low	**High**	Patients and carers were aware of the treatment assignments; large proportion of withdrawals potentially related to outcomes; subset received MRI; all participants included in analysis, but details on ITT analysis lacking
BEYOND[82]	ARR; CDP; AE	Low	Low	Low	Low	Some concerns	**Some concerns**	Protocol not available
Calabrese 2012[83]	ARR	Some concerns	Some concerns	Low	Some concerns	Some concerns	**Some concerns**	Insufficient information on allocation concealment; no evidence of baseline imbalance; patients and carers were aware of the treatment assignments but no evidence of protocol deviations because of trial context; no information on blinding of outcome assessors; protocol not available
CAMMS223[84]	ARR; CDP	Some concerns	Some concerns	High	Low	Low	**High**	Insufficient information on allocation concealment; patients and carers aware of treatment assignment but deviations from intended intervention low; large proportion of missing data potentially related to outcome - all participants included in analysis but details on ITT analysis lacking

Study	Outcome	Domain					Overall	Rationale
		1	2	3	4	5		
	AE			Low				Outcome data available for most participants
CARE-MS I[85]	ARR; CDP; MRI; AE; QoL	Some concerns	High	Low	Low	Low	**High**	Insufficient information on allocation concealment; patients and carers were aware of the treatment assignments
CLARITY[86]	ARR; CDP; MRI; QoL	Low	Low	High	Low	Low	**High**	Over 10% of participants did not complete study & only subset of these had MRI data; missingness could depend on true value. Only 80% of participants had data for QoL
	AEs	Low	Low	Low	Low	Low	**Low**	Data available for all participants
CombiRx[87]	ARR; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
	MRI			Some concerns			**Some concerns**	MRI data only available for subset of patients, unclear how selected; no sensitivity analysis and missingness could depend on true value
CONFIDENCE[88]	AE	Some concerns	Low	Low	High	Some concerns	**High**	Insufficient information on randomisation and allocation concealments; outcome assessors unblinded; no protocol
CONFIRM[89]	ARR; CDP; QoL (except VAS)	Low	Low	Some concerns	Low	Low	**Some concerns**	Data missing for 20% of participants but sensitivity analysis suggest that this did not impact results; protocol not available
	AE; QoL (VAS)			Low			**Low**	AE data for all participants; QoL VAS for >90%
Copolymer 1 Multiple Sclerosis Study Group[90]	ARR; CDP; AE	Some concerns	Low	Low	Low	Some concerns	**Some concerns**	Insufficient information on allocation concealment; no evidence of baseline imbalance; protocol not available
Etemedifar 2006[91]	ARR	Some concerns	Some concerns	Low	Low	Some concerns	**Some concerns**	Insufficient information on allocation concealment; no evidence of baseline imbalance; patients and carers were aware of the treatment assignments but no evidence of protocol deviations because of trial context; protocol not available
European/ Canadian glatiramer acetate study group[92]	ARR; AE	Some concerns	Low	Low	Low	Low	**Some concerns**	Insufficient information on allocation concealment; no evidence of baseline imbalance

Study	Outcome	Domain					Overall	Rationale
		1	2	3	4	5		
EVIDENCE[93]	ARR; CDP; MRI; AE	Low	Some concerns	Low	Low	Some concerns	**Some concerns**	Patients and carers were aware of the treatment assignments but no evidence of protocol deviations because of trial context; protocol not available
FREEDOMS[74]	ARR; CDP; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
	MRI			Some concerns			**Some concerns**	MRI data only available for subset of patients, unclear how selected; no sensitivity analysis and missingness could depend on true value
FREEDOMS II[73]	ARR; CDP; MRI; QoL	Low	Low	High	Low	Low	**High**	Over 25% of participants did not complete study & only subset of these had MRI data; missingness could depend on true value
	AE			Low			**Low**	AE data available for all participants
GALA[94]	ARR; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
GATE[95]	ARR; MRI; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
GOLDEN[96]	ARR	Some concerns	High	High	Low	Some concerns	**High**	Insufficient information on allocation concealment; patients and carers were aware of the treatment assignments; large proportion of missing data potentially related to outcome; protocol not available
	AE			Low				Safety data available for all participants
IMPROVE[98]	ARR; MRI; AE	Some concerns	Some concerns	Low	Low	Some concerns	**Some concerns**	Insufficient information on allocation concealment; no evidence of baseline imbalance; patients and carers were aware of the treatment assignments but no evidence of protocol deviations because of trial context; protocol not available
INCOMIN[99]	ARR; CDP;	Low	High	Low	High	Some concerns	**High**	Patients and carers were aware of the treatment assignments; outcome assessors unblinded; no protocol available
	MRI		Some concerns				**High**	MRI outcome data only available for 80% of participants
IFNB Multiple Sclerosis Study Group[97]	ARR; AE	Some concerns	Low	Low	Low	Some concerns	**Some concerns**	Insufficient information on randomisation and allocation concealment; no evidence of baseline imbalance

Study	Outcome	Domain					Overall	Rationale
		1	2	3	4	5		
Kappos 2011[100]		Low	Low	Low	Low	Low	**Low**	No concerns for any domains
Multiple Sclerosis Collaborative Research Group[105]	ARR; CDP; AE	Some concerns	Low	Low	Low	Low	**Some concerns**	Insufficient information on allocation concealment; no evidence of baseline imbalance
	MRI			Some concerns				MRI data available for 85% of participants
OPERA I[67]	ARR; CDP; MRI; AE; QoL	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
OPERA II[67]	ARR; CDP; MRI; AE; QoL	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
OPTIMUM[70]	ARR; CDP; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
PEGINTEGRITY[65]	ARR; CDP;	Some concerns	High	High	Some concerns	Low	**High**	Insufficient information on allocation concealment and blinding of outcome assessors; patients and carers were aware of the treatment assignments; large proportion of missing data potentially related to outcome
	AE			Low				AE data available for >95% participants
Ponesimod Phase II study Group[101]	ARR; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
PRISMS[102]	ARR; CDP; MRI	Low	Low	Low	Low	Some concerns	**Some concerns**	Protocol not available
REGARD[103]	ARR; CDP; MRI; AE	Low	Low	Low	Low	Some concerns	**Some concerns**	Protocol not available.
REVEAL[78]	ARR; AE	Some concerns	Low	Low	Some concerns	Some concerns	**Some concerns**	Insufficient information on allocation concealment; no evidence of baseline imbalance; no information on blinding of outcome assessors; protocol not available
	MRI			Some concerns				MRI outcomes available for <90% of participants
Saida 2012[104]	ARR; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains

Study	Outcome	Domain					Overall	Rationale
		1	2	3	4	5		
	MRI			Some concerns			**Some concerns**	MRI outcome data only available for 88% of participants
Saida 2017[79]	ARR; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
TRANSFORMS[75]	ARR; CDP; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
	MRI			Some concerns				MRI data available for 85% participants

Domain 1: Risk of bias arising from the randomization process; Domain 2: Risk of bias due to deviations from the intended interventions; Domain 3: Risk of bias due to missing outcome data; Domain 4: Risk of bias in measurement of the outcome; Domain 5: Risk of bias in selection of the reported result

ARR: annualised relapse rate; CDP: confirmed disease progression; AE: adverse event; QoL: Quality of Life

5.1 General RRMS population

Forty studies (21 671 participants) reported data for a general RRMS population.

Table 45 (Appendix 3) provides a summary of the baseline characteristics of participants included in the RRMS studies. All studies were considered to be sufficiently similar for inclusion in the NMAs. AHSCT was the only intervention not evaluated in the general RRMS population – this was only evaluated in the HARRMS population. Four studies included a small proportion of participants that did not have RRMS – in ASCLEPIOS I and II 6% of participants had SPMS, in OPTIMUM 3% had SPMS, and in Saida 2012 2% had SPMS. Mean age ranged from 30 to 41 years (median 36.7 years), the proportion of female participants ranged from 31 to 91% (median 68%), baseline EDSS score from 1.0 to 3.5 (median 2.4), baseline annual relapse rate ranged from 0.7 to 2.4 (median 1.5), and mean disease duration at baseline ranged from 0.3 to 8 years (median 5.7 years). The proportion of participants who had received previous treatment with a DMT ranged from 0 to 91% (median 30%). The majority of participants were white (median 92%) although the proportion ranged from 0 to 100% - this is because one study (Saida 2007[79]) was conducted only in Japanese patients and the APOLITOS study[69] was conducted in Japan and Russia. Publication years spanned almost 30 years ranging from 1993 for the earliest study of interferon beta-1b to 2024, with a median of 2012.

5.1.1 Risk of bias

Table 7 provides a summary of the risk of bias assessment for studies in the RRMS population, stratified according to outcome. Results tables in Appendix 4, also include the overall risk of bias for each study for each outcome evaluated.

Domain 1: Risk of bias arising from the randomization process

No studies were judged as being at high risk of bias for the randomisation process, but 14 (35%) were judged at some concerns as they did not report sufficient information on randomisation and/or allocation concealment and there was no evidence of baseline imbalance between intervention groups. All other studies were judged as low risk of bias for this domain. Where studies reported multiple outcomes, risk of bias judgements were the same for all outcomes for this domain.

Domain 2: Risk of bias due to deviations from the intended interventions

Five studies (13%) were judged at high risk of bias due to deviations from the intended intervention – in these studies patients were aware of their treatment assignment and there was a differential rate of treatment discontinuation between the groups, which may have been associated with the outcome. Five studies (13%) were judged as some concerns for this domain as patients were aware of their treatment assignment but there was no evidence of deviations from the intended interventions. Where studies reported multiple outcomes, risk of bias judgements were the same for all outcomes for this domain.

Domain 3: Risk of bias due to missing outcome data

Six studies were judged at high risk of bias due to missing outcome data for the ARR outcome – these studies had a large proportion of missing outcome data (at least 10%) and this was considered to be potentially related to the outcome. Most of these studies did conduct an intention-to-treat (ITT) analysis based either on all randomised patients or on all patients that received at least one dose of the intervention, but studies did not report sufficient details of how the ITT analysis was conducted. One study was judged as some concerns for this domain as although outcome data were missing for 20% of participants, sensitivity analysis suggested that this did not impact results.

Fourteen studies had different risk of bias judgements for the missing outcome domain for other outcomes reported. In eight studies, this was because MRI data were only available for <90% of participants, reasons for this were not reported and this was considered potentially related to the outcome. In six studies the missing outcome data domain was judged as some concerns for risk of bias for ARR, but at low risk of bias for safety data as outcome data were missing for ARR but were available for all, or almost all, participants for the adverse event outcomes.

Domain 4: Risk of bias in measurement of the outcome

Ony two studies were judged at high risk of bias for the measurement of the outcome domain – these specified that outcome assessors were unblinded. Three studies were judged at some concerns as it was unclear whether outcome assessors were blinded. Where studies reported multiple outcomes, risk of bias judgements were the same for all outcomes for this domain.

Domain 5: Risk of bias in selection of the reported result

No studies were judged as being at high risk of bias due to selective outcome reporting, but 14 (35%) were judged at some concerns as no protocol or trial registry entry was available, or the outcome was not specified in the trial registry entry. In the AFFIRM study, only two of the reported outcomes were specified in the trial registry entry – ARR and MRI. The study was therefore judged at low risk of selective outcome reporting for these outcomes but as some concerns for the other outcomes reported – disease progression and quality of life (QoL).

5.1.2 Annualised Relapse Rate (ARR)

All but one (CONFIDENCE[88]) of the 40 studies that reported results for the general RRMS population reported data on ARR and data were available for all interventions evaluated in the general RRMS population. Estimates of ARR for each study arm are summarised in Table 49 (Appendix 3). Studies reported ARR at between 4 and 36 months follow-up, with a median of 24 months follow-up. Included studies defined a "relapse" in different ways. Relapse definitions, broken down into definition components, are summarised in Table 47 (Appendix 3). Relapses were generally defined in terms of:

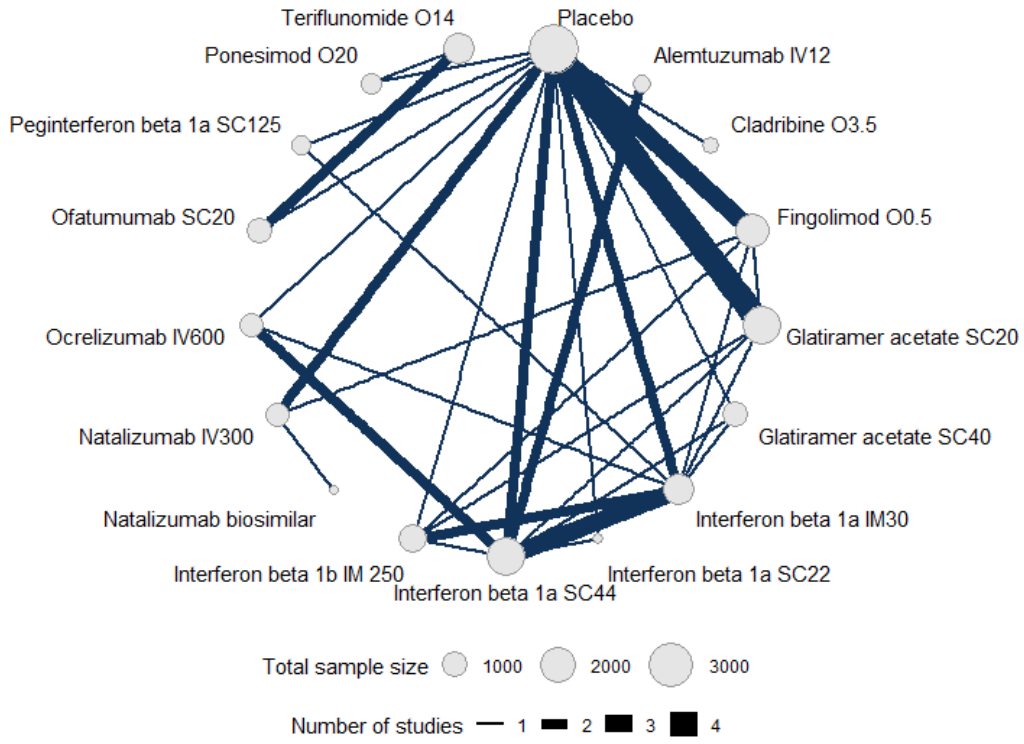
- *Symptoms*: combinations of new, recurrent or worsening of existing symptoms

- *Symptom duration*: at least 24 or 48 hours
- *Exclusion of specific clinical features*: fever, infection, heat intolerance, adverse reaction to medication
- *Neurological examination*: some studies specified that new objective neurologic findings were required, others were more specific specifying an EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one
- *Previous period of stability* – where required this was always a minimum of 30 days
- *Verification* – some studies specified that verification was required by a specific examiner, and some that this had to be within 7 days of notification of the potential relapse

Our clinical advisors suggested that these definitions were sufficiently similar for it to be appropriate to combine results across studies. For ARR, 17 (44%) studies were at low risk of bias, 15 (38%) had some concerns regarding risk of bias, and 7 (18%) were at high risk of bias.

The 39 studies (20, 810 participants) created a connected network for 17 interventions of interest for this appraisal. The network geometry for this analysis is shown in Figure 3, displaying the treatment nodes and connections, with line thickness representing the number of studies for each comparison and node size the number of patients on each treatment. The placebo group served as the reference group throughout. Natalizumab biosimilar was only directly compared with natalizumab. Natalizumab was also directly compared to placebo and fingolimod and so could be compared to other treatments via these nodes.

Figure 3 Network plot for NMA for ARR



The DIC (77.7 vs 79.9)and residual deviance was also very similar for both fixed and random effects (49.8 vs 49.9 on 55 data points) (Table 59) were both similar for the fixed and random effects models, and indicated good fit for both models with limited heterogeneity in treatment effects across studies. This was confirmed by the heterogeneity standard deviation estimated by the random effects model (tau of 0.05, 95% CrI (0.002, 0.14), Table 59) being very low compared to the average treatment effect on the log rate ratio scale (-0.59 in Table 59). We therefore present results for the fixed effect models for this outcome. Figure 28 (Appendix 5) shows how well each study fits the NMA model. The fixed effects model had a good fit to the data from most studies included in the network, with the exception of the REVEAL and GOLDEN studies, which also had high residual deviance under random effects. REVEAL compared natalizumab with fingolimod and GOLDEN compared fingolimod with interferon beta 1b. Both were multi-centre international studies and there were no clear differences between these two studies and other studies included in the network in terms of study design, outcome definition, or participant characteristics.

Figure 4 shows the Rate ratio (RR) and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected fixed effects model, stratified to show estimates from direct and indirect evidence and the overall NMA estimate. Comparison of estimates derived from direct and indirect evidence were similar. Most interventions were associated with a greater reduction (i.e., RR<1 AND 95% CrI excluding 1.00) in the risk of relapses compared to placebo. The exceptions were Teriflunomide and Ponesimod where the risk was similar to placebo. Results were very similar for both random and fixed effects models (Table 59 in Appendix 5). The ranking of

interventions and the probability that each intervention would be ranked first is shown in Table 8, with Table 61 (Appendix 5) showing the probability that each intervention will rank in a specific position. Alemtuzumab had the highest mean ranking (1.4, 95 % CrI 1, 3) and the greatest probability of ranking first (72%) followed by natalizumab (2.2, 95 % CrI 1, 4; 17%). There was greater uncertainty for natalizumab biosimilar which had a 4% probability of ranking first but a mean ranking of 6.6 (95% CrI 1, 15). The different interferon and glatiramer acetate interventions were ranked similarly to each other and as less effective than most of the newer drugs. The exception to this were ponesimod and teriflunomide. Ponesimod had similar efficacy to the interferon and glatiramer acetate interventions, whilst teriflunomide was similar to placebo. Table 60 (Appendix 4) shows the RR (95% CrI) for each intervention pair comparison evaluated in the NMA. This shows that the RR (95% CrI) for natalizumab compared to natalizumab biosimilar, the key comparison for this appraisal, was 0.65 (0.33, 1.23), suggesting no difference between the ARR for these two interventions.

Figure 4 Forest plot of annualised relapse rate (ARR) ratios and 95% credible intervals (fixed effects NMA; RRMS population)

Blue lines indicate result from the NMA, green lines indicate results from direct evidence and purple lines from indirect evidence. P-values relate to comparisons between direct and indirect evidence. Note that the indirect evidence lines are only included if there is also direct evidence.

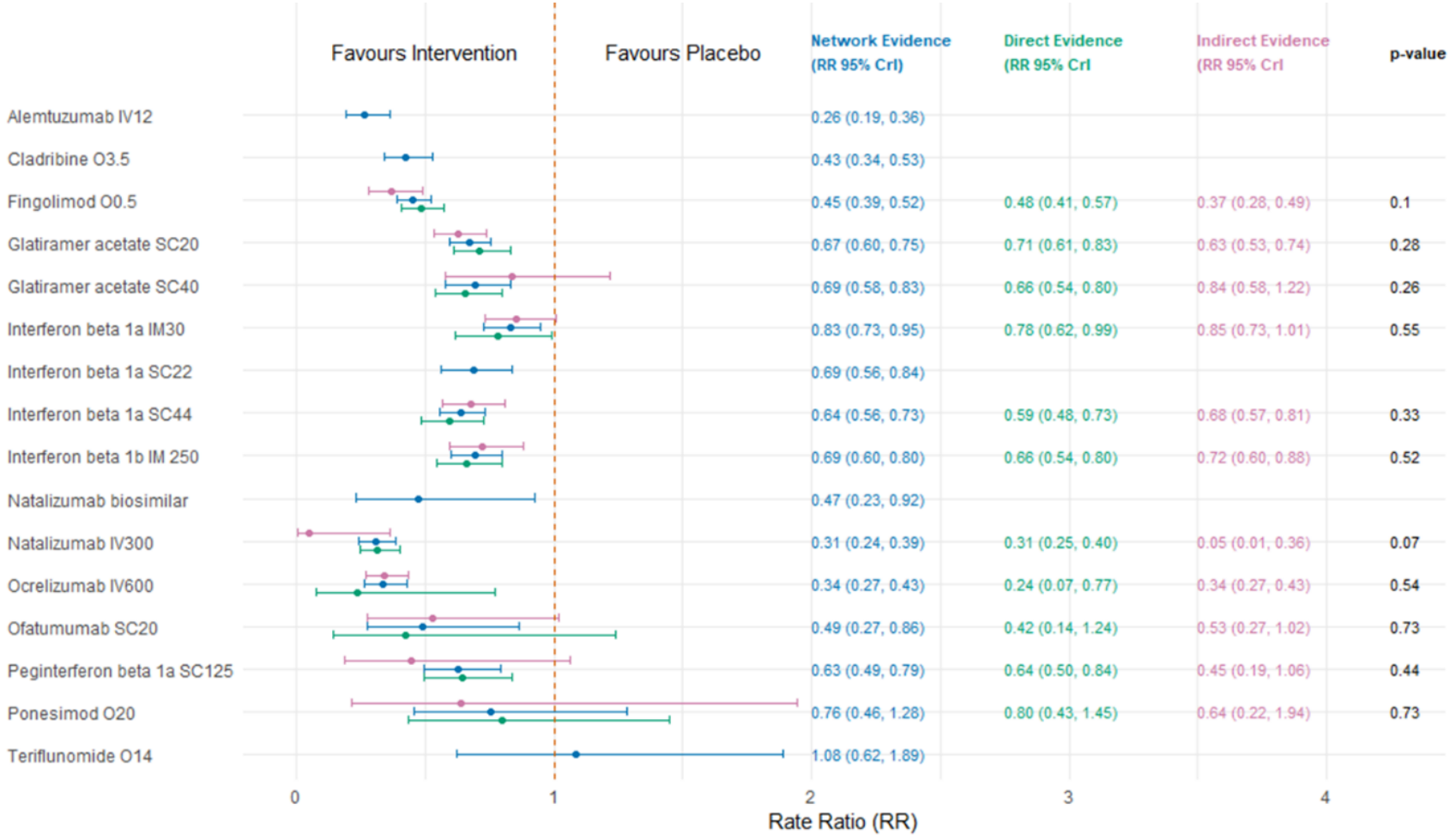


Figure 5 Forest plot of hazard ratios (HR) and 95% credible intervals for time to CDP3 (fixed effects NMA; RRMS population)

Blue lines indicate result from the NMA, green lines indicate results from direct evidence and purple lines from indirect evidence. P-values relate to comparisons between direct and indirect evidence. Note that the indirect evidence lines are only included if there is also direct evidence.

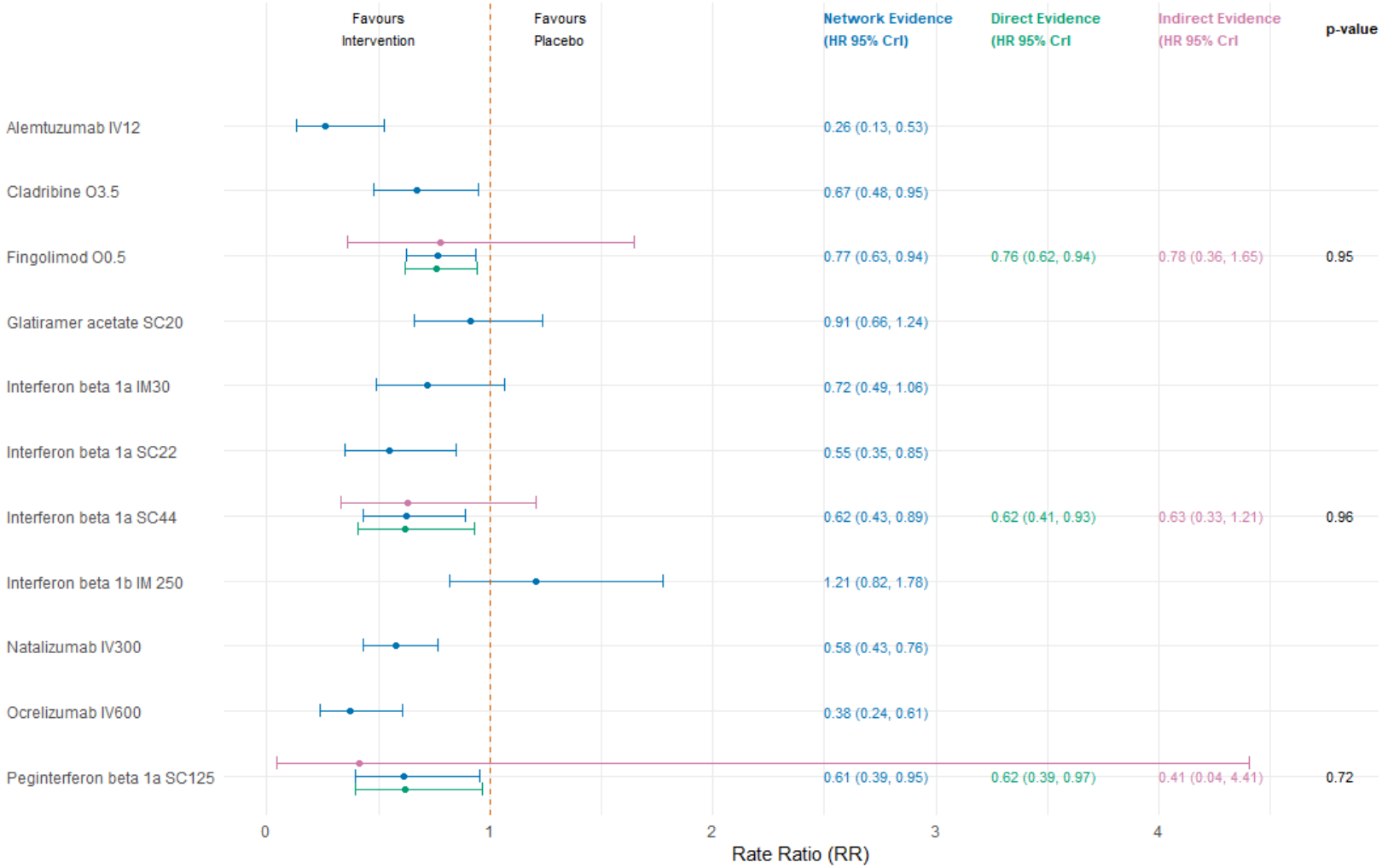


Figure 6 Forest plot of hazard ratios (HR) and 95% credible intervals from fixed effects NMA for time to CDP6 (fixed effects NMA; RRMS population).
Green lines indicate results from direct evidence and purple lines from indirect evidence.

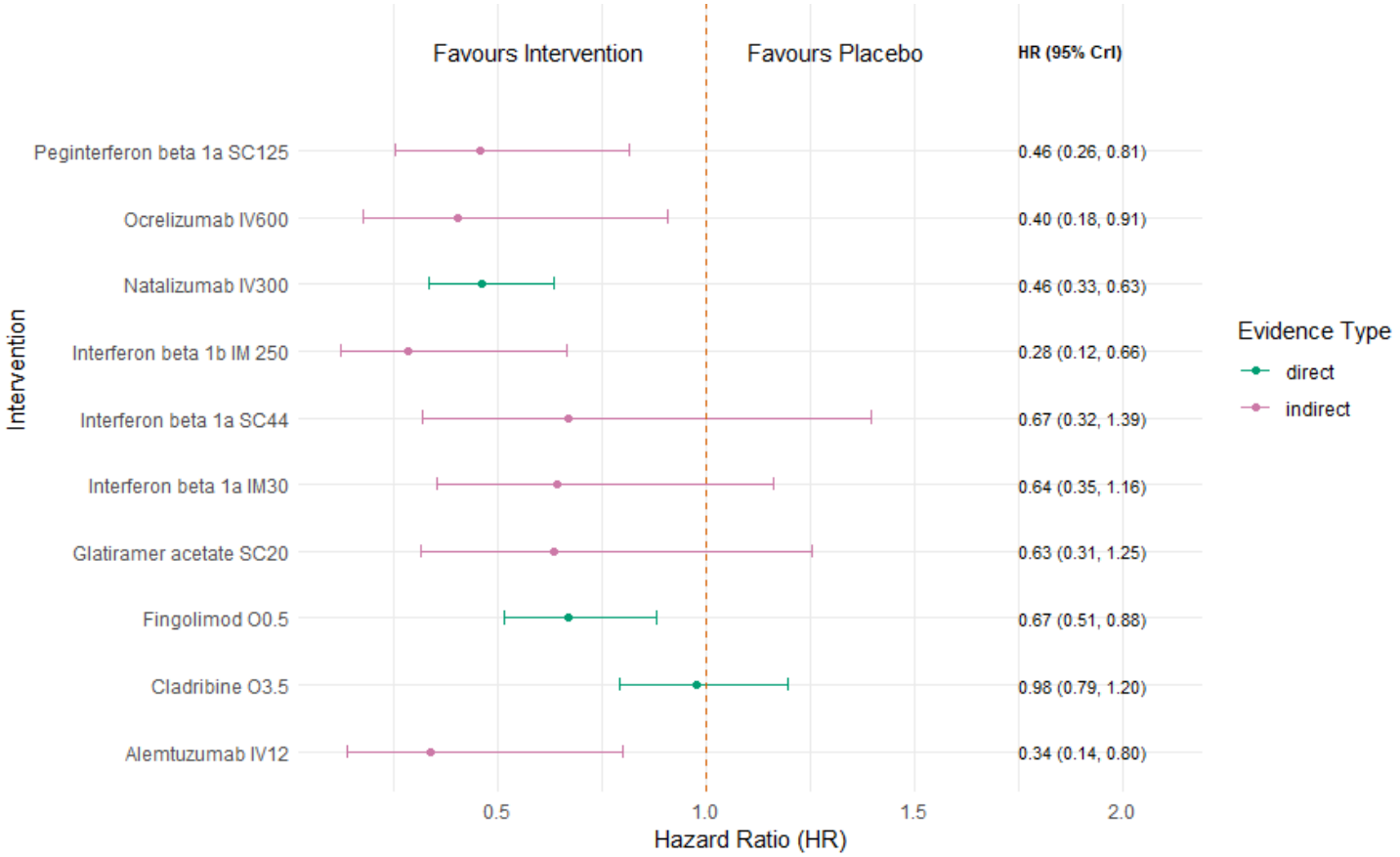


Figure 7 Forest plot of hazard ratios (HR) and 95% credible intervals for time to developing at least one Gd+ MRI lesion (fixed effects NMA; RRMS population)

Blue lines indicate result from the NMA, green lines indicate results from direct evidence and purple lines from indirect evidence. P-values relate to comparisons between direct and indirect evidence. Note that the indirect evidence lines are only included if there is also direct evidence.

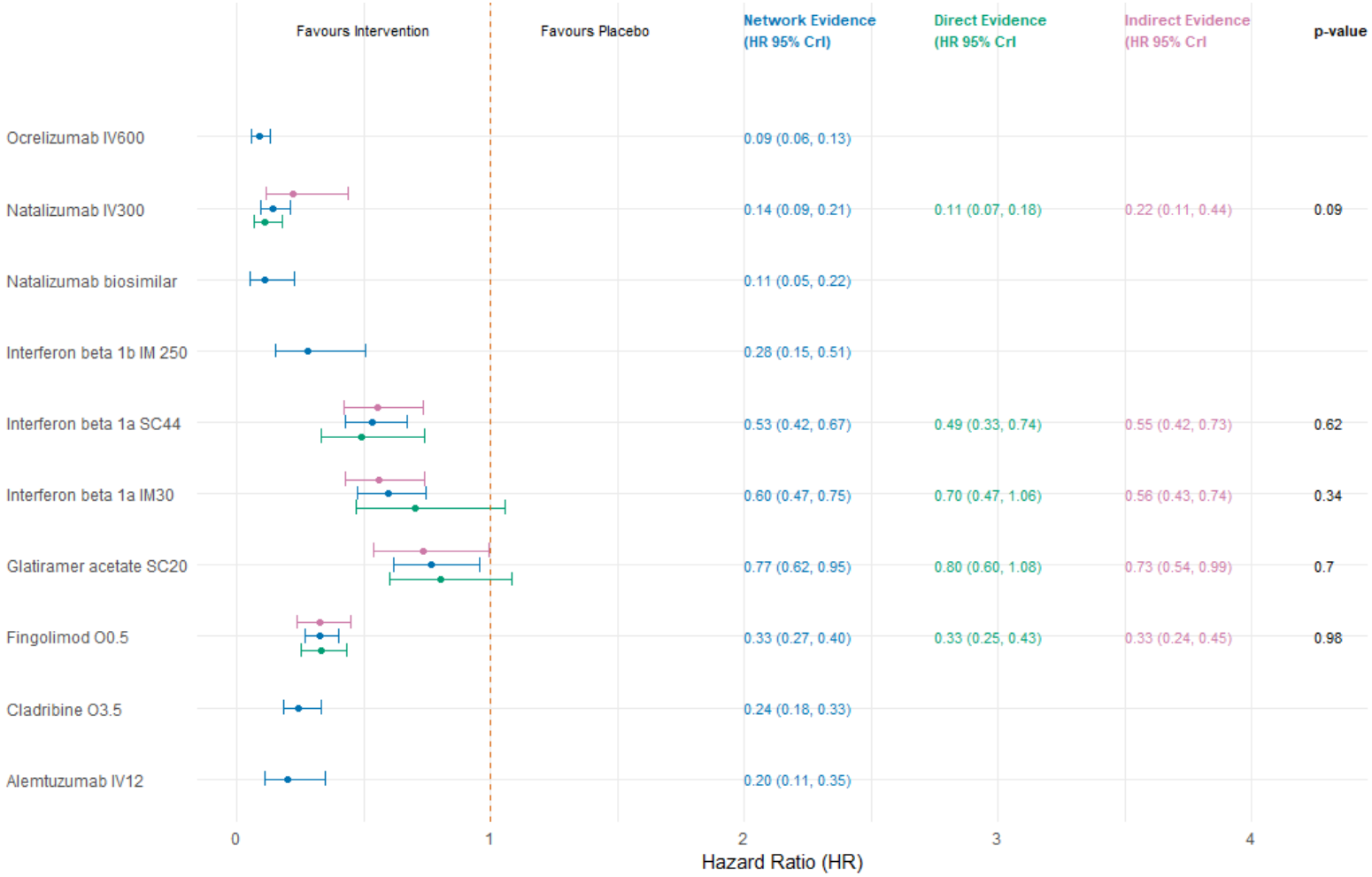


Figure 8 Forest plot of hazard ratios (HR) and 95% credible intervals for time to developing at least one new or enlarging T2 weighted MRI lesions (fixed effects NMA; RRMS population).

Blue lines indicate result from the NMA, green lines indicate results from direct evidence and purple lines from indirect evidence. P-values relate to comparisons between direct and indirect evidence. Note that the indirect evidence lines are only included if there is also direct evidence.

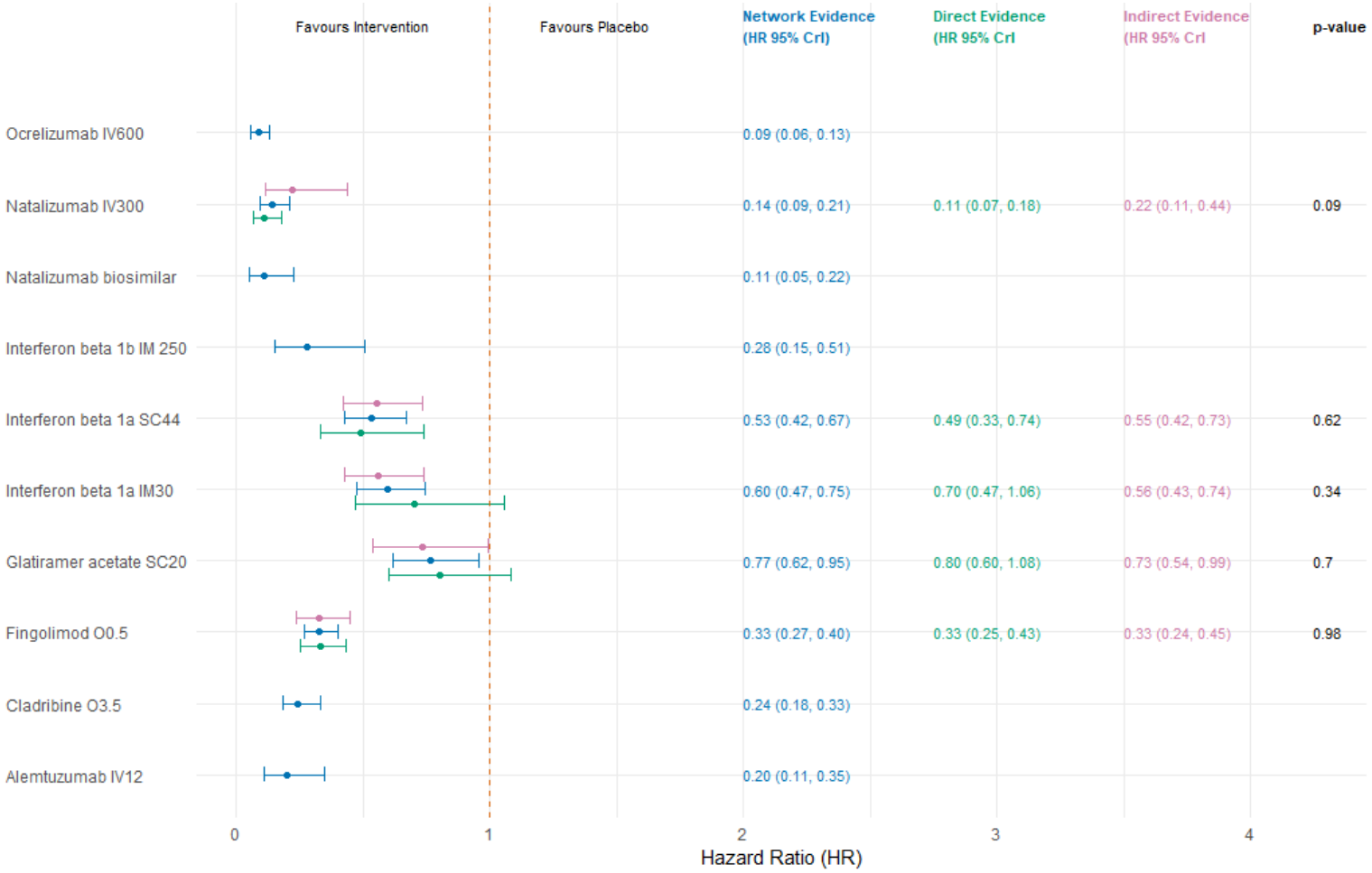


Table 8 Mean ranking of interventions and probability that each intervention would be ranked first from NMAs for each of the outcomes evaluated

Intervention	ARR		CDP3		CDP6		MRI: Gd+		MRI: T2		ARR (highly active)	
	Mean rank (95% CrI)	Pr(best) (%)	Mean rank (95% CrI)	Pr(best) (%)	Mean rank (95% CrI)	Pr(best) (%)	Mean rank (95% CrI)	Pr(best) (%)	Mean rank (95% CrI)	Pr(best) (%)	Mean rank (95% CrI)	Pr(best) (%)
Alemtuzumab IV12	1.4 (1, 3)	72	1.2 (1, 3)	83	2.6 (1, 6)	26	4.2 (2, 7)	68	6.0 (3, 9)	3	3.8 (2, 5)	1
Natalizumab IV300	2.3 (1, 4)	17	4.8 (2, 9)	0	4.3 (1, 8)	5	2.9 (2, 4)	1	3.5 (1, 6)	4	1.8 (1, 5)	53
Natalizumab biosimilar	6.6 (1, 15)	5	NA	NA	NA	NA	2.1 (1, 4)	30	3.0 (1, 7)	31	NA	NA
Ocrelizumab IV600	3.1 (1, 5)	4	2.1 (1, 4)	14	3.6 (1, 7)	5	1.4 (1, 3)	0	2.2 (1, 5)	30	1.8 (1, 5)	44
Ofatumumab SC20	6.6 (2, 14)	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cladribine O3.5	5.0 (3, 7)	0	6.5 (3, 10)	0	10.0 (7, 11)	0	5.1 (4, 7)	0	4.2 (1, 7)	0	4.1 (2, 6)	2
Fingolimod O0.5	5.5 (4, 7)	0	8.1 (5, 10)	0	7.3 (4, 9)	0	6.6 (5, 7)	0	6.4 (5, 8)	0	3.7 (2, 5)	0
Peginterferon beta 1a SC125	9.3 (6, 14)	0	5.5 (2, 10)	1	4.4 (1, 9)	10	NA	NA	8.2 (7, 10)	0	NA	NA
Interferon beta 1a SC44	9.4 (7, 13)	0	5.6 (3, 9)	0	7.6 (4, 11)	0	8.1 (8, 9)	0	NA	NA	6.5 (5, 7)	0
Interferon beta 1a SC22	11.2 (7, 15)	0	4.5 (2, 9)	2	NA	NA	NA	NA	10.6 (8, 12)	0		
Interferon beta 1a IM30	14.6 (13,16)	0	7.4 (3, 11)	0	7.2 (4, 10)	0	8.9 (8, 9)	0	9.2 (7, 11)	0		
Glatiramer acetate SC20	10.7 (8, 14)	0	9.6 (6, 11)	0	7.0 (4, 11)	0	10.0 (10, 10)	0	NA	NA	NA	NA
Glatiramer acetate SC40	11.3 (7, 15)	0	NA	NA	NA	NA	NA	NA	9.8 (8, 11)	0	NA	NA
Interferon beta 1b IM 250	11.4 (8, 15)	0	11.7 (10, 12)	0	1.9 (1, 5)	54	5.7 (3, 7)	0	3.1 (1, 8)	32	NA	NA
Ponesimod O20	12.3 (6, 16)	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Teriflunomide O14	16.1 (10, 17)	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Placebo	16.2 (15, 17)	0	10.8 (10, 12)	0	10.2 (7, 11)	0	11.0 (11, 11)	0	11.8 (11, 12)	0	6.4 (6, 7)	0

Sensitivity analysis for ARR

We had intended to conduct a meta-regression to investigate potential reasons for heterogeneity. However, as heterogeneity was low and covariates were broadly similar across groups this was not appropriate. Instead, we conducted a sensitivity analysis restricted to studies judged at low risk of bias. This analysis included 17 studies and created a connected network (Figure 29, Appendix 5), although data were not available for the following interventions: alemtuzumab, cladribine, interferon beta 1a (SC22), or interferon beta 1b. Estimates of RR for the interventions for which data were available were very similar to those obtained for the full set of studies, suggesting that risk of bias in these studies did not have a substantial impact on results. We investigated whether it was possible to carry out analyses separately for studies that reported data for 6, 12 and 24 month follow-up, but there were insufficient data and networks did not connect for follow-up of less than 24 months; the network for 24 months was almost the same as that for all studies combined.

5.1.3 Disease Progression

Only 23 of the 40 studies that reported results for the general RRMS population reported data on disease progression – 12 studies reported both CDP3 and CDP6, six studies reported CDP3 only and five reported CDP6 only. Estimates of CDP for each study arm are summarised in Table 49 (Appendix 4). Studies reported disease progression at between 6 and 24 months follow-up, with a median of 24 months follow-up. Included studies defined disease progression in different ways. Disease progression definitions, broken down into definition components, are also summarised in Table 49 (Appendix 4). All studies defined criteria for disease progression based on increase in EDSS scores and baseline EDSS scores – some simply specified an increase of at least one point regardless of baseline EDSS, others specified an increase of at least 1.5 points in those with a baseline EDSS score of 0 with an increase of at least one point in those with an EDSS score of at least one, and some specified an increase in EDSS score of 0.5 points in those with higher baseline EDSS scores (most commonly a baseline EDSS of more than 5 but in some this was more than 4.5 or 5.5). Our clinical advisors suggested that these definitions were sufficiently similar for it to be appropriate to combine results across studies.

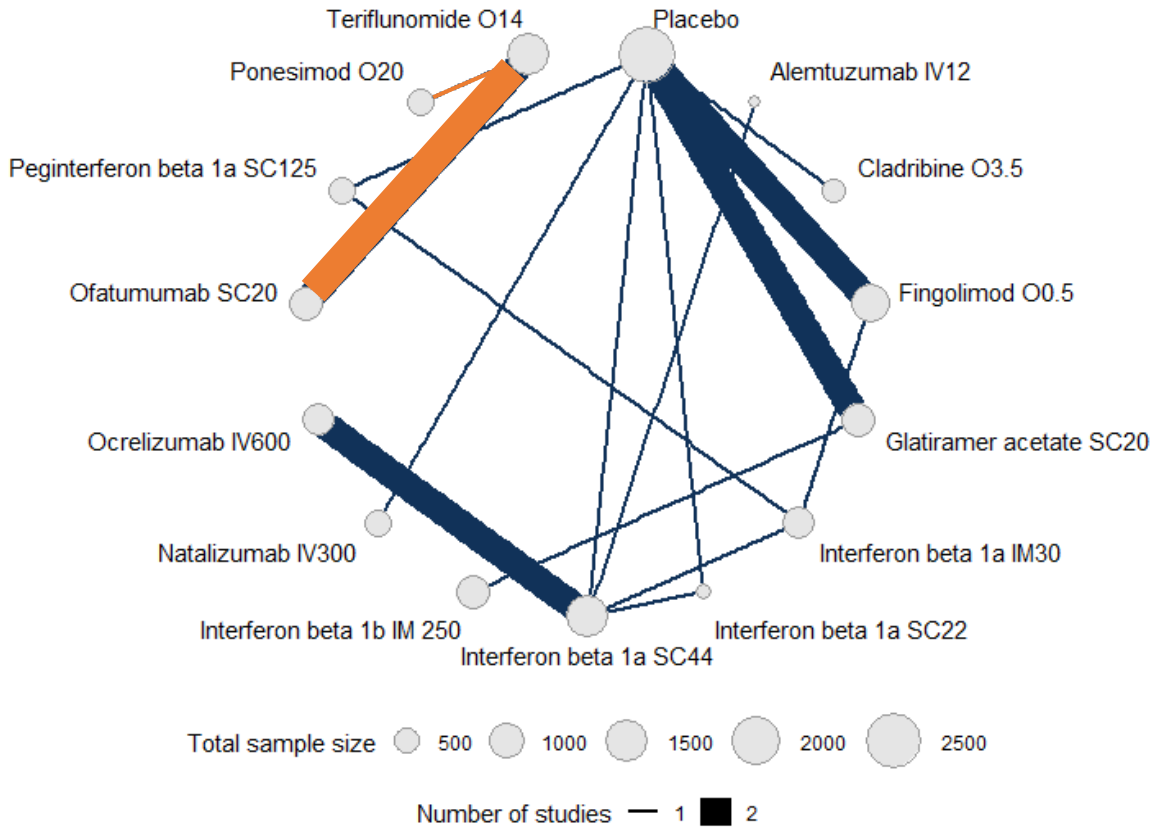
Studies reporting data on CDP3 and CDP6 did not create a completely connected network for either outcome – for both outcomes, teriflunomide, ponesimod and ofatumumab did not connect to the network. We were therefore unable to include these interventions in the NMA. Studies of natalizumab biosimilar and glatiramer acetate SC40 did not report on disease progression and so these interventions were also excluded from the networks for CDP3 and CDP6.

Of the 20 studies that were included in the NMAs for CDP3 and CDP6, six studies were judged at low risk of bias, nine at some concerns regarding risk of bias and five at high risk of bias.

CDP3

Following exclusion of the three studies that did not connect to the network (OPTIMUM, ASCLEPIOS I and ASCLEPIOS II), the remaining 15 studies (10, 635 participants) created a connected network for 11 interventions. The network geometry for this analysis is shown in Figure 9, displaying the treatment nodes and connections, with line thickness representing the number of studies for each comparison and node size the number of patients on each treatment. The placebo group served as the reference group throughout.

Figure 9 Network plot of CDP3 NMA including disconnected treatments (shown with orange lines)



The DIC for the fixed effects model was slightly lower than for the random effects model (22.8 vs 25.1), suggesting that this model gives a better trade off between fit and complexity for the dataset (Table 64 in Appendix 3). The residual deviance was also lower for the fixed effects model than for the random effects model (11.8 vs 12.8 on 16 data points) indicating better fit for the fixed effects model. The DIC and residual deviance together indicate limited heterogeneity in treatment effects across studies. This was confirmed by the heterogeneity standard deviation estimated by the random effects model (tau (95% CrI) of 0.14 (0.005, 0.50), Table 64) being low compared to the average treatment effect on the log rate ratio scale (-0.48). We therefore present results for the fixed effect models for this outcome.

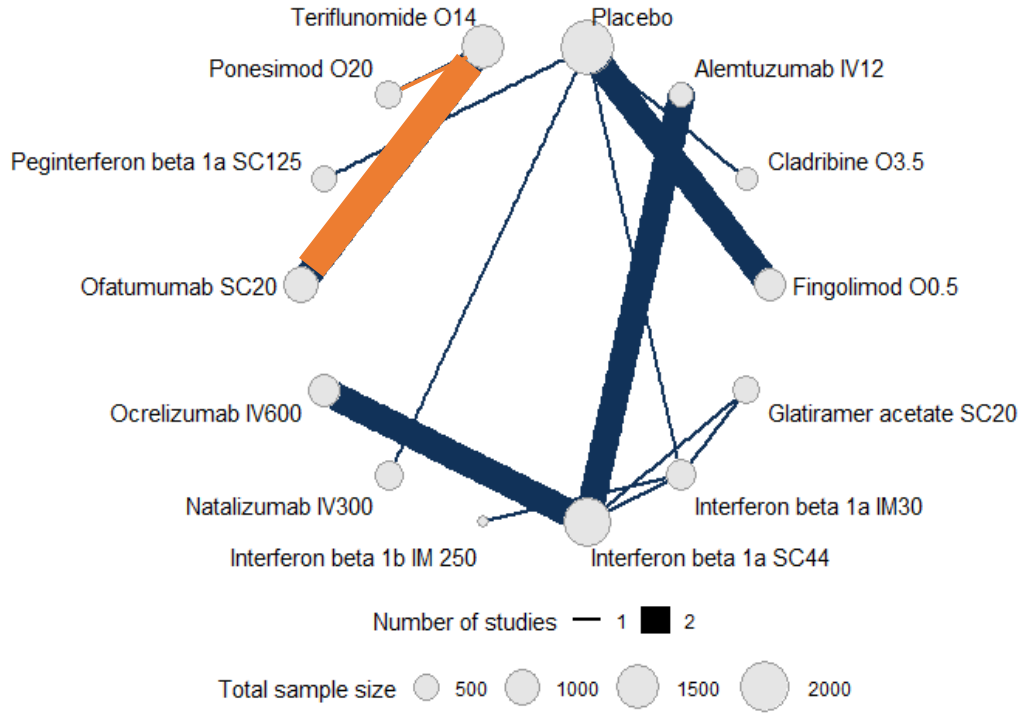
Figure 30 (Appendix 5) shows how well each study fits the NMA model. Both random and fixed effects model had a good fit to the data from all studies included in the network.

Figure 5 shows the HR and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected random effects model, stratified to show estimates from direct and indirect evidence and the overall NMA estimate. Comparison of estimates derived from direct and indirect evidence were similar. Alemtuzumab, ocrelizumab, natalizumab, fingolimod, cladribine and interferon beta 1a (SC22 and SC44) were associated with a greater reduction (i.e., HR<1 AND 95% CrI excluding 1.00) in the risk of CDP3 compared to placebo. There was little evidence to suggest a difference in the risk of CDP3 between those treated with glatiramer acetate or other interferon beta interventions and placebo. Results were very similar for both random and fixed effects models (Table 64 in Appendix 5). The ranking of interventions and the probability that each intervention would be ranked first is shown in Table 8 with Table 61 (Appendix 5) showing the probability that each intervention will rank in a specific position. Alemtuzumab had the highest mean ranking (1.2, 95 % CrI 1, 3) and the greatest probability of ranking first (83%) followed by ocrelizumab (2.1, 95 % CrI 1, 4; 14%). All other interventions in the network, including natalizumab, had a <5% probability of ranking first. Table 65 (Appendix 4) shows the HR (95% CrI) for each intervention pair comparison evaluated in the NMA.

CDP6

In addition to studies of natalizumab biosimilar and glatiramer acetate SC40 not reporting any data on disease progression, the studies of interferon beta 1a SC22 did not report on CDP6 and so this intervention was also excluded from the CDP6 network. The remaining 14 studies (n=9,306) created a connected network for the remaining 10 interventions of interest for this appraisal. The network geometry for this analysis is shown in Figure 10, displaying the treatment nodes and connections, with line thickness representing the number of studies for each comparison and node size the number of patients on each treatment. The placebo group served as the reference group throughout.

Figure 10 Network plot of CDP6 NMA including disconnected treatments (shown with orange lines)



The DIC for the random and fixed effects models were very similar (27.9 vs 28.0) (Table 67). The residual deviance was close to the number of data points for both studies (14.9 vs 17.9 on 14 data points) indicating a good fit for both models. The DIC and residual deviance together indicate limited heterogeneity in treatment effects across studies. The heterogeneity standard deviation estimated by the random effects model (tau (95% CrI) of 0.39 (0.02, 1.19) in Table 64) suggested moderate heterogeneity. Figure 31 (Appendix 5) shows how well each study fits the NMA model. The fixed effects model had a good fit to the data from all studies included in the network. We therefore present results for the fixed effect model for this outcome.

Figure 6 shows the HR and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected random effects model. Note that for this analysis there were no interventions for which both direct and indirect evidence were available – the plot shows which estimates were derived from each type of evidence. alemtuzumab, fingolimod, interferon beta 1b, natalizumab, ocrelizumab, peginterferon beta 1a SC125 were associated with a lower risk of CDP6 than placebo. Results were similar for both random and fixed effects models (Table 67 in Appendix 5), although credible intervals were wider for the random effects model. There was considerable uncertainty in the ranking of interventions and the probability that each intervention would be ranked first (Table 8 and Table 72 (Appendix 5)). Table 71 (Appendix 4) shows the HR (95% CrI) for each intervention pair comparison evaluated in the NMA.

CDP3/6 combined

We conducted a sensitivity analysis where we included the six studies that only reported CDP3 in the analysis for CDP6 to maximise the number of studies that contributed to this analysis. We included 20 studies (n=13,298) evaluating 11 interventions in this analysis. The network geometry for this analysis is the same as for the CDP3 analysis as this combined analysis allowed us to include interferon beta 1a SC22 which was not included in the CDP6 analysis (Figure 9). Results were very similar to those obtained for CDP6 alone (Appendix 5), although with narrower credible intervals.

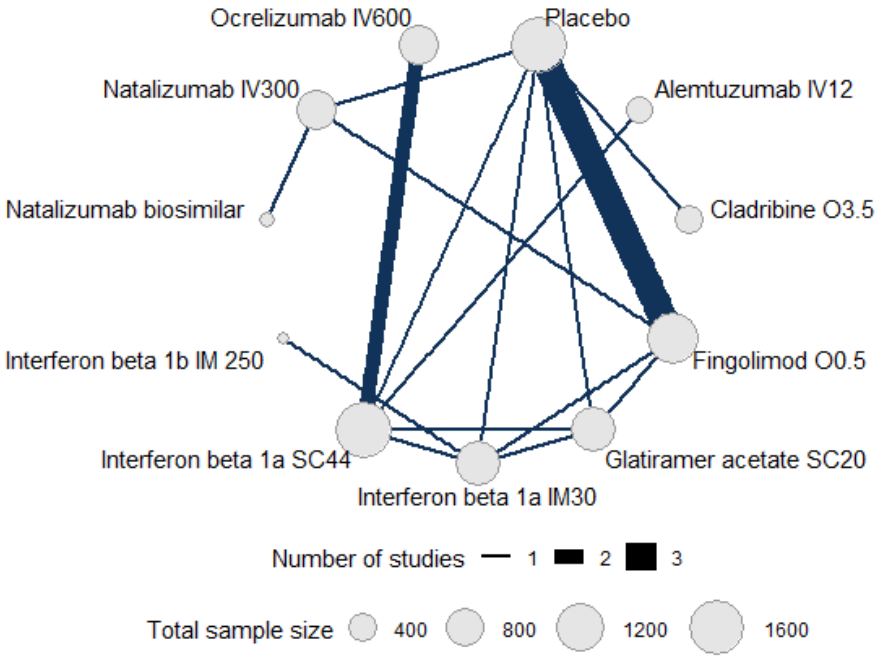
5.1.4 MRI Outcomes

Twenty studies reported data on at least one of the two MRI outcomes of interest for this appraisal: the proportion of patients with gadolinium enhancing (Gd+) or new or enlarging T2 lesions. All but one of these (PRISMS) reported data on Gd+ lesions, and all but three (CombiRx, GATE and Multiple Sclerosis Collaborative Research Group) reported data on T2 lesions. For Gd+ lesions, most studies reported on the proportion of patients with "any" Gd+ lesions, some reported only on new lesions. Studies reported MRI outcomes at between 4 and 24 months follow-up, with a median of 24 months. There were no data on MRI outcomes of interest for studies of the following interventions and so these were not able to be included in the NMAs for these outcomes: ofatumumab, glatiramer acetate (SC40), ponesimod, teriflunomide, and peginterferon beta 1a. Data were only available for T2 lesions for interferon beta 1a (SC22) and so this was only included for this outcome. Natalizumab biosimilar was only directly compared with natalizumab. Natalizumab was also directly compared to placebo and fingolimod and so could be compared to other treatments via these nodes.

Gadolinium (Gd+) enhancing lesions

Nineteen studies (9, 471 participants) reported data on Gd+ lesions and created a connected network for 11 interventions of interest for this appraisal (Figure 11). The placebo group served as the reference group throughout.

Figure 11 Network plot for NMA for proportion of participants with Gd+ lesions



The DIC (27.9 vs 28.5) and residual deviance (17.8 vs 16.5 on 19 data points) were similar for both fixed and random effects models and indicated good fit for both models with limited heterogeneity (Table 73). This was confirmed by the heterogeneity standard deviation estimated by the random effects model (tau (95% CrI) of 0.11 (0.006, 0.32) in Table 73). We therefore present results for the fixed effect models for this outcome. Figure 28 (Appendix 5) shows how well each study fits the NMA model. The fixed effects model had a good fit to the data from all studies included in the network.

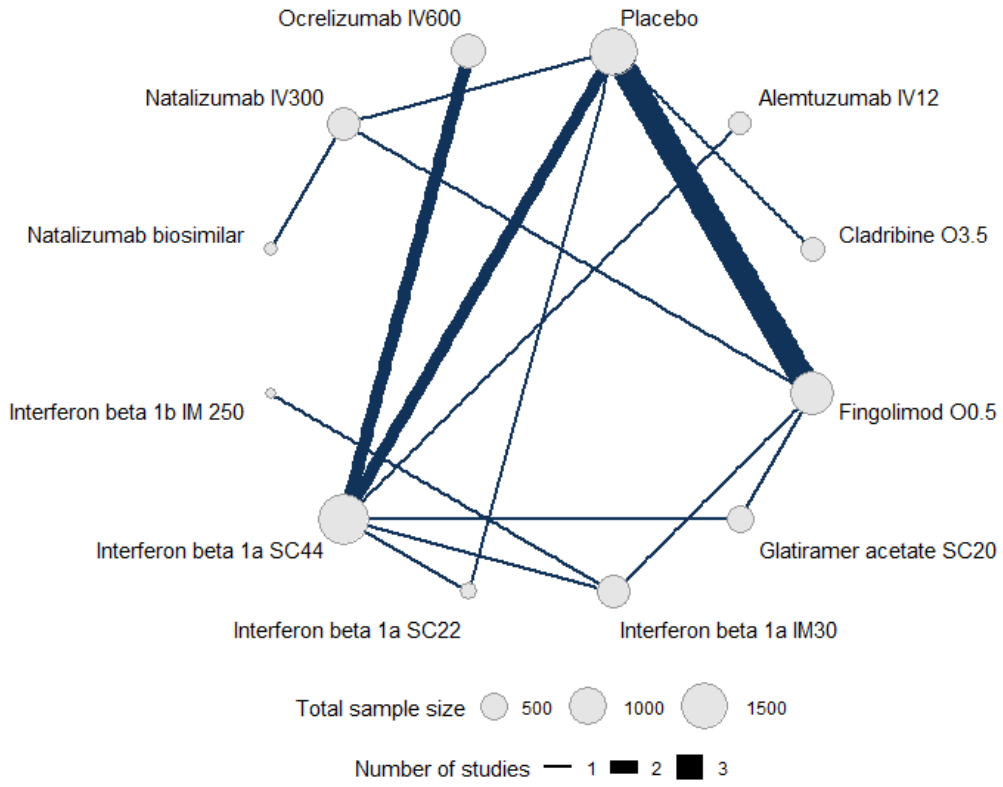
Figure 7 shows the hazard ratio (HR) and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected fixed effects model, stratified to show estimates from direct and indirect evidence and the overall NMA estimate. Comparison of estimates derived from direct and indirect evidence were similar. All interventions were associated with a greater reduction (i.e., HR<1 AND 95% CrI excluding 1.00) in the risk of developing Gd+ lesions compared to placebo. Results were very similar for both random and fixed effects models (Table 73 in Appendix 5). The ranking of interventions and the probability that each intervention would be ranked first is shown in Table 8, with Table 75 (Appendix 5) showing the probability that each intervention will rank in a specific position. Ocrelizumab had the highest mean ranking (1.4, 95 % CrI 1, 3) and the greatest probability of ranking first (68%) followed by natalizumab biosimilar (2.1, 95 % CrI 1, 4; 30%) and natalizumab (2.9, 95% CrI 2, 4; 1%). All other interventions had a 0% probability of ranking first. The different interferon and glatiramer acetate interventions were ranked similarly to each other and as less effective than the newer drugs. Table 74 (Appendix 4) shows the HR (95% CrI) for each intervention pair comparison evaluated in the

NMA. This shows that the HR (95% CrI) for natalizumab compared to natalizumab biosimilar, the key comparison for this appraisal, was 1.29 (0.69, 2.37), suggesting no difference between the HR for these two interventions.

New or enlarging T2 weighted lesions

The 17 studies (8,883 participants) that reported data on T2 weighted lesions created a connected network for 12 interventions of interest for this appraisal (Figure 1). The placebo group served as the reference group throughout.

Figure 12 Network plot for NMA for proportion of participants with new or enlarging T2 lesions



The DIC (26.4 vs 27.9) and residual deviance (14.5 vs 15.6 on 18 data points) were very similar for both fixed and random effects models and indicated good fit for both models with limited heterogeneity in treatment effects across studies (Table 76). This was confirmed by the heterogeneity standard deviation estimated by the random effects model (tau 95% of 0.07 (0.002, 0.25) in Table 76). We therefore present results for the fixed effect models for this outcome. Figure 34 (Appendix 5) shows how well each study fits the NMA model. The fixed effects model had a good fit to the data from all studies included in the network, except the IMPROVE study. This study reported data at very short follow-up (4 months) and compared interferon beta 1a SC44 to placebo.

Figure 7 shows the hazard ratio (HR) and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected fixed effects model, stratified to show estimates from direct and indirect evidence and the overall NMA estimate. Comparison of estimates derived from direct and indirect evidence were similar. All interventions except interferon beta 1a SC44 were associated with a greater reduction (i.e., HR<1 AND 95% CrI excluding 1.00) in the risk of relapses compared to placebo. Results were very similar for both random and fixed effects models (Table 76 in Appendix 5). The ranking of interventions and the probability that each intervention would be ranked first is shown in Table 8, with Table 81 (Appendix 5) showing the probability that each intervention will rank in a specific position. Ocrelizumab had the highest mean ranking (2.2, 95 % CrI 1, 5) and a similar probability of ranking first (30%) to natalizumab biosimilar (3.0, 95 % CrI 1, 7; 31%) and interferon beta 1b (3.1, 95% CrI 1, 8; 32%). Natalizumab had the next highest ranking (3.5, 95% CrI 1, 6) and a 4% probability of ranking first. All other interventions had a 0% probability of ranking first. The different interferon beta 1a and glatiramer acetate interventions were ranked similarly to each other and as less effective than the newer drugs. Table 77 (Appendix 4) shows the HR (95% CrI) for each intervention pair comparison evaluated in the NMA. This shows that the HR (95% CrI) for natalizumab compared to natalizumab biosimilar, the key comparison for this appraisal, was 1.07 (0.73, 1.57) suggesting no difference between the HR for these two interventions.

5.1.5 Adverse events

All but four of the included studies reported at least one of the adverse events outcomes of interest. Etemedifir 2006 and Calabrese 2012 did not report any data on adverse events; INCOMIN and PRISMS only reported data on the incidence of specific adverse events and so could not be included in our synthesis. Adverse events reported in the studies included a range of symptoms and reactions. These encompass injection site issues such as erythema, pain, pruritus, swelling, bruising, and immediate post-injection reactions, as well as systemic symptoms like influenza-like illness, chills, pyrexia, and fatigue. Common neurological and musculoskeletal complaints included headache, migraine, myalgia, arthralgia, dizziness, blurred vision, paraesthesia, and muscular weakness. Infections were frequently noted, including nasopharyngitis, urinary tract infections, upper respiratory tract infections, oral herpes, bronchitis, sinusitis, and meningitis. Other adverse events span gastrointestinal symptoms like nausea, diarrhoea, constipation, and abdominal pain, alongside more serious conditions such as hepatic toxicity, liver failure, and neoplasms. Psychiatric conditions, particularly depression and anxiety, were reported, as were dermatological issues like rash, alopecia, and hypoesthesia. Cardiovascular effects such as hypertension and bradycardia were also mentioned. Additionally, rare but serious conditions included autoimmune events and thyroid disorders.

Mortality (from any cause) was only reported in 27 trials, and where reported this was very rare. The majority of studies reported no deaths, with a maximum of 2 deaths in any treatment group. Only four studies reported on progressive multifocal leukoencephalopathy

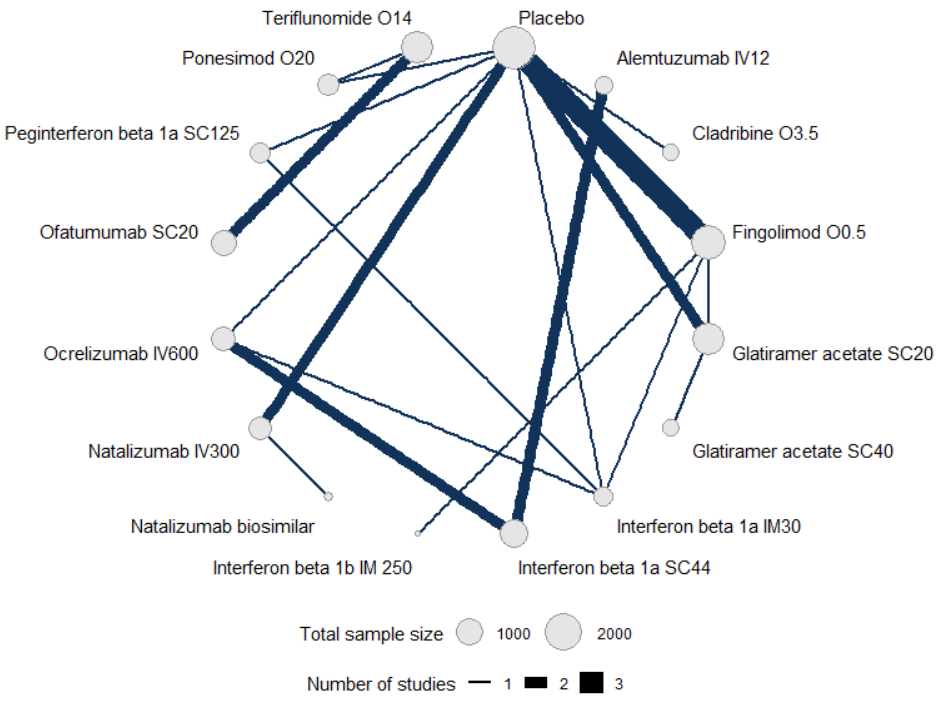
(PML) – none of these reported any cases of PML. None of the included studies reported data on grade 3-4 AEs.

Twenty studies were judged at low risk of bias for adverse events, eleven were judged at some concerns and five were judged at high risk of bias.

Any AEs

Twenty four studies (9, 471 participants) reported data on the incidence of any adverse events. These studies created a connected network for 16 interventions of interest for this appraisal (Figure 13) – the only intervention for which data on any AEs were not available was interferon beta 1a (SC22). The placebo group served as the reference group throughout. Follow-up duration ranged from 6 to 24 months with a median of 18 months – slightly shorter than for the effectiveness outcomes.

Figure 13 Network plot for NMA for any AEs



The DIC for the fixed effects model was lower than for the random effects model (32.6 vs 34.8), suggesting that this model gives a better trade off between fit and complexity for the dataset (Table 79). The residual deviance was also lower for the fixed effects model (17.8 vs 18.7 on 25 data points). However both indicated good fit for their respective models. The DIC and residual deviance together indicate limited heterogeneity in treatment effects across studies. This was confirmed by the heterogeneity standard deviation estimated by the random effects model (tau (95% CrI) of 0.03 (0.002, 0.11) in Table 79). We therefore present results for the fixed effects model for this outcome. Figure 35 (Appendix 5) shows

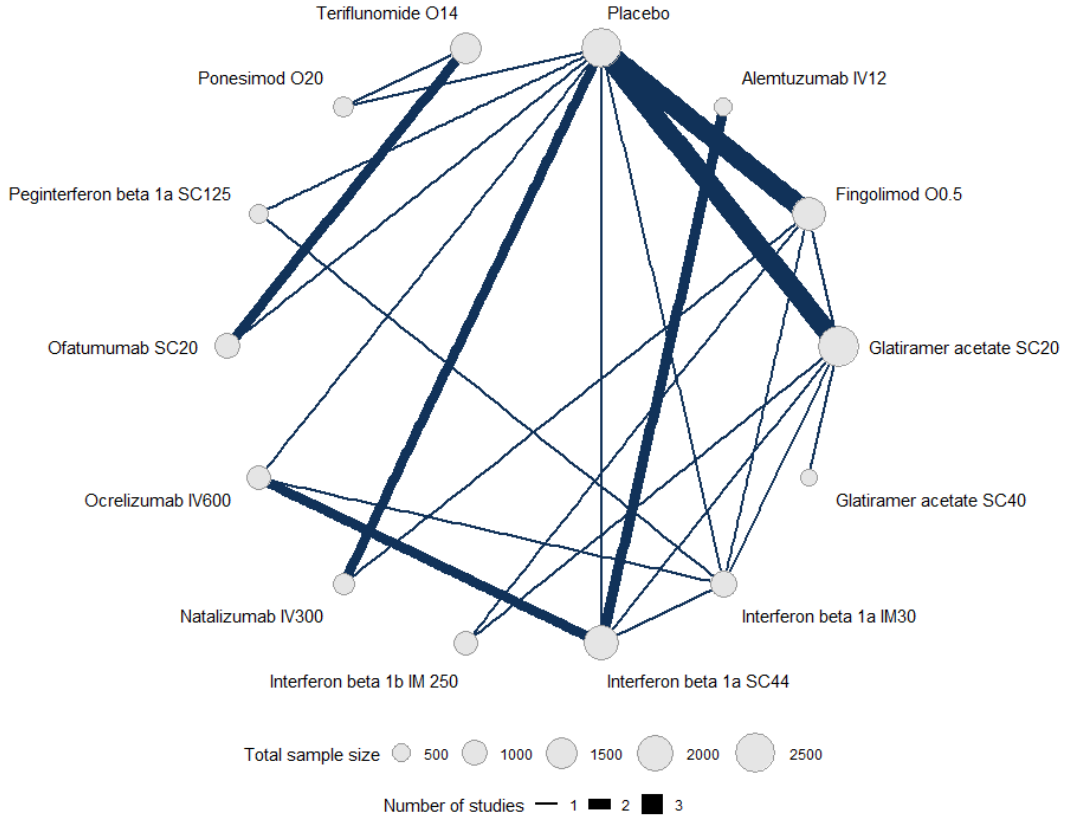
how well each study fits the NMA model. The fixed effects model had a good fit to the data from all studies included in the network.

Figure 16 shows the hazard ratio (HR) and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected fixed effects model, stratified to show estimates from direct and indirect evidence and the overall NMA estimate. Comparison of estimates derived from direct and indirect evidence were similar. There was no evidence of a difference in the risk of developing any AE between any of the interventions and placebo (i.e., HR<1 AND 95% CrI excluding 1.00). Results were very similar for both random and fixed effects models (Table 79 in Appendix 5). Table 81 (Appendix 5) showing the probability that each intervention will rank in a specific position with better rankings suggesting a lower risk of AEs. Table 80 (Appendix 4) shows the HR (95% CrI) for each intervention pair comparison evaluated in the NMA. This shows that the HR (95% CrI) for natalizumab compared to natalizumab biosimilar, the key comparison for this appraisal, was 1.06 (0.77, 1.46) suggesting no difference between the HR for these two interventions.

Serious AEs

Thirty studies (18, 748 participants) reported data on the incidence of serious adverse events (SAEs). These studies created a connected network for 14 interventions of interest for this appraisal (Figure 13Figure 11) – data on any SAEs were not available for interferon beta 1a (SC22), cladribine or natalizumab biosimilar. The placebo group served as the reference group throughout. Duration of follow-up ranged from 6 to 36 months with a median of 18 months.

Figure 14 Network plot for NMA for serious AEs



The DIC for the fixed effects model was slightly lower than for the random effects model (36.8 vs 37.8), suggesting that this model gives a better trade off between fit and complexity for the dataset (Table 82). Both models have residual deviances lower than the number of data points (23.7 vs 23.1 on 31 data points) with the fixed effects model suggesting a slightly better fit. The DIC and residual deviance together indicate limited heterogeneity in treatment effects across studies. This was confirmed by the heterogeneity standard deviation estimated by the random effects model (tau (95% CrI) of 0.11 (0.004, 0.32) in Table 82). We therefore present results for the fixed effect models for this outcome. Figure 36 shows how well each study fits the NMA model. Although FREEDOMS shows a higher residual deviance than the rest of studies, it's 95% CrI fall within the acceptable range, so we consider the fixed effects model had a good fit to the data from all studies included in the network.

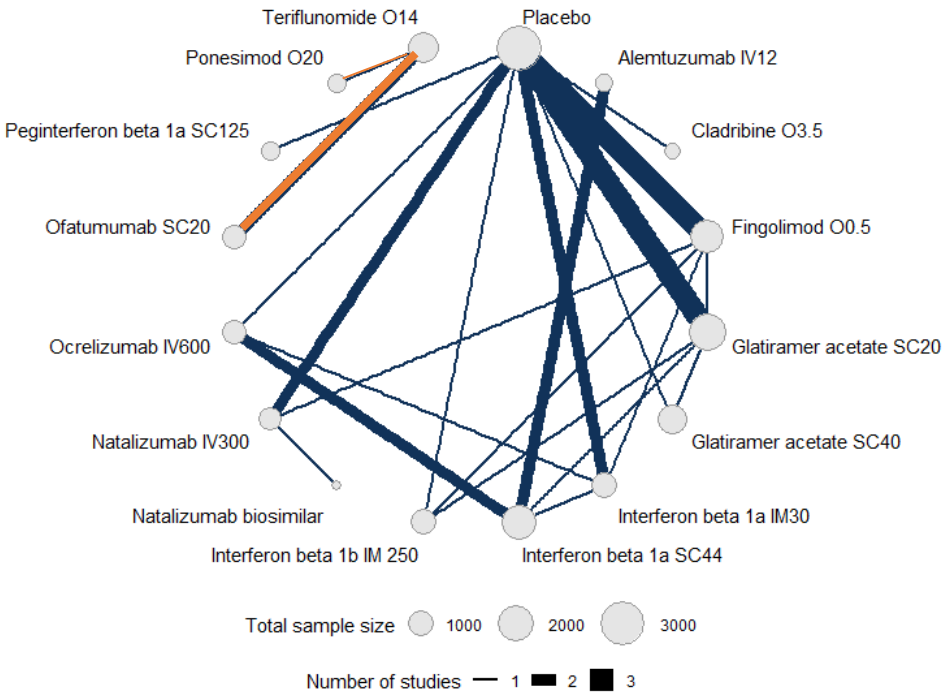
Figure 17 shows the hazard ratio (HR) and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected fixed effects model, stratified to show estimates from direct and indirect evidence and the overall NMA estimate. Comparison of estimates derived from direct and indirect evidence were similar. There was no evidence of a difference in the risk of developing serious AE between any of the interventions and placebo (i.e., HR<1 AND 95% CrI excluding 1.00). Results were very similar for both random and fixed effects models (Table 82 Comparison of results from fixed

and random effects NMA for SAEs (RRMS population)Table 79 in Appendix 5). Table 84 (Appendix 5) shows the probability that each intervention will rank in a specific position. Table 83 shows the HR (95% CrI) for each intervention pair comparison evaluated in the NMA. There was no data on frequency of serious AE for natalizumab biosimilar, so a comparison to Natalizumab was not possible.

AEs leading to treatment discontinuation

Twenty nine studies (17,892 participants) reported data on the incidence of AEs leading to treatment discontinuation. These did not create a completely connected network – teriflunomide, ponesimod and ofatumumab did not connect to the network (Figure 15). We were therefore unable to include these interventions in the NMA. Data on any AEs leading to treatment discontinuation were not available for interferon beta 1a (SC22) and this was also not included in the network. The placebo group served as the reference group throughout.

Figure 15 Network plot for NMA for AEs leading to treatment discontinuation including disconnected treatments (shown with orange lines)



The DIC for the fixed effects model was slightly lower than for the random effects model (41.2 vs. 41.7), suggesting that this model gives a slightly better trade-off between fit and complexity for the dataset (Table 85). Both models have residual deviances close to the number of data points (29.2 vs 26 on 28 data points) with the fixed effects model suggesting a slightly better fit. The DIC and residual deviance together indicate limited heterogeneity in treatment effects across studies. This was confirmed by the heterogeneity standard

deviation estimated by the random effects model (tau (95% CrI) of 0.27 (0.01, 0.69) in Table 85). We therefore present results for the fixed effect models for this outcome. Figure 37 Model fit for discontinuation due to AEs assessed by individual study residual deviance (fixed effects analysis; RRMS population) shows how well each study fits the NMA model. Although FREEDOMS and TRANSFORMS show a higher residual deviance than the rest of studies, its 95% CrI fall within the acceptable range. GATE shows a high residual deviance, but this is a very small study, so we consider the fixed effects model had a good fit to the data from studies included in the network in general.

Figure 18 shows the hazard ratio (HR) and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected fixed effects model, stratified to show estimates from direct and indirect evidence and the overall NMA estimate. Comparison of estimates derived from direct and indirect evidence were similar. There was evidence of an increased risk of presenting with an adverse event leading to discontinuation for fingolimod HR (95% CRI), glatiramer acetate, interferon beta 1a SC44, interferon beta 1b, and peginterferon beta 1a compared with placebo. There was no evidence of a difference in the risk of AEs leading to treatment discontinuation between any of the other interventions and placebo. Results were very similar for both random and fixed effects models (Table 82in Appendix 5). Table 87 (Appendix 5) shows the probability that each intervention will rank in a specific position. Table 86 shows the HR (95% CrI) for each intervention pair comparison evaluated in the NMA. This shows that the HR (95% CrI) for natalizumab compared to natalizumab biosimilar, the key comparison for this appraisal, was 0.48 (0.13, 1.76) suggesting no difference between the HR for these two interventions.

Treatment related AEs

Only eight studies (3,361 participants) reported data on treatment related adverse events. These did not create a connected network and so an NMA was not possible. Instead, we provide a summary of the results from these studies in Table 9. Interventions evaluated included Peginterferon beta 1a, natalizumab, natalizumab biosimilar, ofatumumab, ocrelizumab, glatiramer acetate, interferon beta 1a, and peginterferon beta 1a. There was no difference between interventions in the proportion of treatment related AEs for any of the studies.

Table 9 Summary of studies that reported data on treatment related AEs, including RR and 95% CIs for the difference in risk between intervention and comparator groups

Study Name	Intervention	Comparator	Follow-up	RR (95% CI)
ADVANCE[80]	Peginterferon beta 1a SC125	Placebo	12	1.69 (0.54, 0.65)
ANTELOPE[76]	Natalizumab IV300	Natalizumab biosimilar	6	1.11 (0.56, 1.46)
APOLITOS[69]	Ofatumumab SC20	Placebo	6	0.86 (0.87, 1.54)
CONFIDENCE[88]	Glatiramer acetate SC40	Glatiramer acetate SC20	6	1.0 (0.83, 1.21)
Kappos 2011[100]	Interferon beta 1a IM30	Placebo	6	0.76 (0.83, 2.09)
	Ocrelizumab IV600	Placebo	6	0.67 (0.92, 2.44)
PEGINTEGRITY[65]	Peginterferon beta 1a SC125	Interferon beta 1a IM30	24	0.94 (0.9, 1.25)
REGARD[103]	Glatiramer acetate SC20	Interferon beta 1a SC44	24	0.99 (0.89, 1.11)

Study Name	Intervention	Comparator	Follow-up	RR (95% CI)
REVEAL[78]	Natalizumab IV300	Fingolimod O0.5	6	0.72 (0.95, 2.04)

5.1.6 Quality of life

Only eight studies provided data on quality of life assessed using the EQ-5D or SF-36 tools. Results from these studies are summarised in Table 57 (Appendix 4). Six studies provided data on the SF-36 (ADVANCE, CARE-MS I, CONFIRM, AFFIRM, OPERA I, OPERA II) and five studies provided data on EQ-5D (CLARITY, FREEDOMS II, ADVANCE, CARE-MS I, CONFIRM). Four studies were judged at high risk of bias, three were at low risk of bias, and one was at low concerns for the EQ-5D visual analogue scale and some concerns for the EQ-5D utility score and SF-36 measures.

There was no evidence of a difference between groups for any of the studies that reported data on the EQ-5D mean utility or VAS scores. Interventions evaluated in these studies were cladribine, fingolimod, peginterferon beta and glatiramer acetate vs placebo and alemtuzumab vs interferon beta 1a. Three studies (ADVANCE, AFFIRM and CARE-MS I) reported no differences between groups for either the physical component summary (PCS) or mental component summary (MCS) component of the SF-36. These studies compared peginterferon beta 1a and natalizumab with placebo and alemtuzumab with interferon beta 1a. The CONFIRM study reported a greater improvement in PCS with glatiramer acetate than with placebo ($p<0.05$) but found no difference for MSC. OPERA I reported no difference in change from baseline in PCS between ocrelizumab and interferon beta 1a ($p=0.22$), while OPERA II found a greater improvement in PCS with ocrelizumab compared to placebo ($p=0.04$).

A further four studies provided data on QoL but did not use the standard EQ-5D or SF-36 specified as in scope for this appraisal. The used the MSQoL-54[106] (GOLDEN, PEGINTEGRITY), MSIS-29 (ASSESS)[107] and a 0-100 VAS to measure global wellbeing VAS (Saida 2017).

5.1.7 Summary

Table 10 provides an overview of the results for each outcome in the general RRMS population. For each outcome, it provides a summary of the number of studies that contributed to the synthesis, the number of interventions included in the synthesis and any interventions for which data were not available for this outcome, the most and least effective interventions, and any information available on the comparison of natalizumab biosimilar and natalizumab, or where data were not available on natalizumab biosimilar we summarise evidence on natalizumab compared to placebo.

Figure 16 Forest plot of hazard ratio (HR) and 95% credible intervals for time to developing at least one adverse event (fixed effects NMA; RRMS population).

Blue lines indicate result from the NMA, green lines indicate results from direct evidence and purple lines from indirect evidence. P-values relate to comparisons between direct and indirect evidence. Note that the indirect evidence lines are only included if there is also direct evidence

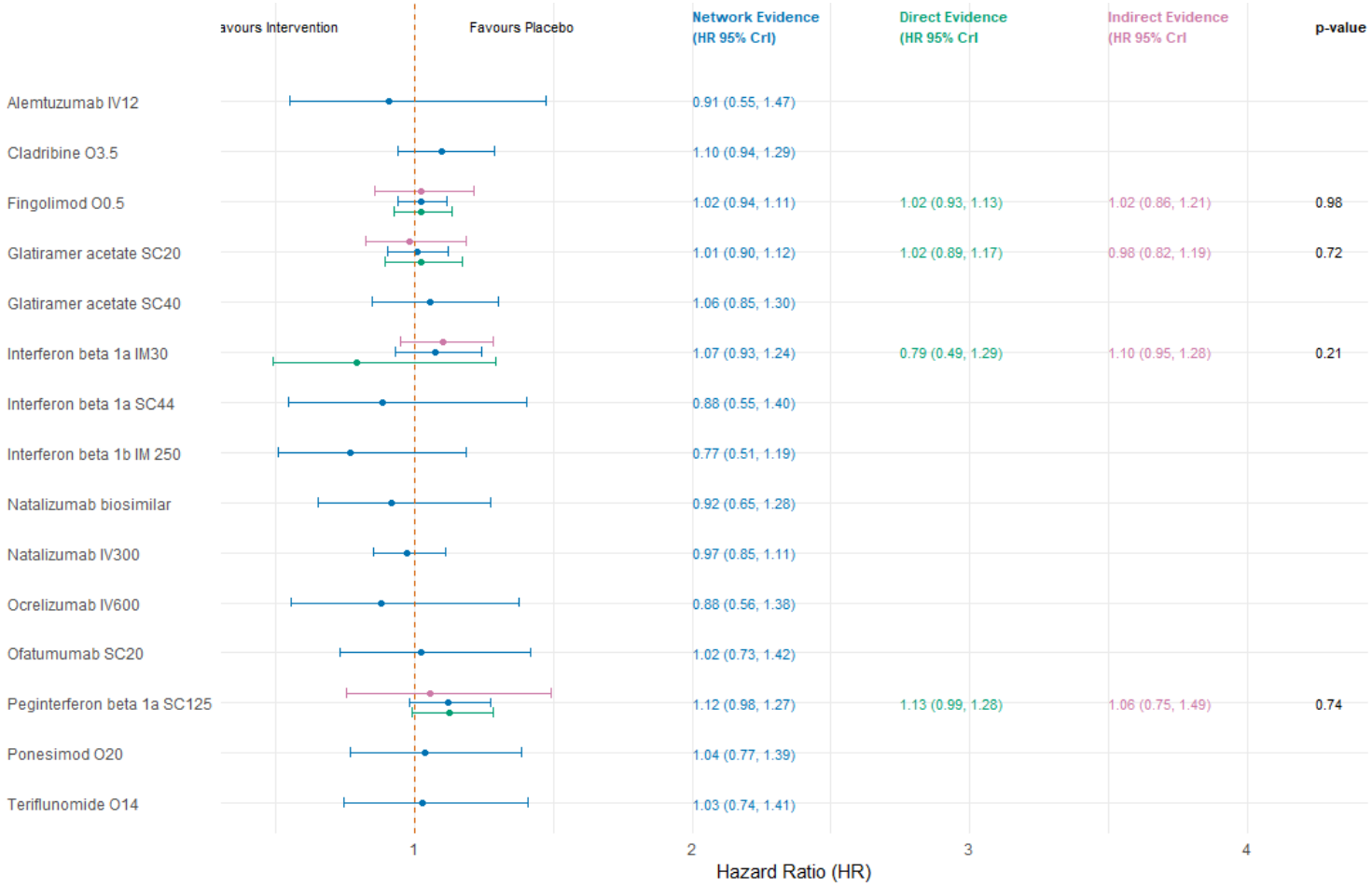


Figure 17 Forest plot of hazard ratio (HR) and 95% credible intervals for time to developing at least one serious adverse event (fixed effects NMA; RRMS population).

Blue lines indicate result from the NMA, green lines indicate results from direct evidence and purple lines from indirect evidence. P-values relate to comparisons between direct and indirect evidence. Note that the indirect evidence lines are only included if there is also direct evidence

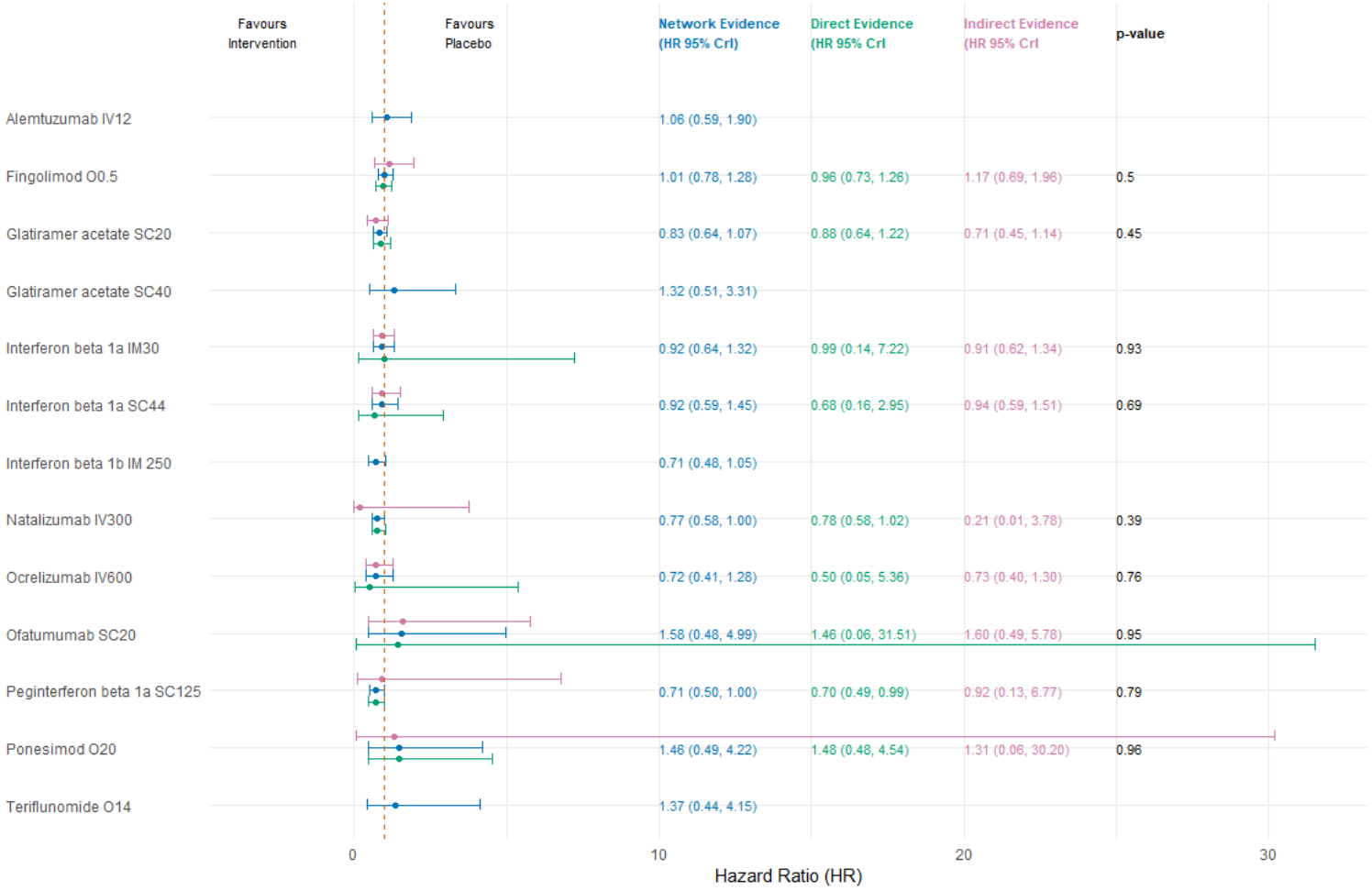


Figure 18 Forest plot of hazard ratio (HR) and 95% credible intervals for time to treatment discontinuation (fixed effects NMA; RRMS population).

Blue lines indicate result from the NMA, green lines indicate results from direct evidence and purple lines from indirect evidence. P-values relate to comparisons between direct and indirect evidence. Note that the indirect evidence lines are only included if there is also direct evidence

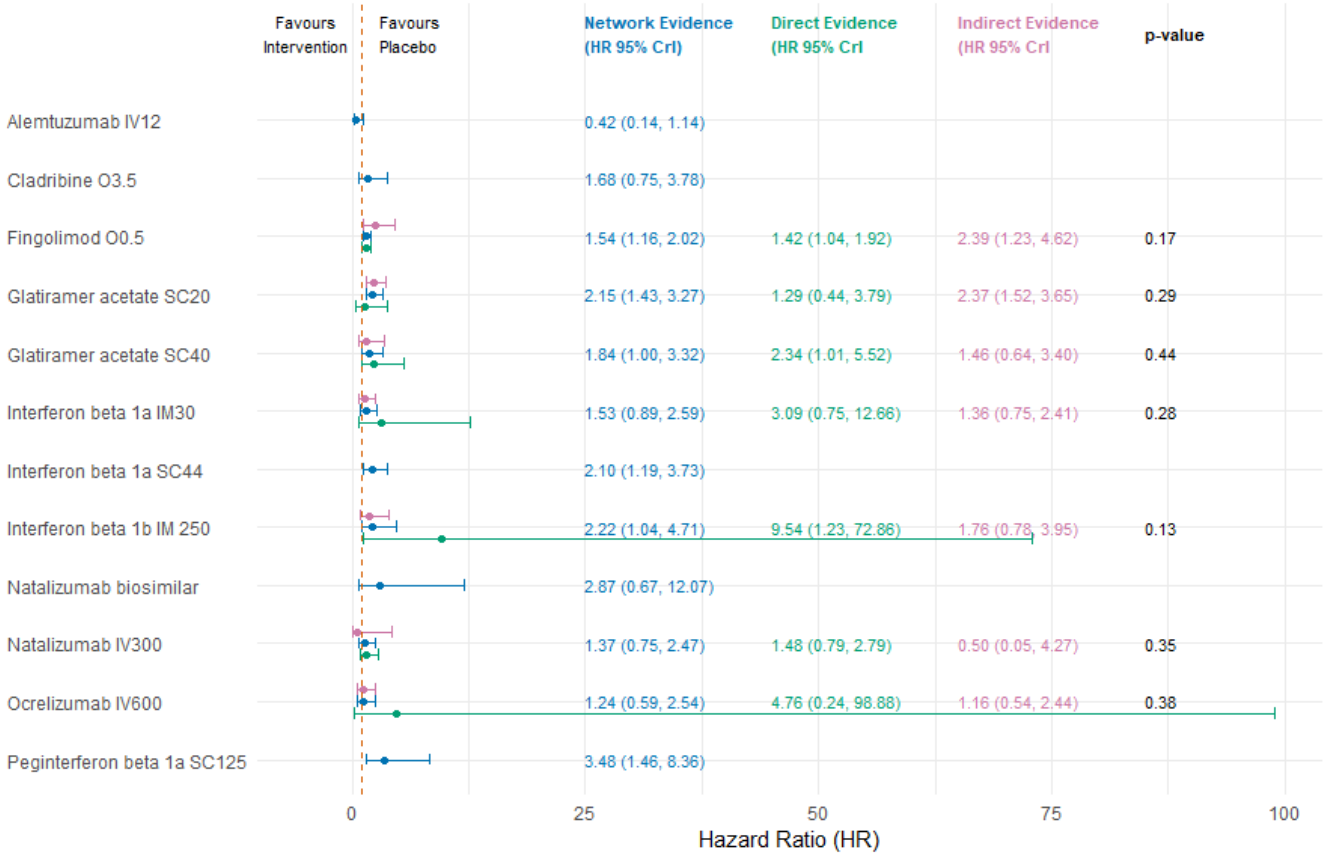


Table 10 Summary of results for each outcome evaluated in the RRMS studies

Outcome	Number of studies (participants)	Number of interventions in network	Interventions excluded from network/synthesis	Most effective interventions	Least effective interventions	Data on Natalizumab and Natalizumab biosimilar
ARR	39 (20, 810)	17	AHSCT	Alemtuzumab, natalizumab and ocrelizumab	Interferon beta, glatiramer acetate, ponesimod, teriflunomide	Natalizumab vs natalizumab biosimilar: RR 0.65 (95% CI 0.33, 1.23)
CDP3	15 (10, 635)	12	AHSCT, teriflunomide, ponesimod, ofatumumab, natalizumab biosimilar, glatiramer acetate SC40	Alemtuzumab, cladribine, fingolimod, natalizumab, ocrelizumab, interferon beta 1a (SC22 & 44) and peginterferon beta 1a	Other interferon beta and glatiramer acetate	Natalizumab vs placebo HR 0.58 (0.43, 0.76)
CDP6	14 (9,306)	11	AHSCT, teriflunomide, ponesimod, ofatumumab, natalizumab biosimilar, glatiramer acetate SC40, interferon beta 1a SC22	Alemtuzumab, fingolimod, natalizumab ocrelizumab, interferon beta 1b and peginterferon beta 1a	Other interferon beta, glatiramer acetate, cladribine	Natalizumab vs placebo: HR 0.46 (0.33, 0.63)
MRI Gd+	19 (10, 562)	11	AHSCT, ofatumumab, interferon beta 1a (SC22), glatiramer acetate (SC40), ponesimod, teriflunomide, peginterferon beta 1a	Alemtuzumab, cladribine, fingolimod, natalizumab, natalizumab biosimilar, ocrelizumab, interferon beta 1b	Interferon beta 1a and glatiramer acetate	Natalizumab vs natalizumab biosimilar: HR 1.29 (0.69, 2.37),
MRI T2	17 (8,883)	12	AHSCT, ofatumumab, glatiramer acetate (SC40), ponesimod, teriflunomide, peginterferon beta 1a	Alemtuzumab, cladribine, fingolimod, natalizumab, natalizumab biosimilar, ocrelizumab, interferon beta 1b	Interferon beta 1a and glatiramer acetate	Natalizumab vs natalizumab biosimilar: HR 1.07 (0.73, 1.57)
AEs: Any	24 (16, 673)	16	AHSCT, interferon beta 1a (SC22),	No evidence of a difference between interventions		Natalizumab vs natalizumab biosimilar: HR 1.07 (0.73, 1.57)

Outcome	Number of studies (participants)	Number of interventions in network	Interventions excluded from network/synthesis	Most effective interventions	Least effective interventions	Data on Natalizumab and Natalizumab biosimilar
AEs: SAE	30 (18, 748)	14	AHSCT , iterferon beta 1a (SC22), cladribine, natalizumab biosimilar	No evidence of a difference between interventions		Natalizumab vs placebo: HR 0.77 (0.58, 1.00)
AEs: Treatment discon-tinuation	29 (17, 892)	13	AHSCT, ofatumumab, interferon beta 1a (SC22), ponesimod, teriflunomide	No evidence of a difference for all other interventions	Fingolimod, glatiramer acetate, interferon beta 1a (SC44), interferon beta 1b, & peginterferon beta 1a	Natalizumab vs natalizumab biosimilar: HR 0.48 (0.13, 1.76)
Treatment related AEs	8 (3,361)	7	All except: Peginterferon beta 1a, natalizumab, natalizumab biosimilar, ofatumumab, glatiramer acetate, interferon beta 1a, ocrelizumab	No evidence of a difference between interventions		Natalizumab vs natalizumab biosimilar: RR 1.11 (0.56, 1.46)
Quality of Life	8	4	All except: cladribine, fingolimod, peginterferon beta and glatiramer acetate	Little evidence of any effect on QoL		No data

5.2 Highly active MS (HARRMS) population

Eight studies (2,097 participants) reported data on patients with HARRMS. Two of these studies (CARE-MS II[71] and MIST[72]) were conducted exclusively in patients with HARRMS the others were conducted in the general RRMS population but reported results separately for the highly active population. For OPERA I & II[67] and for FREEDOMS and FREEDOMS II[73], results were only available for the two studies combined – we therefore consider these as single studies in this section. None of the studies evaluated natalizumab or natalizumab biosimilar, the technologies of interest for this appraisal. However, one of the studies that compared natalizumab with placebo was conducted in a population where participant were required to have had at least one relapse in the previous year and a very high proportion of participants (88%) had previously been treated with a DMT (IFN beta 1a, IFN beta 1b, azathioprine, or fingolimod) – this was close to the definition that we set in section 4.3.6 of at least 90% having highly active disease. This study was conducted exclusively in Japanese patients. We included this study in the analysis for the HARRMS population as the best available evidence. However, this study only reported data on ARR and AEs.

Table 5 provides an overview of the interventions evaluated by the included studies. Interventions evaluated in the HARRMS included: fingolimod, ocrelizumab, alemtuzumab, and cladribine with Saida 2017 evaluating natalizumab. Two studies included a placebo control group, four studies included beta-interferon as the comparator and one compared AHSCT to a DMT as chosen by the investigators.

Table 46 (Appendix 3) provides a summary of the baseline characteristics of participants included in the HARRMS studies. OPERA I/II[67] did not report baseline characteristics separately for the HARRMS population. For the other studies, mean age ranged from 35 to 39 years (median 37 years – similar to the overall RRMS population), the proportion of female participants ranged from 62 to 76% (median 69%, also similar to the overall RRMS population), baseline EDSS score from 1.0 to 3.5 (median 2.7 – slightly higher than overall RRMS), baseline annual relapse rate was only reported for CARE-MS II and FREEDOMS II and ranged from 1.5 to 1.7 (lower than RRMS population), and mean disease duration at baseline ranged from 4.5 to 7 years (median 6.2 years), ethnicity was not reported in these studies. All participants had received previous treatment with DMTs – the actual treatments varied across studies but generally included interferon beta 1a, interferon beta 1b, and glatiramer acetate. Publication years ranged from 2010 to 2019.

Definitions of highly active disease varied across studies – all required previous treatment with DMT, some definitions specified that this should have been either interferon beta or glatiramer acetate others did not specify which treatments. Studies also included requirements for relapses in the previous year, despite treatment, but the specific requirements varied across studies from at least one relapse in the previous year with MRI evidence of progression, at least the same number of relapses in the previous year as in the previous 2 years or the preceding year.

5.2.1 Risk of bias

Table 11 provides a summary of the risk of bias assessment for studies in the HARRMS population, stratified according to outcome. Results tables in Appendix 4 also include the overall risk of bias for each study for each outcome evaluated. All studies had the same overall risk of bias judgement for all outcomes; three (CARE-MS II, MIST and FREEDOMS I/II) were judged at high risk of bias – in CARE-MS II and MIST participants were aware of treatment allocation, and in FREEDOMS II there was a large proportion of missing data which was considered potentially related to the outcome. The CLARITY study was judged at some concerns as there was missing data, but all randomised participants were included in the analysis. The other two studies in the HARRMS population (FREEDOMS and TRANSFORMS) and Saida 2017 were judged at low risk of bias.

5.2.2 Annualised Relapse Rate (ARR)

All studies except MIST reported data on ARR. The studies did not create a connected network, but by assuming a class effect for the two different interferon beta 1a comparators (IM30 and SC44) and combining these into a single node we were able to create a connected network.

We therefore included six studies (2,162 participants) evaluating seven interventions in the NMA for ARR in the highly active population. The network geometry for this analysis is shown in Figure 19. The placebo group served as the reference group throughout. The DIC for the fixed effects model was similar to that for the random effects model (16.2 vs 16.1) (Table 88). The residual deviance was very similar for both fixed and random effects (8.1 vs 8.0 on 8 data points) and indicated good fit for both models. The heterogeneity standard deviation estimated by the random effects model (tau (95% CrI) of 1.40 (0.05, 3.95) in Table 59) was high when compared to the average treatment effect on the log rate ratio scale (-0.58 in Table 59) but its 95% CrI were wide suggesting limited evidence to estimate it, thus supporting the use of fixed effects. We therefore present results for the fixed effects model for this outcome. Figure 38 (Appendix 5) shows very good fit for each study to the NMA model.

Figure 19 Network plot for NMA for ARR (highly active population)

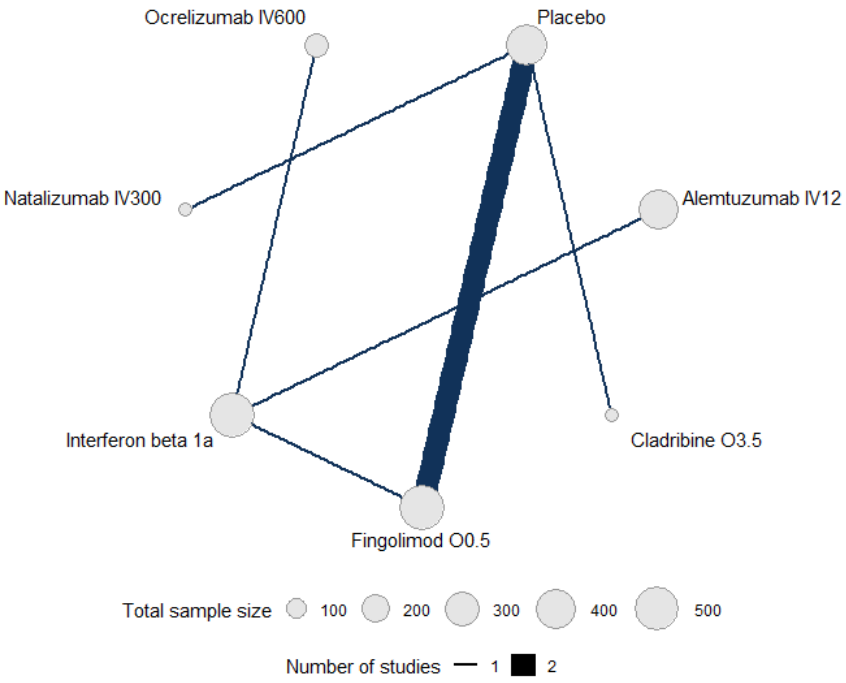
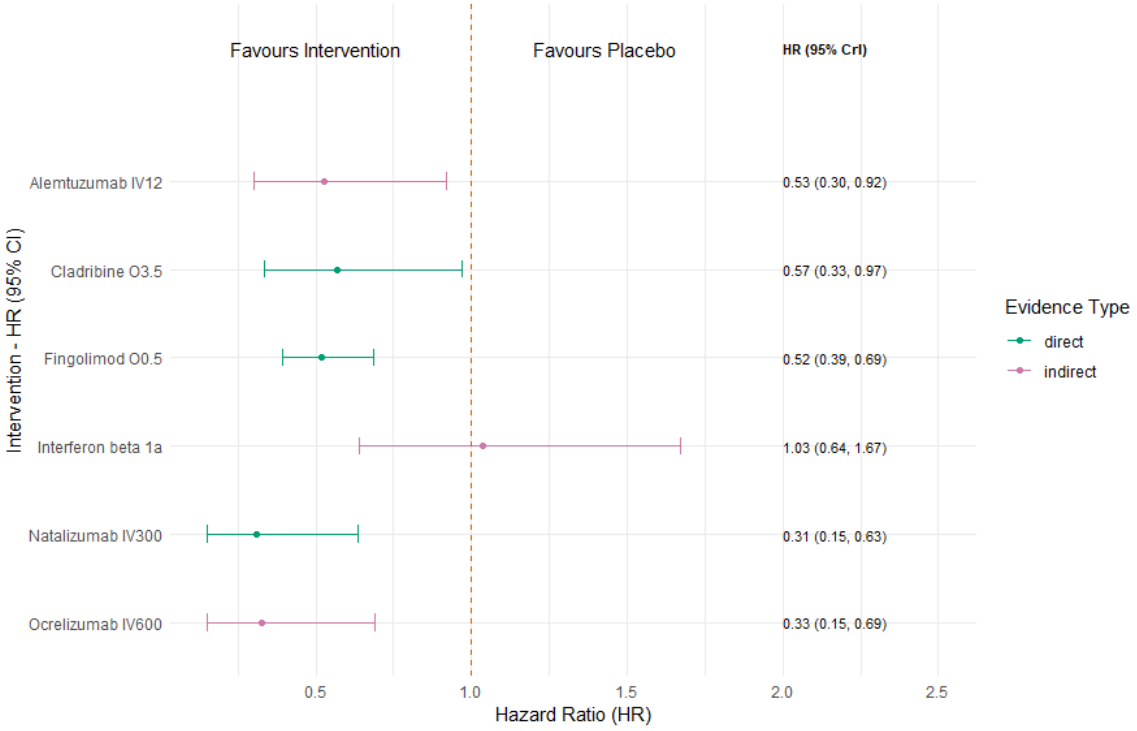


Figure 20 shows the rate ratio (RR) and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo. All interventions with the exception of interferon beta 1a were associated with a greater reduction (i.e., RR<1 AND 95% CrI excluding 1.00) in the risk of relapses compared to placebo. Results were similar for both random and fixed effects models, although credible intervals were very wide from random effects models (Table 88 in Appendix 5). The ranking of interventions and the probability that each intervention would be ranked first is shown in Table 8, with Table 90 (Appendix 5) showing the probability that each intervention will rank in a specific position. Ocrelizumab and natalizumab had the highest mean rankings (both 1.8 (95 CrI 1, 5)) with Natalizumab having a higher probability of ranking first (53% vs 44%). All other interventions in the network had ≤2% probability of ranking first. Table 89(Appendix 4) shows the RR (95% CrI) for each intervention pair comparison evaluated in the NMA.

Figure 20 Forest plot of rate ratios (RR) and 95% credible intervals from fixed effects NMA for ARR (fixed effects NMA; HA population).
Green lines indicate results from direct evidence and purple lines from indirect evidence.

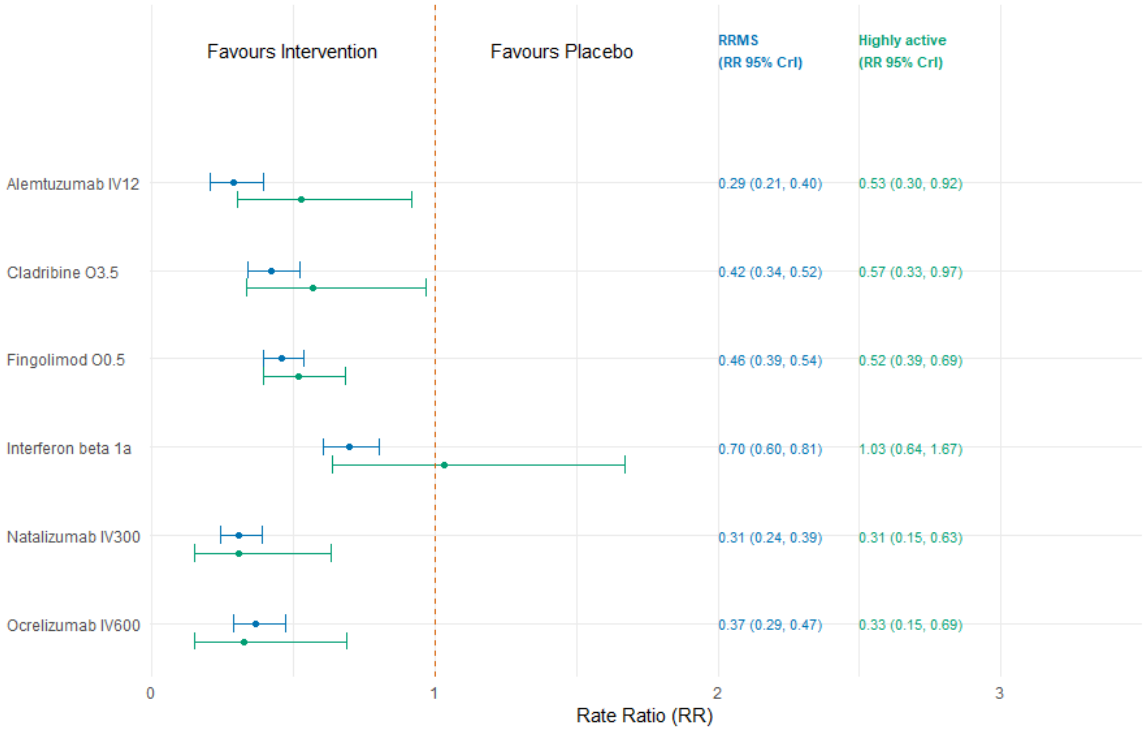


Comparison of ARR results between highly active and RRMS population

As we only had data on a limited number of interventions in the highly active population, we conducted an ad hoc analysis to determine whether there was any evidence of a difference in the relative effectiveness of interventions in the highly active and RRMS population. To allow direct comparisons between populations, we conducted a sensitivity analysis in the RRMS population where we restricted the network to the seven interventions in the network for ARR in the highly active population. As we had combined the interferon beta 1a interventions into a single node for the highly active population, we did the same for the RRMS population. Figure 21 shows that estimates of RR for ARR derived from the two different MS populations were very similar, although 95% credible intervals were wider in the highly active population. This would be expected as fewer studies contributed to these estimates.

Figure 21 Forest plot of rate ratios (RR) and 95% credible intervals from NMA for ARR in the highly active and RRMS populations (fixed effects NMA)

Blue lines indicate results in the general RRMS population and green lines in the highly active population



5.2.3 Disease progression

All studies except TRANSFORMS and Saida 2017 reported data on disease progression. Two studies reported data for CDP3 (CLARITY, FREEDOMS and OPERA I/II) and five reported data for CDP6 (CARE-MS II, CLARITY, FREEDOMS I/II, OPERA I/II and MIST). We could not create a connected network for either disease progression outcome and so a NMA was not performed. Results from these studies, including HRs and 95% CIs, are reported in Table 12. All interventions (alemtuzumab, cladribine, fingolimod, ocrelizumab and AHSCT) were associated with a reduced risk of disease progression confirmed at both 3 and 6 months compared to comparator interventions (interferon beta 1a, placebo or iDMT). To allow comparison of the effect in the highly active population and the general RRMS population we also included data from these studies in the RRMS population in Table 12. There were no clear differences in effect between the highly active or general RRMS population for disease progression, although HR estimates tended to be slightly lower (i.e. suggesting greater effect) in the highly active population, 95% CIs were wide and overlapped with those from estimates from the general RRMS population.

5.2.4 MRI outcomes

CARE-MS II was the only study to report data on MRI outcomes in the HARRMS population. This study reported that alemtuzumab was associated with a lower risk of both Gd+ lesions (RR 0.40, 95% CI 0.27, 0.60) and new or enlarging T2 lesions (RR 0.68, 95% CI 0.59, 0.79) than beta interferon 1a. The related CARE-MS I study, which was conducted in the general RRMS population, reported similar results - alemtuzumab was associated with a lower risk of both Gd+ lesions (RR 0.37, 95% CI 0.23, 0.60) and new or enlarging T2 lesions (RR 0.84, 95% CI 0.71, 0.99) than beta interferon 1a.

5.2.5 Adverse events

CARE-MS II was the only study to report data on adverse events specifically in the HARRMS population. Data on adverse event were also available for Saida 2017 – these are included in the analysis for the general RRMS population and suggest fewer AEs in the Natalizumab arm compared to placebo, although with no strong evidence of a difference between groups. CARE-MS II reported that alemtuzumab was associated with a very small increased risk of any adverse event (RR 1.04, 95% CI 1.00, 1.08) but a lower risk of treatment discontinuation (RR 0.43, 95% CI 0.21, 0.88) than beta interferon 1a. There was no difference in the risk of serious AEs (RR 0.83, 95% CI 0.67, 1.04). Comparison with the related CARE-MS I study suggested similar results for serious AEs (RR 0.79, 95% CI 0.52, 1.18). However, there was a very small decreased risk of any adverse event (RR 0.94, 95% CI 0.90, 0.99) and a large increased risk of treatment discontinuation (RR 4.42, 95% CI 1.56, 12.55) for alemtuzumab compared to beta interferon 1a. Both CARE-MS I and II were judged at high risk of bias.

5.2.6 Quality of life (QoL)

CARE-MS II and MIST were the only studies to report data on adverse events in the highly active MS population. Both studies were judged at high risk of bias. MIST reported that QoL was better in those treated with AHCT compared to those in the comparator DMT group ($p<0.001$). CARE-MS II found no difference between groups in the SF-36 MCS score, but a significantly greater improvement with alemtuzumab on the PCS score compared to interferon beta 1a. The related CARE-MS I study, conducted in the general RRMS population, found no difference in QoL between intervention groups.

Table 11 Risk of bias for studies in the HARRMS population

Study	Outcome	Domain					Overall	Rationale
		1	2	3	4	5		
CARE-MS II[71]	ARR; MRI; AE; QoL	Low	High	Some concerns	Low	Low	**High**	Patients and carers were aware of the treatment assignments; missing outcome data but sensitivity analyses performed
CLARITY[86]	ARR; CDP	Low	Low	Some concerns	Low	Low	**Some concerns**	Some missing data potentially related to outcome but all randomised participants included in analysis
FREEDOMS 1/II[108]	ARR; CDP	Low	Low	High	Low	Low	**High**	Large proportion of missing data potentially related to outcome
MIST[72]	CDP	Some concerns	High	Low	Low	Low	**High**	Patients and carers were aware of the treatment assignments
	QoL					Some concerns		QoL not specified as outcome in trial registry entry - only outcome specified was disease progression
OPERA I/II[67]	ARR; CDP	Low	Low	Low	Low	Low	**Low**	No concerns
Saida 2017[79]	ARR; AE	Low	Low	Low	Low	Low	**Low**	No concerns
TRANSFORMS[75]	ARR; CDP; AE	Low	Low	Low	Low	Low	**Low**	No concerns

Domain 1: Risk of bias arising from the randomization process; Domain 2: Risk of bias due to deviations from the intended interventions; Domain 3: Risk of bias due to missing outcome data; Domain 4: Risk of bias in measurement of the outcome; Domain 5: Risk of bias in selection of the reported result

ARR: annualised relapse rate; CDP: confirmed disease progression; AE: adverse event; QoL: Quality of Life

Table 12 Estimates of HR and 95% CIs for disease progression confirmed at 3 (CDP3) and 6 (CDP6) months in the highly active and general RRMS populations from studies that reported data in people with HARRMS

Study Name	Intervention	Comparator	Follow-up (mths)	HARRMSpopulation		General RRMS Population	
				CDP3: HR (95% CI)	CDP6: HR (95% CI)	CDP3: HR (95% CI)	CDP6: HR (95% CI)
CARE-MS II[71] (HA) & CARE-MS I (RRMS)	Alemtuzumab	Interferon beta 1a (SC44)	24	NR	0.58 (0.38, 0.87)	NR	0.70 (0.40, 1.23)
CLARITY[86]	Cladribine	Placebo	24	0.25 (0.07, 0.89)	0.20 (0.04, 0.91)	0.67 (0.48, 0.93)	NR
FREEDOMS[74]	Fingolimod	Placebo	24	0.59 (0.29, 1.20)	0.50 (0.34, 0.90)	0.70 (0.52, 0.96)	1.59 (1.11, 2.27)
FREEDOMS II[73]	Fingolimod	Placebo	24	NR		0.83 (0.61, 1.12)	0.72 (0.48, 1.07)
OPERA II[67]	Ocrelizumab	Interferon beta 1a (SC44)	24	0.47 (0.23, 0.95)	0.50 (0.23, 1.09)	0.57 (0.37, 0.9)	0.57 (0.34, 0.95)
OPERA II[67]						0.63 (0.42, 0.92)	0.63 (0.40, 0.98)
MIST[72]	AHSCT	iDMT	34	NR	0.07 (0.02, 0.24)	NA	

6 Assessment of cost effectiveness

Sections of this Chapter have been reproduced from the study's Protocol document, available at the NICE website.[1]

6.1 Systematic review of existing cost-effectiveness evidence

We conducted a review to summarise evaluations of the cost effectiveness of interventions for highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy and to identify studies/evaluations reporting UK costs data to inform the model. The review followed the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the NICE Health Technology Evaluations Manual.[46, 47] The review is reported according to the PRISMA 2020 guidance [48]

6.1.1 Study identification

On the 15th May 2024, we searched:

- MEDLINE (MEDALL) 1946 to May 14, 2024;
- Embase 1974 to 2024 May 14;
- Econtlit 1981-current; and
- NHS Economic Evaluations Database (NHS EED) via https://www.crd.york.ac.uk/CRDWeb/HomePage.asp.

Economic evaluations identified by the clinical effectiveness searches were flagged by the reviewers for potential inclusion in the review of economic models.

6.1.2 Selection criteria

Studies were selected by two researchers if they reported an:

- economic evaluation in HARRMS; OR
- economic evaluation or costs study in RRMS if done in the UK.

We excluded evaluations where the focus was on the perspectives of payers in countries other than the UK to align our review to the needs of NICE decision-makers.

6.1.3 Results

A flowchart detailing the study identification and selection process is reported in Figure 22. Table 13 Studies included in the systematic review of economic evaluations. Studies excluded at full text are reported in Table 42 with reasons for exclusion. We identified seven evaluations (in eight reports). The review (in particular the studies by Noon and Montgomery),[109, 110] and review of NICE TAs, highlighted that DES, rather the Markov multistate modelling, is a suitable way to model disease progression for cost-effectiveness analysis in RRMS.

Figure 22 PRISMA flowchart for systematic review of economic evaluations

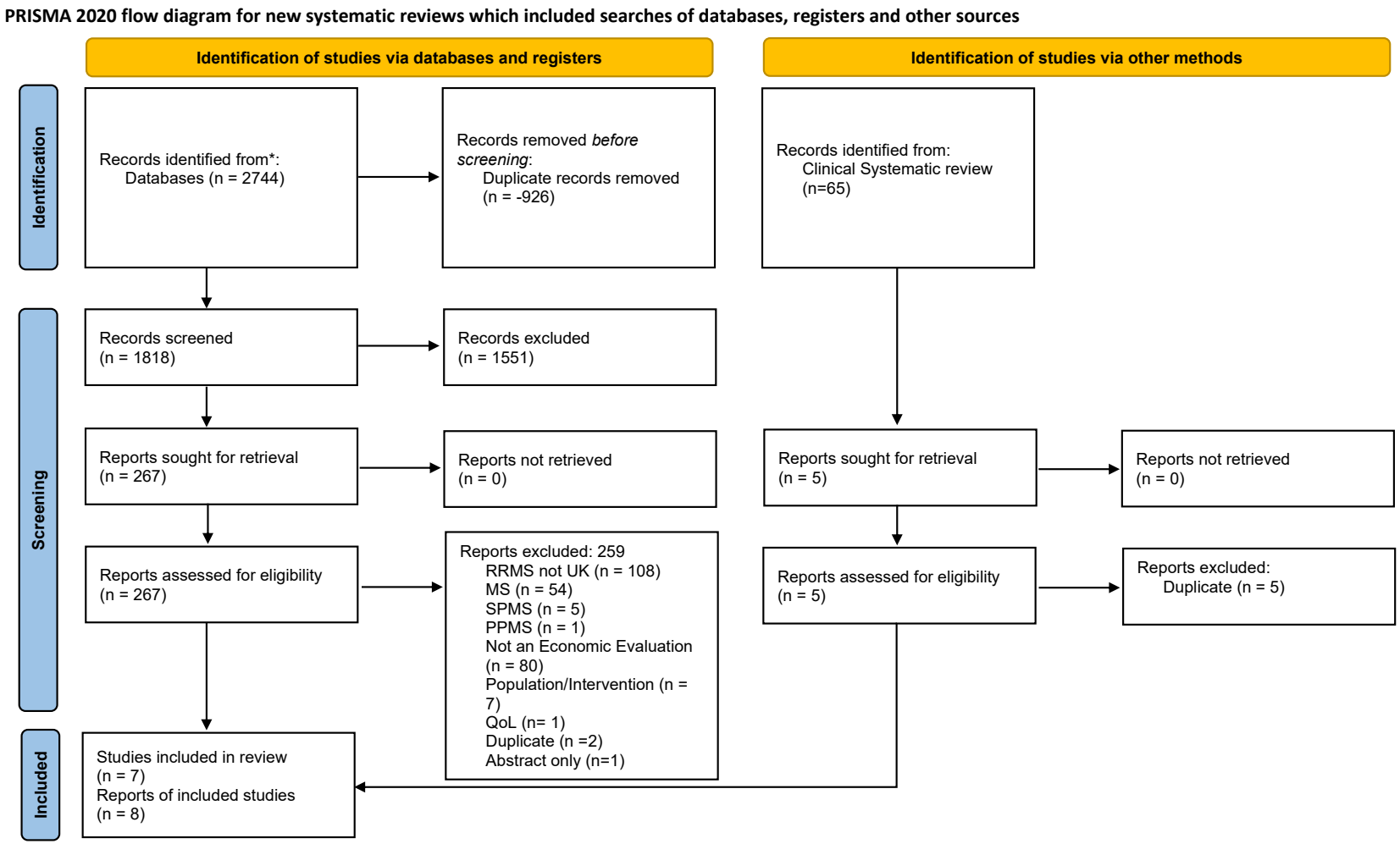


Table 13 Studies included in the systematic review of economic evaluations

Study	Aim	Model type and perspective	Population	Data inputs	Time horizon and discount
Spelman[111]	To evaluate clinical and cost-effectiveness of natalizumab and fingolimod	Markov Model (annual cycle length). NHS perspective.	Adults (>18) with RES - RRMS (≥2 relapses in prior year) starting treatment with natalizumab, fingolimod, or BRACETD, or were previously naïve to DMTs or treated with a different BRACETD.	Clinical IPD from MSBase Registry[112] • ARR • TtfR • CDW6M • CDI6M Costs UK MS burden of illness study[113] • Annualised acquisition, administration and monitoring (UK list price). • Direct and indirect (edss0-9) • Relapse (direct). • Adverse Events. Utilities UK MS burden of illness study[113] • RRMS (EDSS 0-9) • SPMS (EDSS 0-9) • Caregiver • Relapse • Adverse events	Lifetime Horizon. Discount Rate:3.5%
Noon[109]	To investigate the impact of economic model type on the cost-effectiveness of disease-modifying therapies (DMTs) for RRMS.	Markov and discrete event simulation (DES) models. UK payer perspective.	Adults 18-55 with HA RRMS or RES RRMS, >1 relapse in year prior and EDSS 0-5.5. (FREEDOMS[74], FREEDOMS II[114] and TRANSFORMS[75])	Clinical Natural History data from placebo arm of FREEDOMS and FREEDOMS II. EDSS >8 calculated based on London Ontario dataset.[115] • ARR Costs	Markov: baseline cohort age + 50 yrs and DES: tracked each simulated patient until death (capped at 100 yrs). Discount Rate 3.5%.

Study	Aim	Model type and perspective	Population	Data inputs	Time horizon and discount
				• Drug costs based on list price (without discount). • Resource use (administration, monitoring, AEs and drug acquisition) • Relapses (NHS National Tarif) (Costs and QALYs calculated in annual cycles with ½ cycle correction in the Markov and applied on a continuous-time basis in the DES) <u>Utilities</u> • EQ-5D • EDSS • Disutilities associated with AEs were matched across models (adverse events, retreatment).	
Hettle[116]	To assess the cost-effectiveness of cladribine tablets in HDA-RRMS compared with alemtuzumab and natalizumab	Markov (annual cycle length). NHS Perspective	Adults with RRMS, >1 relapse within 12 months, and EDSS <5.5. Based on CLARITY[86]	<u>Clinical</u> Natural History reference model using data on disability and relapse for people receiving Best Supportive Care and treatment-adjusted model combing the Natural History model with comparative efficacy and safety of treatment vs placebo.[117] • 6-months confirmed disability progression • ARR <u>Costs</u> • Drug acquisition, administration and monitoring based on list price (without discount). • Annualised direct medical costs taken from Hawton and Green[118]	50 year horizon. 3.5% discount.

Study	Aim	Model type and perspective	Population	Data inputs	Time horizon and discount
				Utilities • EDSS from CLAIRTY trial[86] • Health State Utilities from Hawton and Green.[118] • EDSS-related utility loss for caregivers.	
Melendez-Torres[119]	HTA to determine effectiveness and cost effectiveness of beta-interferon and glatiramer acetate for RRMS/SPMS.	Markov (annual cycle length). NHS and Personal and Social Services (PSS)	RRMS patients	Clinical Systematic Review and Natural History from British Columbia Multiple Sclerosis database (closed since 2009) Costs Systematic review and[120] • Resource use • Unit costs Utilities MS Trust surveys • EQ-5D converted to EQ-5D index score.	50 year horizon. 3.5% discount.
Palace[121]	To assess the long-term effectiveness and cost-effectiveness of interferon beta and glatiramer acetate.	Markov and a multilevel model (to model treatments in the RSS)	Adults >18 with 2 significant relapses in prior 2 yrs and EDSS >5.5.	Clinical UK RSS clinical cohort compared to the BCMS database. • accumulation of disability measured as EDSS progression and loss of utility.	20 years. 3.5% discount.
Herring[122]	To estimate the comparative effectiveness of switching to	Markov. UK NHS.	Adults with HA RRMS with inadequate response after >1 year on first line DMT who switched to	Clinical MSBase Registry and published trials.	Lifetime. 3.5% discount.

Study	Aim	Model type and perspective	Population	Data inputs	Time horizon and discount
	natalizumab or fingolimod or within BRACETD using real-world data and to evaluate the cost-effectiveness of switching to natalizumab versus fingolimod using a United Kingdom (UK) third-party payer perspective.		natalizumab, fingolimod, or another BRACETD. Primary endpoint: change in EDSS.	Costs/utilities: 2015 UK MS burden of illness survey used to estimate indirect costs and utility values. treatment costs were list price and standard UK costs.	
Montgomery[110, 123] (1 study in two eligible reports)	to model IPD from key trials in DES for the cost-effectiveness analysis of the treatments fingolimod and alemtuzumab recommended by NICE for use in HA RRMS patients,	DES model in C++. NHS and Personal and Social Services (PSS)	Adults 18-55 with RRMS, >1 relapse in year prior and EDSS 0-5.5. (from from FREEDOMS, FREEDOMS II and TRANSFORMS)	<u>Clinical</u> • IPD from placebo arms of HARRMS subgroup of the Key trials; FREEDOMS, FREEDOMS II and TRANSFORMS for EDSS 0-7 supplemented with data from London Ontario for EDSS >8.[17] • ARR, AEs from FREEDOMS, FREEDOMS II and TRANSFORMS. <u>Costs</u> • Drug acquisition based list price (no discount) • Treatment acquisition, administration and monitoring. • Relapse cost from NGS National Tariff • EDSS costs from previous NICE submissions[21]	Life time horizon (capped at 100). Primary output: Costs and QALYS discounted at 3.5%. ICER and NMB.

Study	Aim	Model type and perspective	Population	Data inputs	Time horizon and discount
				Utilities • EQ-5D • Disutitlties based on [9,17,21,13]	

AAR: annualized relapse rate; CDI3M: time to 3-month–confirmed disability improvement; CDI6M: time to 6-month–confirmed disability improvement; CDW3M: 3-month–confirmed disability worsening; CDW6M: 6-month–confirmed disability worsening; DES: Discrete simulation model; EDSS: Expanded Disability Status Scale; IPD: Individual Patient Data; MS: Multiple Sclerosis; QoL: Quality of Life; RES-RMMS: Rapidly Evolving Severe Relapsing-Remitting Multiple Sclerosis; RSS: Risk Sharing Scheme; SPMS: Secondary Progressive Multiple Sclerosis; SRRMS: Relapsing-Remitting Multiple Sclerosis; TtfR: time to first relapse.

6.2 Independent economic assessment

An economic model was developed to compare the cost-effectiveness of treatments for HARRMS after at least one disease modifying therapy.

The target population for our economic evaluation was people with HARRMS who have received at least one previous DMT. As the evidence on this population is limited, we used evidence in any RRMS (including studies with at least 90% of participants with RRMS) to fill any gaps.

The interventions were Natalizumab (Tysabri), delivered subcutaneously or intravenously, and intravenous natalizumab biosimilar (Tyruko). Comparators are aligned with those of the overall appraisal (Table 4):

- Glatiramer acetate
- Interferon beta 1a
- Interferon beta 1b
- Alemtuzumab
- Cladribine tablets
- Fingolimod
- Ocrelizumab
- Ofatumumab
- Ponesimod
- Autologous haematopoietic stem cell transplantation

Only comparators with efficacy and safety data, as identified by the clinical SLR, necessary for the economic model were assessed. There was no clinical evidence identified on autologous haematopoietic stem cell transplantation so this was not included in the economic model.

We aligned with recommendations of the NICE reference case. We therefore took an NHS and NHS and personal and social services (PSS) perspective and lifetime horizon. Health benefits were measured using Quality Adjusted Life Years (QALYs). Discounting was applied to both costs and benefits at the annual 3.5% rate.

The model and cost-effectiveness analysis were fully probabilistic with any specific parameter or structural sensitivity analyses also probabilistic.[124, 125]

6.3 Models used in relevant TAs

We reviewed the economic models used in relevant NICE TAs. These were the TAs for natalizumab and the comparators listed in Table 3 that were categorised as "Recommended for RRMS in specific situations or specific subtypes" or "Recommended for previously treated RRMS" in Table 3. TAs were identified by informally searching the NICE website and supplemented by any additional assessments identified by the cost-effectiveness review of Section 6.1.

6.3.1 TA767 Ponesimod

TA767 2022[42] assessed the cost-effectiveness of Ponesimod (Ponvory, Janssen) for RRMS at first or second line. The Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS & 10 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients was based on the British Columbia Multiple Sclerosis registry.[126] Annual relapse rates by disability[127] were based on population data from the burden of illness 2005 UK MS Survey[128] and patient data from a prospective study.[129] Conversion from RRMS to SPMS was based on data from the London Ontario MS database.[127] The placebo arm of the AFFIRM trial was used to modify the natural history for the HA RRMS subgroup.[34]

The model inputs for patients on treatment with Ponesimod were reported by OPTIMUM & OPTIMUM-LT trials. The CDP-3 & CDP-6 outcomes modify disability progression, the ARR to estimate the number of relapses, and the proportion experiencing AEs. The model accounts for treatment waning, discontinuation, and excess mortality due to MS. Health state costs[130] and utilities[128] were included. Disutilities were applied for disability, relapse, AEs, and caregivers. The External Assessment Group (EAG) was critical of the model not allowing for treatment switching or sequencing and considered this to be an oversimplification of clinical practice, they acknowledged limitations maybe due to the availability of data.

6.3.2 TA699 Ofatumumab

TA699 2021[41] assessed the cost-effectiveness of Ofatumumab (Kesimpta, Novartis) for RRMS at first or second line. The Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS & 10 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients was based on the British Columbia Multiple Sclerosis registry.[126] Annual relapse rates by disability[127] were based on population data from the burden of illness 2005 UK MS Survey[128] and patient data from a prospective study.[129] Conversion from RRMS to SPMS was based on data from the London Ontario MS database[127] supplemented by data from the EXPAND trial. The HA RRMS subgroup was modelled but not considered suitable for decision making.

The model inputs for patients on treatment with Ofatumumab were reported by ASCLEPIOS I & II trials. The CDP-3 & CDP-6 outcomes modify disability progression, the ARR to estimate the number of relapses, the proportion experiencing AEs, and quality of life data. The model

accounts for treatment discontinuation, and excess mortality due to MS. Health state costs were included,[130] and disutilities were applied for disability, relapse, AEs, and caregivers. The EAG was critical of the model not having incorporated loss of treatment effectiveness, they accepted treatment discontinuation as a proxy to waning as in TA533.

6.3.3 TA616 Cladribine

TA616 2019[38] assessed the cost-effectiveness of Cladribine tablets (Mavenclad, Merck Serono) for RES RRMS at first or second line and HA RRMS (SOT RRMS) at second line. The Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS & 10 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients from the British Columbia Multiple Sclerosis registry[126] adjusted to account for higher probability of progression on the RES and SOT subgroups using CDP-6 from CLARITY.

The model inputs for patients on treatment with Cladribine tablets were from an NMA and Meta-regression that included the key trials CLATIRY & CLARITY-EXT. The CDP-3 & CDP-6 outcomes modify disability progression, the ARR to estimate the number of relapses, the proportion experiencing AEs and quality of life data. The model accounts for treatment discontinuation, and excess mortality due to MS. Health state costs[118, 130, 131] and utilities were included,[118, 128] and disutilities were applied for disability, relapse, AEs, and caregivers. The EAG was critical of the company assuming loss of treatment effectiveness to be delayed for Cladribine tablets, they accepted treatment discontinuation as a proxy to waning to as in previous appraisals.

6.3.4 TA533 Ocrelizumab

TA533 2018[33] assessed the cost-effectiveness of Ocrelizumab (Ocrevus, Roche) for RRMS at first or second line. The multi—state Markov model simulates a cohort of patients over a lifetime progressing through 20 RRMS & 10 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients was based on the British Columbia Multiple Sclerosis registry.[126] Annual relapse rates by disability were based on population data from the burden of illness 2005 UK MS Survey[128] and patent data from a prospective study.[129] Conversion from RRMS to SPMS was based on data from the London Ontario MS database.[127] The placebo arm of the AFFIRM trial was used to modify the natural history for the HA RRMS subgroup.

The model inputs for patients on treatment with Ocrelizumab were reported by OPERA I & II trials. The CDP-3 & CDP-6 outcomes modify disability progression, the ARR to estimate the number of relapses, the proportion experiencing AEs and quality of life data. The model accounts for treatment discontinuation, and excess mortality due to MS. Health state costs were included,[130] and disutilities were applied for disability, relapse, AEs, and caregivers. The EAG was critical of the model not having incorporated loss of treatment effectiveness which in clinical practice would lead to patients switching on to other treatments, they accepted treatment discontinuation as a proxy.

6.3.5 TA312 Alemtuzumab

TA312 2014[39] assessed the cost-effectiveness of Alemtuzumab (Lemtrada, Sanofi) for Active RRMS at first line RES RRMS at first or second line and HA RRMS at second line. The multi-state Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS & 9 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients and converting to SPMS states was based on the London Ontario MS database.[127] Annual relapse rates by disability were based on population data from the burden of illness UK MS Survey[128] and patent data from two prospective studies.[129, 132]

The model inputs for patients on treatment with Alemtuzumab were from an NMAs specific to the RRMS and RES RRMS and HA RRMS subgroups that included the key trials CAMMS223, CARE-MS I & II. The Sustained Accumulation of Disability (SAD-3 & SAD-6) outcomes modify disability progression, the ARR to estimate the number of relapses, the proportion experiencing AEs and quality of life data. The model accounts for treatment discontinuation, and excess mortality due to MS. Health state costs,[130, 131, 133] were included and disutilities were applied for disability, relapse, AEs, and caregivers. The EAG was critical of the company assuming no loss of treatment effectiveness for Alemtuzumab, clinical advice was that patients would be offered alternative treatments after discontinuation but as treatment switching was not implemented in the model, the committee concluded it was appropriate to model long-term treatment waning.

6.3.6 TA254 Fingolimod

TA254 2012[40] assessed the cost-effectiveness of Fingolimod (Gilenya, Novartis) for HA RRMS at second line. The Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS & 10 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients and converting to SPMS states was based on the London Ontario MS database.[115] Annual relapse rates by disability were based on population data from the burden of illness UK MS Survey[128] and patient data from a prospective study.[129]

The model inputs for patients on treatment with Fingolimod versus Avonex were reported on the TRANSFORMS & FREEDOMS trials. An NMA was undertaken to estimate relative treatment effects of other beta interferons. The SAD-3 & SAD-6 outcomes modify disability progression, the ARR to estimate the number of relapses, the proportion experiencing AEs. The model accounts for treatment discontinuation, and excess mortality due to MS. Health state costs,[34] utilities[128], were included and disutilities were applied for disability, relapse, AEs, and caregivers. The model has many limitations which were critiqued by the EAG and are summarised in Table 92, they called for a new decision model, one that better reflects clinical practice in future appraisals of Multiple Sclerosis.

6.3.7 TA127 Natalizumab

TA127 2007[34] assessed the cost-effectiveness of Natalizumab (Tysabri, Biogen Idec) for RES RRMS at first or second line. The multi-state Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS & 10 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients and converting to SPMS states was based on the London Ontario MS database.[115] Annual relapse rates by disability were based on population data from the burden of illness UK MS Survey[128] and patient data from a prospective study.[129] The placebo arm of the AFFIRM trial was used to modify the natural history for the HA RRMS subgroup.

The model inputs were obtained from a number of sources. The Hazard ratios for disability progression and annual relapse of RES RRMS patients on treatment with Natalizumab was obtained from the AFFIRM trial and converted to risk ratios. The risk ratios for disability progression and annual relapse for patients on beta interferon or glatiramer acetate were obtained from pairwise meta-analyses, data from two Cochrane reviews.[134, 135] The analyses derived relative treatment effects contrasting the risk ratios from the Intention to Treat (ITT) and RES Natalizumab groups versus either of the beta interferon or glatiramer acetate ITT groups' risk ratios. The risk ratios for disability progression could be multiplied directly with the natural history transition matrices. However, the relapse risk ratios describe had to be transformed into relative relapse rates using the annualised relapse rate from the placebo groups in AFFIRM from the RES RRMS sub group, and the ITT main group as a proxy for the SOT RRMS subgroup. Health state costs and utilities[128], were included and disutilities were applied for disability, relapse, AEs, and caregivers. The ERG was critical of the company excluding the SENTINEL trial SOT RRMS subgroup data from the model, especially that it was relied on for the marketing authorisation.

6.3.8 Common criticisms

1. Treatment sequencing and variable treatment waning was an issue in all the reviewed submissions (TA767, TA699, TA616, TA533, TA312, TA254 and TA127) to varying degrees. These TAs explain that clinical practice is to switch patients to alternative treatments if their current drug is no longer effective. The ERGs have accepted treatment discontinuation as proxy for loss of effectiveness over time, despite lack of evidence on waning from the key trials. This is because treatment switching was not modelled in any of these submissions.

2. Previous models (TA767) have modelled relative risk of death being applied to each EDSS health state, taken from Pokorski (1997) which demonstrated that risk of death because of multiple sclerosis was primarily dependent on disability. But this dataset is quite old and has been criticised by clinicians for this reason.

3. Previous models in Multiple sclerosis have had limited ability to accurately reflect the course of the condition. In TA767 and TA699 an implausible number of patients were found in high EDSS states contrary to what would be observed in clinical

practice. In TA699 and TA127 issues with converting from RRMS to SPMS were discussed. In TA254 and TA127 issues with unrealistic disability progression when treatment effects were applied to the natural history was discussed.

6.4 Model structure

To overcome the key criticisms of the previous manufacturer models for RRMS submitted to NICE (Section 6.3.8), we adopted an individual-level discrete-event simulation (DES) model.[136] This makes it possible to model treatment sequences and enable treatment-specific waning patterns. The inflexibility of cohort Markov models made it difficult to accurately reflect the course of MS, leading to implausible numbers of patients in the high EDSS states.[42] The flexibility of DES better reflects the natural course of MS, and eases the inclusion of new standardised mortality rates by EDSS (TA767).[42, 137]
Our model structure was influenced by the recent Dutch clinical guidelines models on RRMS which was a microsimulation accounting for treatment sequences. [138-141] However, rather than using a DES, this microsimulation used an underlying multistate structure defined by EDSS and SPMS status, similar to the Markov models used in previous NICE submissions (Section 6.3). Our justification for adopting event-based rather than state-based modelling is that the target of RRMS treatment is to reduce the events of relapse and disability progression, rather than to directly affect EDSS severity or SPMS status. A DES is therefore better tailored to RCT data and the focus of RRMS treatment.

The model is illustrated in Figure 23. The attributes of the DES represent important demographic and disease characteristics. The modelled disease characteristics included EDSS ($\in (0, \ldots, 9)$) and SPMS status to thus capture health state information of the previous RRMS Markov models (Section 6.3). Age and gender were modelled as demographic attributes and determine the rate of background mortality. Treatment status was included and described in more detail below.

Event rates depended on some or all of these attributes. If a patient has not yet progressed to SPMS, events included increase in severity (i.e., EDSS increase), decrease in severity (i.e., EDSS reduction), progression to SPMS, relapse, adverse events, treatment change not driven by an event, and death. If a patient has progressed to SPMS, the events included increase in severity (i.e., EDSS increase), relapse, adverse events, and death.

Treatment status is a key attribute, and the sequence of treatment is represented in Figure 24. The initial treatment was any of the interventions/comparators in highly active RRMS. Following this, rescue therapy and later line therapy will follow the currently recommended pathway described in Section 1.3.5. Patients can progress to SPMS on any line of RRMS therapy and are then assumed to receive an average 'basket' of approved therapies, as described in Section 1.3.5.

We resolved competing risks using the "event-specific" approach, which requires sampling times for all competing events and simulating the event that is the first to occur.[142, 143] The

alternatives (sampling the event to occur first and then the time-to-event; sampling the time-to-event and then the event) required data to be analysed in a joint manner, which was not possible in this setting as rates of (for example) CDP3/6, ARR, and adverse events were estimated independently.

Progressive Multifocal Leucoencephalopathy (PML) is an important side effect of some MS drugs, particularly natalizumab and its biosimilar.[76, 144] It is caused by suppression of the immune system which can cause the John Cunningham human polyomavirus (JCV), to become active.[144] Biogen, the manufacturer of natalizumab, currently fund JCV testing and report a risk of PML.[145] However, our clinical advice was that this scheme is not widely implemented so the cost of JCV testing was included for natalizumab. Testing is also not routinely done for the biosimilar and would need to be funded by the NHS. We therefore included this JCV virus testing for the biosimilar in the base case .

Figure 23 Model diagram for cost-effectiveness DES model

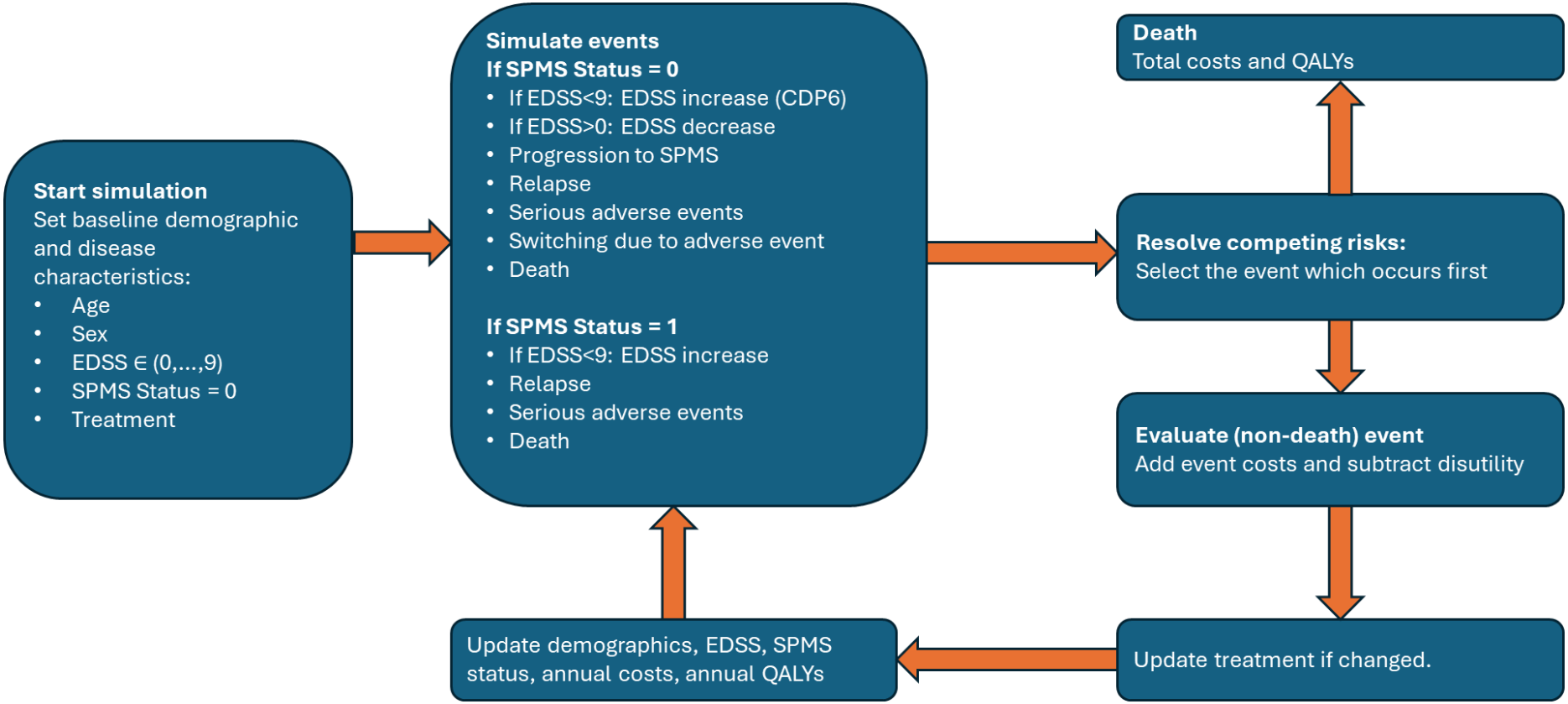
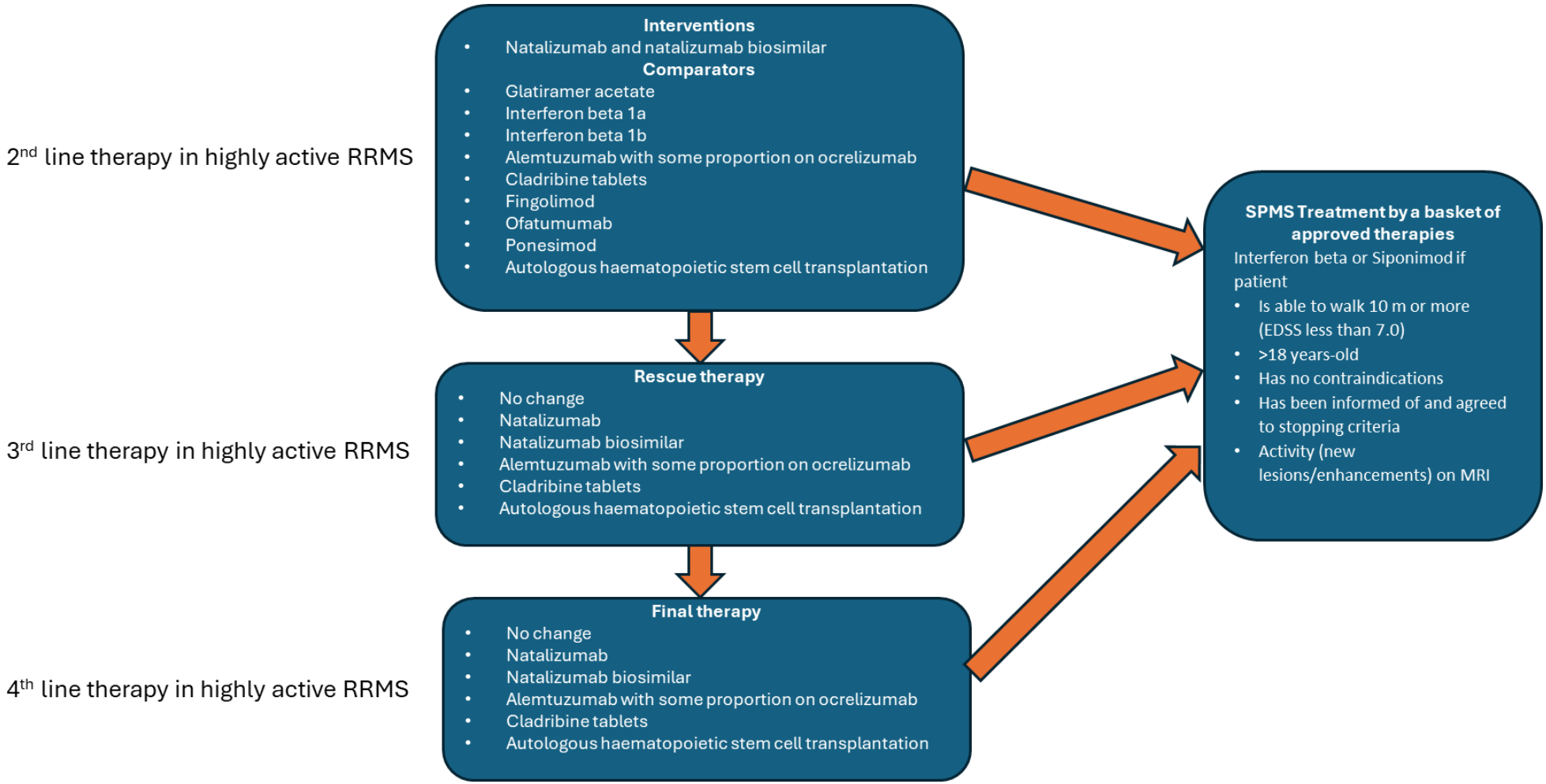


Figure 24 Treatment sequence in the cost-effectiveness DES model



6.5 Input data

6.5.1 Clinical outcomes and treatment effects

The event rates were a combination of natural history (informed by analyses of MS registry data described below) and treatment effects. Treatment effects came from the NMA described in Section 4.3.6. Events for patients with RRMS (i.e., SPMS status = 0) with treatment effects were EDSS increase (i.e., CDP6), relapse (i.e., ARR), serious adverse events, and discontinuation due to adverse events. No treatment effect was assumed for progression to SPMS, EDSS decrease, or mortality. Events for patients with SPMS (i.e., SPMS status = 1) were assumed not to be affected by the RRMS treatment. The natural history data for SPMS patients represents outcomes on the basket of treatments described in Figure 24, and was again informed by MS registry analyses described below.

Proportion of relapses leading to hospitalisation were from observational studies on the costs and utilities of relapses.[118]

Relapse rates in SPMS were informed by the MS registry analyses and included regression on EDSS severity. Rates were expected to decrease with increasing severity, following EAG recommendations in TA699 and rates reported in TA527.[31, 41] In TA767 For people who progressed to SPMS, people were assumed to transition through health states based on the London Ontario dataset.[42]

Regarding the choice of CDP6 instead of CDP3 to represent EDSS decrease, in TA767 the EAG recommended that CDP6 was a more appropriate measure of disease progression following clinical advice that CDP3 may potentially overestimate progression due to natural fluctuations in the disease.[42] CDP6 was also preferred in other previous appraisals.[39]

Baseline rates of discontinuation due to AEs provided a proxy to waning as in previous appraisals, and were assumed to follow the AFFIRM study for natalizumab and ANTELOPE study for natalizumab biosimilar. For comparators we used the NMA on discontinuation due to AEs (Section 5.1.5**Error! Reference source not found.**) and applied treatment effects to the baseline rates from AFFIRM.

6.5.2 MS Registry analyses

The following data specification was shared with the MS Registry on 8th August 2024. Analyses are separated into those that are essential and those that are desirable. Published sources will be used in place of those that are desirable but infeasible.

6.5.2.1 Requested analyses

We requested rates of events using exponential survival and continuous-time multistate models fit to interval censored data. Covariates were included in some of these models. Outputs needed were model parameters and their covariance matrices on the natural scale (e.g., log rates for exponential and multistate models). Age and sex were considered as covariates in all models but were removed due to limited data.

The model specification is provided in Table 14.

Unless otherwise specified, analyses were conducted in highly active RRMS, any RRMS, and SPMS. The RRMS populations matched those of the NMA, namely highly active RRMS who have received at least one previous DMT, and any RRMS. As noted in Table 2 there is no consensus definition of highly active RRMS. Previous appraisals for NICE have used different definitions. The MS registry aimed to align as closely as possible with our selected definition: Unchanged or increased clinical or radiological evidence of disease activity despite treatment with at least one DMT.

A covariate effect was included to represent treatment. However we did not use the MS registry to estimate hazard ratios as these come from the NMA based on RCT data. The covariate for treatment is only used to obtain baseline rates specific to natalizumab, to which the NMA hazard ratios were applied. Treatments included are the interventions, noting that that Natalizumab biosimilar (Tyruko) was not included in the registry, and the comparators:

- Natalizumab (Tysabri), delivered subcutaneously or intravenously,
- Glatiramer acetate
- Interferon beta 1a
- Interferon beta 1b
- Alemtuzumab
- Cladribine tablets
- Fingolimod
- Ocrelizumab
- Ofatumumab
- Ponesimod

We requested sample sizes and total exposure times to be reported for all analyses in Table 14 and Table 15.

We furthermore requested the EDSS distribution at baseline so as to inform the starting point for our model.

Table 14 Essential requested analyses in RRMS and Highly Active RRMS.*

Event	Effect estimate	Model	Covariates
EDSS increase (i.e., confirmed disability progression)	Rate	Exponential	Treatment, current EDSS
EDSS decrease	Rate	Exponential	Current EDSS
EDSS increase or decrease	Rates	Multistate model with state for each EDSS category (0, 1, …, 9)	Treatment on EDSS increase only
Relapse	Rate	Exponential	Treatment, current EDSS

Progression to SPMS	Rate	Exponential	Current EDSS

*Rates are required separately in two populations: highly active RRMS who have received at least one previous DMT, any RRMS

Table 15 Essential requested analyses in SPMS.

Event	Effect estimate	Model	Covariates
EDSS increase (i.e., confirmed disability progression)	Rate	Exponential	Current EDSS
EDSS increase or decrease	Rates	Multistate model with state for each EDSS category (0, 1, …, 9)	
Relapse	Rate	Exponential	Current EDSS

6.5.3 Utilities

Utilities associated with model attributes (EDSS and SPMS status) were derived from previous appraisals and the SLR on cost-effectiveness evidence (Section 6.1). Disutilities for events (i.e., relapse, adverse events) were also derived from these sources.

The base case utilities are from the UK MS Survey 2005, a cross-sectional study of MS patients (n=2048) with self-reported EQ-5D quality of life and resource use via a postal questionnaire.[128] The authors report the questionnaire was adapted from a descriptive cost of illness study conducted in the UK in 1999 by Kobelt et al[146] the design of which closely follows a cross-sectional study in Sweden by Henriksson et al.[147]

Unlike the studies by Kobelt et al or Henriksson et al, the UK MS Survey patients were self-reporting and had not been assessed in clinic. Disease severity was self-assessed on the Adapted Patient Determined Disease Steps (APDDS) scale but reported by Expanded Disability Scale (EDSS) strata, these scales are used interchangeably by authors although they do not cite evidence in support of this assumption.[148] The distribution of patient characteristics were reported grouped by APDSS 0-3 (21%) APDSS 4-6.5 (60%) and APDSS 7-9.5 (19%).

Multivariate linear regression analysis was used to fit an ANOVA model, and authors reported mean (95% CI) utility stratified by APDSS, relapse, SPMS, PPMS, education (college, university, postgraduate), sex and years since diagnosis. The presented model has moderate explanatory power (R^2=0.478), alternative models were not available. The uncertainty in the estimates for the 11 stratified severity states is such that confidence intervals overlap with each other.

The UK MS Survey 2005 was the source of utility values in TA767, TA699, TA533, TA312, TA254, and TA127. A variation of these utility values were reproduced in TA127 with slightly higher mean estimates by excluding the education variables. Furthermore, disutility of relapse was stratified by severity using data from the AFFIRM trial. Uncertainty was not reported for this analysis, limiting its applicability for our fully probabilistic model.

Trial utilities stratified by severity were used in TA533 by pooling both treatment and placebo arms of OPERA I & II (EDSS 0-5) and combined with Orme et al. (EDSS 6-9). They were used in TA616 by pooling both treatment and placebo arms of CLARITY & CLARITY-EXT (EDSS 0-5) and combined with Hawton et al (EDSS6-8) and Orme et al (EDSS 9) as shown in Table 17. Trial utilities were redacted from TA696 (ASCLEPIOS), TA254 (TRAMSFORMS & FREEDOMS).

A systematic review of utilities in MS identified 16 studies reporting utilities associated with health states in MS as measured by EDSS, 3 of these were UK studies.[149] The manufacturer in TA624 and the ERG in TA767 ran scenarios using the utilities reported in a study by Thompson et al. That data was from the study by Kolbet et al and utility values are broadly similar to Orme. Uncertainty was again not reported for this analysis, limiting its applicability for our fully probabilistic model.

The committee in TA254 preferred utility data from Orme was combined with utility data from key trials. The TA533 committee thought utilities for the rapidly evolving severe subgroup were over estimated.

Table 16 Health state and relapse utilities used in economic model as calculated from the UK MS Survey 2005

	RRMS		**SPMS**	
	Mean	**sd**	**Mean**	**sd**
EDSS0	0.870	0.045	0.825	0.061
EDSS1	0.799	0.093	0.754	0.109
EDSS2	0.705	0.093	0.660	0.108
EDSS3	0.574	0.097	0.529	0.113
EDSS4	0.610	0.093	0.565	0.108
EDSS5	0.518	0.092	0.473	0.108
EDSS6	0.458	0.092	0.413	0.108
EDSS7	0.297	0.094	0.252	0.110
EDSS8	-0.049	0.095	-0.094	0.111
EDSS9	-0.195	0.119	-0.240	0.135
	Mean		**sd**	
Relapse	-0.071		0.016	
Years since diagnosis	0.002		0.001	

Table 17 Health State utility values stratified by severity for RRMS patients. UK MS Survey 2005 model formula and pooled estimates from key trials.

	UK MS Survey 2005			OPERA		CLARITY	
	Mean	LCI	UCI	Mean	SE	Mean	SE
EDSS0	0.87	0.782	0.958	0.8809	0.0154	0.906	0.026
EDSS1	-0.071	-0.165	0.023	0.8438	0.0072	0.845	0.046
EDSS2	-0.165	-0.259	-0.072	0.7699	0.0061	0.804	0.012
EDSS3	-0.296	-0.398	-0.195	0.7048	0.0069	0.701	0.701
EDSS4	-0.26	-0.354	-0.167	0.6438	0.0088	0.655	0.013
EDSS5	-0.352	-0.444	-0.26	0.6003	0.013	0.565	0.026
EDSS6	-0.412	-0.505	-0.319	0.4909	0.0205	0.573	0.225
EDSS6.5	-0.408	-0.502	-0.314	-	-	0.573	0.225
EDSS7	-0.573	-0.67	-0.477	0.4387	0.0989	0.573	0.225
EDSS8	-0.919	-1.017	-0.82	-	-	0.573	0.225
EDSS9	-1.065	-1.21	-0.919	-	-	0.573	0.225
Recent relapse‡	-0.071	-0.096	-0.046	-0.1006	0.0201	-	-
SPMS	-0.045	-0.076	-0.014	-	-	-	-
Years since diagnosis	0.002	0.001	0.003	-	-	-	-

‡binary variable indicating presence or absence of relapse in the past 3 months.

Carer disutilities for our base case used data from a commonly cited study. This online survey of 200 caregivers by Acaster et al, matched care givers (n=200) with controls from the general population asked (n=400). Respondents self-reported EQ-5D, SF-36 and HADS, MS Disease severity was stratified for using the self-reported PDSS. Authors report significant differences between cases and controls as measured on the SF-36 scale and HADS but the results for EQ-5D uncertain. The manufacturer of Natalizumab utilized caregiver disutilities for patients suffering from Alzheimer's disease in their 2008 submission for TA127.[150]

Table 18 Carer disutilities

	TA127		Acaster et al	
	Mean	SE	Mean	SE
EDSS0	0.000	-	-0.002	0.053
EDSS1	-0.001	-	-0.002	0.053
EDSS2	-0.003	-	-0.045	0.057
EDSS3	-0.009	-	-0.045	0.057
EDSS4	-0.009	-	-0.142	0.062
EDSS5	-0.020	-	-0.16	0.055
EDSS6	-0.027	-	-0.173	0.054
EDSS7	-0.053	-	-0.03	0.038
EDSS8	-0.107	-	-0.095	0.075
EDSS9	-0.140	-	-‡	-

‡ we assumed these to be the same as EDSS8

Serious Adverse Events utility decrements are assumed to be a single Natalizumab specific utility decrement that was calculated as a weighted average of those reported in the AFFIRM trial.[77] The proportion of patients experiencing PML was provided by Biogen[151] using data from the 15 year final Analysis of the TOP study for the global population (n=6321) treated with Natalizumab.[152] The annual utility decrements associated with Serious AEs for Natalizumab have been reported in previous RRMS appraisals as outlined in Table 19.

Table 19 Serious Adverse Events utility decrements assumed for treatments in the model based on the AFFIRM trial

Serious Adverse Events	Utility decrement (annual)	Duration (days)	Utility decrement (per event)	source
Urinary tract infection	-0.10	5	-0.0014	TA767, TA699
Depression	-0.56	365.25	-0.5600	TA699
Anaphylactic reaction	-1.00	7	-0.0192	TA312
Hypersensitivity reaction	-1.00	7	-0.0192	TA616
Breast cancer	-0.1160	365.25	-0.1160	TA616
Gastritis	-0.07	24.5	-0.0047	TA616
PML	-0.30	365.25	-0.3000	TA767, TA699

6.5.4 Costs and resource use

Drug costs were derived from previous appraisals, the SLR on economic evidence described in Section 6.1, and PAS prices provided by NICE. Event costs were derived from previous appraisals and the SLR.

The categories of costs utilized in the economic model include: drug acquisition, drug administration, drug monitoring and serious adverse events costs obtained from the BNF and manufacturer submissions. Health state and relapse costs were obtained from analyses of observational studies widely used in previous submissions. These are assumed to be from a NHS and PSS perspective, unless otherwise stated. Where necessary, costs were inflated to the financial year 2023/2024.

The annual drug acquisition costs are in line with the costs of Natalizumab, Natalizumab bio similar, Ofatumumab and Ocrelizumab reported in the Sandoz submission. The number of annual doses for Natalizumab are in line with those reported in the Biogen submission. The annual number of units prescribed and annual costs were reported in MS single and multiple technology appraisals. We cross referenced list prices with the BNF and the annual units prescribed with our clinical advisors. Annual drug acquisition costs and proportions of patients treated beyond year two are detailed in Table 20. List drug prices for some generics are detailed in Table 26.

Table 20 Annual Treatment acquisition (list prices) quantities, costs and proportion of patients retreated.

Treatment	Year 1		Year 2 onwards		Patients treated (proportion)		
	Units (n)	Cost (£)	Units (n)	Cost (£)	Year 3	Year 4	Year 5+
Ponesimod 20 mg	1 daily	£14,010	1 daily	£14,010	0.75	0.75	0.75
Ofatumumab 50 mg	15	£22,388	15	£17,910	0.95	0.95	0.95
Alemtuzumab 12 mg	5	£35,225	3	£21,135	0.4	0	0
Cladribine Tablets	12-14	£26,373	12-14	£26,373	0.25	0.25	0
Ocrelizumab300 mg	4	£19,160	4	£19,160	0.95	0.95	0.95
Fingolimod500 µg	1 daily	£19,169	daily	£19,169	0.75	0.75	0.75
Natalizumab-IV300 mg	13	£14,690	13	£14,690	0.8	0.8	0.8
Natalizumab-SC 300 mg	13	£14,690	13	£14,690	0.8	0.8	0.8
Natalizumab-IV-biosimilar 300 mg	13	£13,221	13	£13,221	0.8	0.8	0.8
Natalizumab-SC-biosimilar 300 mg	13	£13,221	13	£13,221	0.8	0.8	0.8
Peginterferon -β-1a SC 125µg	1 bi-weekly	£8,502	1 bi-weekly	£8,502	0.5	0.5	0.5
Interferon-beta-1a SC 44µg	3 weekly	£10,311	3 weekly	£10,311	0.5	0.5	0.5
Interferon-beta-1a SC 22µg	3 weekly	£7,976	3 weekly	£7,976	0.5	0.5	0.5
Interferon-beta-1a IM 30µg	1 weekly	£8,502	1 weekly	£8,502	0.5	0.5	0.5
Interferon-beta-1b SC 250µg	1 every other day	£7,239	1 every other day	£7,239	0.5	0.5	0.5
Glatiramer acetate SC 20 mg	1 daily	£6,681	1 daily	£6,681	0.5	0.5	0.5
Glatiramer acetate SC 40 mg	1 daily	£6,681	1 daily	£6,681	0.5	0.5	0.5
Patients progressing on to SPMS assumed to be treated with an annual cost for the remaining duration.							
Siponimod	£ 7,239				1		
Peginterferon -β-1a SC 125µg	£8,502				1		

Administration Costs

In previous technology appraisals treatment administration visits were classed as neurology outpatient visit by the manufacturers of Natalizumab-IV,[34] and Fingolimod.[40] Classed as day case (admitted patient care) by the manufacturers of Alemtuzumab,[39] Ocrelizumab,[33] further includes comparators Natalizumab-IV and Fingolimod in manufacturers' submissions.[33, 38-41]

Our clinical advisors agreed that all treatment administration visits are day cases. The HRG grouper code AA30# used to cost day cases,[33, 34, 39] arises out of group of procedures/interventions/diagnoses (IC-10 codes). The exact AA30# is dependent the on

the complication and comorbidity (CC) diagnosis for each individual admitted patient.[153] We have assumed that treatment administration visits for Natalizumab-IV, Natalizumab-SC Alemtuzumab and Ocrelizumab require day cases with frequency of visits determined by number of doses.

The manufacturers anticipate cost savings associated with the administration and monitoring of Natalizumab Sub Cutaneous (SC) in comparison to the intravenous (IV) deliver. However, our clinical advisors explained that in practice patients do not see differences between SC and IV in intensity of resource use. Beta interferons and Ofatumumab are self-administered injections requiring nurses' time to train patients. Tablets; Ponesimod, Cladribine do not require administration day cases with exception of Fingolimod. The detailed administration costs are outline in Table 21

Treatment monitoring visits are required for all treatments which we have assumed to be nurse led outpatient visits. Furthermore, the clinical Advisors pointed out annual MRI monitoring should be undertaken for all treatments and are increasingly routine for Natalizumab and B cell therapies. Monitoring Costs were not included in either of the Sandoz or Biogen submissions, so we have relied on previously published estimates supplemented by clinical advice and updated unit costs. The detailed monitoring costs are in Table 22.

Patients progressing on to SPMS are treated with Peginterferon beta 1a or Siponimod. The annual treatment administration and monitoring cost of £733 was reported in TA656.[30]

Table 21 Annual Treatment Administration Costs

Treatment	Year 1		Year 2 onwards		Source
	Resource Use	Cost	Resource Use	Cost	
Ponesimod	redacted	£139	redacted	£0.00	TA767[42]
Ofatumumab	3 hours of nurse time (Band 7) [34] (£68)	£204	3 hours of nurse time (Band 7) [34]	£204	PSSRU[154] Sandoz [34]
Cladribine Tablets	None	£0.00	None	£0.00	TA616[38]
Alemtuzumab	5 x day case (£626.13)	£3,130.65	3 x day case (£626.13)	£1,878.39	AA30F Medical care of patients with multiple sclerosis, with CC score 0-1. Day case.[155]

Treatment	Year 1		Year 2 onwards		Source
	Resource Use	Cost	Resource Use	Cost	
Ocrelizumab	3 x day case (£626.13)	£1,878.39	2 x day case (£626.13)	£1,252.26	AA30F Medical care of patients with multiple sclerosis, with CC score 0-1. Day case[155]
Fingolimod	1 x day case	£626.13	None[40]	£0.00	AA30F Medical care of patients with multiple sclerosis, with CC score 0-1. Day case
Natalizumab – biosimilar-IV Natalizumab-SC	13 x day case (£626.13)	£8,139.69	13 x day case (£626.13)	£8,139.69	AA30F Medical care of patients with multiple sclerosis, with CC score 0-1. Day case[155]
Peginterferon -β-1a SC 25µg Interferon-beta-1a SC 44µg Interferon-beta-1a SC 22µg Interferon-beta-1a IM 30µg Interferon-beta-1b SC 250µg Glatiramer acetate SC 20 mg Glatiramer acetate SC 40 mg	3 hours of nurse time (Band 7)[119]	£204	None[119]	£0.00	PSSRU[154]

Table 22 Annual Treatment Monitoring Costs

Treatment	Year 1		Year 2 onwards		Source
	Resource Use	Cost	Resource Use	Cost	
Ponesimod*	Redacted (£290.20) 1x MRI scan (£334) 0.2 x cardiac day case (£607.29)	£746	Redacted (£228.20) 1x MRI scan (£334) 0.2 x cardiac day case (£607.29)	£684	TA767[42] EB14E Daycase Other Acquired Cardiac Conditions with CC Score 0-2.[38] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[155]
Ofatumumab*	Redacted (£371.11) 1x MRI scan (£334)	£705	Redacted (£306.07) 1x MRI scan (£334)	£641	TA699[41] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[155]
Cladribine Tablets‡	1x neurology (NCL) first visit (£195.74) 2x neurology (NCL) follow up visits (£184.23) 1x MRI scan (£334) 3x Full blood count (£3.37) 1x tuberculin skin test(£60) 1x HBV test(£59)[156] 1x HCV Test(£65)[157]	£1,092	3x neurology (NCL) follow up visits (£184.23) 3x Full blood count (£3.37) 1x HBV test(£59)[156] 1x HCV Test(£65)[157]	£1,021	TA616[38] Consultant Led (CL) / Non-Consultant Led (NCL) 400 Neurology Service WF01B/C Non-Admitted Face-to-Face Attendance, First / Follow-up[155] Pathology services, DAPS04 Clinical biochemistry[155] Multistix 10sg (£41.12 for 100)[158] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[155]

Treatment	Year 1		Year 2 onwards		Source
	Resource Use	Cost	Resource Use	Cost	
Alemtuzumab	1x neurology (NCL) first visit (£195.74) 11x neurology (NCL) follow up visits (£184.23) 12x bio-chemistry test (£1.55) 12x Full blood count (£3.37) 12x Urinalysis (£8.53) 4 x Thyroid function test (£6.48) 1x H. Papilloma V. Test (£85) 1x Tuberculin skin test (£60)[159] 1 x MRI scan (£334)	£2,889	12x neurology (NCL) follow up visits (£184.23) 12x bio-chemistry test (£1.55) 12x Full blood count (£3.37) 12x Urinalysis (£8.53) 4 x Thyroid function test (£6.48) 1x H. Papilloma V. Test (£85) 1 x MRI scan (£334)	£2,817	NCL 400 Neurology Service WF01A/B Non-Admitted Face-to-Face Attendance, First / Follow-up[155] Pathology services, DAPS04 Clinical biochemistry, DAPS05 Haematology, DAPS07 Microbiology[155] Multistix 10sg (£41.12 for 100)[158] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[155] HPV test, Tuberculin skin test.[39, 160]
Ocrelizumab	1x neurology (NCL) first visit (£195.74) 2x neurology (NCL) follow up visits (£184.23) 2x Full blood count (£3.37) 1x liver function (£3.35) 1x varicella zoster virus test (£45)[161] 1 x MRI scan (£334)	£908	3x neurology (NCL) follow up visits (£184.23) 2x Full blood count (£3.37) 1 x MRI scan (£334)	£893	NCL 400 Neurology Service WF01B/C Non-Admitted Face-to-Face Attendance, First / Follow-up[155] Pathology services, DAPS05 Haematology[155] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[155]
Fingolimod	1x neurology (NCL) first visit (£195.74) 3x neurology (NCL) follow up visits (£184.23) 4x Full blood count (£3.37) 4x liver function (£3.35) 2x basic metabolism (£3.35) 0.69x pregnancy test (£3.5) 1x varicella zoster virus test (£45)[161]	£3,719	2x neurology (NCL) follow up visit (£184.23) 2x Full blood count (£3.37) 2x liver function (£3.35) 2x basic metabolism (£3.35) 1 x MRI scan (£334)	£828	NCL 400 Neurology Service WF01A/B Non-Admitted Face-to-Face Attendance, First / Follow-up[155] Pathology services, DAPS04 Clinical biochemistry, DAPS05 Haematology, DAPS09 Other[155] Multistix 10sg (£41.12 for 100)[158] Elective Inpatients DZ22K Unspecified Acute Lower Respiratory Infection with Interventions, with CC Score 9+[8]

Treatment	Year 1		Year 2 onwards		Source
	Resource Use	Cost	Resource Use	Cost	
	0.2x hospitalization (£11,969.84) 1x Ophthalmology (NCL) first visit (£155.06) 1x follow-up Ophthalmology (NCL) visit (£105.46) 1 x MRI scan (£334)				NCL Ophthalmology Service Non-Admitted Face-to-Face Attendance, First / Follow-up[155] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[155]
Natalizumab-IV or SC	1x neurology (NCL) first visit (£195.74) 1 x MRI scan (£334) 1x JC virus PCR (£247) [162] TA127[34] (£89.15)	£777	1x neurology (NCL) follow up visit (£184.23) 1 x MRI scan (£334) 1x JC virus PCR(£247)[162]	£765	NCL 400 Neurology Service WF01A/B Non-Admitted Face-to-Face Attendance, First / Follow-up[155] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[155]
Peginterferon -β-1a SC 125µg Interferon-beta-1a SC 44µg Interferon-beta-1a SC 22µg Interferon-beta-1a IM 30µg Interferon-beta-1b SC 250µg Glatiramer acetate SC 20 mg Glatiramer acetate SC 40 mg	1x neurology (NCL) first visit (£195.74) 4x neurology (NCL) follow up visits (£184.23) 5x liver function test (£3.35) 5x Full blood count (£3.37) 4x renal function test (£3.35) 1x Thyroid function test (£6.48) 1x MRI scan (£334)	£1,320	2x neurology (NCL) follow up visits (£184.23) 2x liver function test (£3.35) 2x renal function test ((£3.35) 1x MRI scan (£334)	£716	CIS Model assumptions[119] Non-Consultant Led (NCL) 400 Neurology Service WF01A/B Non-Admitted Face-to-Face Attendance, First / Follow-up[155] Pathology services, DAPS04 Clinical biochemistry, DAPS05 Haematology[155] Multistix 10sg (£41.12 for 100)[158] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[155]

Health state costs are from the multivariate regression analysis by Tyas et al[130] which combined the per-patient resource use from the 2005 UK MS survey by Orme et al[128] with per unit costs form other data sources to infer per-patient annual costs stratified by severity. These costs have been used extensively in TA767, TA699, TA533, TA312, TA254, T127, MTA (Teva submission). In TA533 it was noted 25% of direct non-medical costs are publicly funded and applicable to the NICE reference case. In TA312 the ERG preferred not to include direct non-medical costs from this analysis. The costs have been inflated to 2022/2023 prices using the NHSCII pay and prices index, details provided in Table 23.[154]

Table 23 Direct medical health state costs by severity, model formula A Tyas et al inflated to 2022/2023 prices

	2022/2023 prices	
	Estimate	**SE**
RRMS‡		
EDSS 0	£355	£2,807
EDSS 1	£121	£1,278
EDSS 2	£303	£1,234
EDSS 3	£1,208	£1,758
EDSS 4	£1,146	£1,257
EDSS 5	£2,017	£1,170
EDSS 6	£3,073	£1,210
EDSS 7	£9,358	£1,414
EDSS 8	£15,297	£1,520
EDSS 9	£21,494	£3,775
SPMS	£398	£1,002

‡ reference category

Serious Adverse Events costs are assumed to be a single Natalizumab specific cost that was calculated as a weighted average of those reported in the AFFIRM trial.[77] The proportion of patients experiencing PML was provided by Biogen[151] using data from the 15 year final Analysis of the TOP study for the global population (n=6321) treated with Natalizumab.[152] Resource use for serious adverse events were based on previous technology appraisals[33, 34, 38] where available and updated to reflect the latest published reference costs.[155] These have been summarised in Table 24.

Table 24 Serious Adverse Events costs assumed for treatments in the model based on the AFFIRM trial

Serious Adverse Events	**Cost**	**Source**
Cholelithiasis	£9,006.35	GA10H Laparoscopic Cholecystectomy, 19 years and over, with CC Score 4+ (average on-elective long stay HRG cost)
Rehabilitation therapy	£618.38	VC12Z Rehabilitation for Other Neurological Disorders (average total HRG cost)
Urinary tract infection	£7,041.01	LA04H Kidney or Urinary Tract Infections, with Interventions, with CC Score 12+ (average non-elective long stay HRG cost)
Depression	£21,521.36	52x WF01B/C Medical Psychotherapy Service Consultant led Non-Admitted Face-to-Face Attendance first visit / follow up visits

Anaphylactic reaction	£3,236.00	DZ22L unspecified acute lower respiratory infection, with interventions, CC 0-8 (average total HRG cost)
Hypersensitivity reaction	£541.61	WH05Z Allergy or Adverse Allergic Reaction (average total HRG Cost)
Breast cancer	£14,212.82	CB0A1 Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, with Interventions, with CC Score 9+ (average non-elective long stay HRG cost)
Gastritis	£706.54	FD05B Abdominal Pain without Interventions (average total HRG cost)
PML	£14,333.02	RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning (average total HRG cost £334) SA44A single Plasma Exchange (average non-elective long stay HRG cost £934) HC72A Diagnostic Spinal Puncture, 19 years and over (average non-elective inpatient long stay HRG cost £1,645.02) WH07A Hospitalisation Infections or other complications of procedures with Multiple Interventions with CC Score 2+ (average non-elective long stay HRG cost £11,420)

Patients who discontinue treatment are allowed to switch onto one of the higher line treatments. Patients who progress on to SPMS are assumed to be treated with Siponimod or Peginterferon beta 1a for the remainder of their time in the model.

The standardized mortality ratio in base case analysis was reported in a case control study of (N=1822) MS patients follow-up up till death (Jick 2014).[137] An all-cause mortality Hazard ratio 1.68 (95% CI: 1.38-2.05) compared to the general population was estimated using a proportional hazards cox model.

6.5.5 Table of Model Inputs

A summary of all model input parameter, stochastic uncertainty and references are provided below in Table 25.

Table 25 Model inputs, stochastic distributions and sources of data.

Parameters	Estimate	Distribution	Source
Time Horizon	74 years (lifetime)	-	NICE reference case
Discounting	3.5%	-	NICE reference case
Population baseline characteristics			
Initial age	36	-	AFFIRM
Sex (female)	0.7	NA	AFFIRM
Initial EDSS Distribution	Table 26	Dirichlet	MS Registry
Initial SPMS	0%	-	Decision problem is for patients without initial SPMS
Serious Adverse Events	Cholelithiasis (1%) Need for rehabilitation therapy (1%) Urinary tract infection NOS (1%)	NA	AFFIRM TOPS

Parameters	Estimate	Distribution	Source
	Depression (1%) Anaphylactic reaction (1%) Hypersensitivity reaction (1%) Fall (1%) Breast cancer, NOS (1%) Convulsion, NOS (1%) Gastritis, NOS (1%) Cervical dysplasia (1%) Alcohol poisoning (1%) Head injury (1%) Thermal burn (1%) PML (1%)		
Natural History			
Time to EDSS increase HARRMS Time to EDSS increase SPMS Time to EDSS decrease RRMS* Time to EDSS decrease SPMS Time to SP conversion HARRMS Time to relapse HARRMS Time to relapse SPMS	Estimates of parameters of the exponential survival models provided in results Section 6.8.1	Multivariate Normal on the log rate scale	MS Registry analysis
Baseline parameter			
Probability of SAEs	119 events on Natalizumab IV300 arm (n=627)	Beta	AFFIRM
Probability of discontinuation	38 events on Natalizumab IV300 arm (n=627)	Beta	AFFIRM
Proportion of relapses leading to hospitalisations	0.03500583		Hawton 2016
Proportion treated with Siponimod	0.556962025	-	MS Registry
Mortality			
Life tables	General population mortality rates by age and sex	Piecewise exponential	ONS
Standard Mortality Ratio (SMR)	HR 1.68 (95%CI: 2.05-1.38) .	Normal on the Log HR	Jick et al
SMR by EDSS	MR: 1.6 (Mild), 1.84(Moderate), 4.4 (severe).	Normal on the Log HR	Pokorski et al
Treatment Effects			
CDP3	Log Hazard Ratios	Normal	NMA Section 5.1.3
CDP6	Log Hazard Ratios	Normal	NMA Section 5.1.3
ARR	Log Rate Ratios	Normal	NMA Section 5.1.2
SAEs	Log Hazard Ratios	Normal	NMA Section 5.1.5
Discontinuation	Log Hazard Ratios	Normal	NMA Section 5.1.5
Utilities			
Health State	Table 17	lognormal	Orme etal
Carer	Table 18	lognormal	Acaster et al

Parameters	Estimate	Distribution	Source
Relapse	Table 17	Half normal	Orme et al
SAEs	Table 19	Half normal	See table for details
Costs			
Health State	Table 23	Gamma	Tyas et al
Treatment	Table 20	-	BNF
Administration	Table 21	Gamma	See table for details
Monitoring	Table 22	Gamma	See table for details
Relapse	Table 23	Gamma	Hawton et al
SAEs	Table 24	Gamma	See table for details

* The MS Registry found no patients with highly active RRMS who decreased in EDSS so analysis could not be conducted. Model instead uses rate of EDSS decrease from all RRMS.

6.6 Analyses

The model and cost-effectiveness analysis were fully probabilistic with any specific parameter or structural sensitivity analyses also probabilistic.[124, 125]

6.6.1 Validation

A lack of validation and transparency for cost-effectiveness models can be significant barrier to their acceptance by stakeholders and decision makers in Health Technology Assessments (HTA).[163]

The International Society for Outcomes Research (ISPOR) and Society for Medical Decision Making (SMDM) taskforce on modelling have published significant guidelines on the need and methods for validation.[164] The taskforce identified five forms of validation: face validity, verification, cross validation, external validation, and predictive validation. Face validity of the RRMS model has been checked by clinical opinion and verification was checked by Javier Sanchez Alvarez at Evidera. Cross validation is conducted by comparing the estimates of one model with those of others, but this will not be conducted as requires full access to multiple RRMS models. External validation requires the comparison of model estimates with reports from independent external data. Given concerns about estimated occupancy of high EDSS states in TA767 and TA699 and the conversion to SPMS in TA699 and TA127, this is of importance to our RRMS model.[34, 41, 42] We therefore conducted an informal external validation of estimated EDSS against long-term data identified by the searches.

6.6.2 Cost-effectiveness analysis

Lifetime costs and QALYs were estimated. The mean over patient simulations was first calculated, removing individual variation and giving a lifetime cost and QALY estimate for each parameter sample. These were then summarised for each intervention/comparator using their mean and 95% CrI over parameter samples. Incremental costs and QALYs, summarised by means and 95% CrI, were calculated for each comparator compared to natalizumab and natalizumab biosimilar. Base case analyses used 1000 patients and 1000 samples while sensitivities used 100 patients and 100 samples. The number of patients to

simulate and parameters to sample were tested by comparing the mean and 95% CrI, as calculated above, for 100, 250, 500, and 1000 patients and samples.

The primary analysis was a multiple treatment comparison under the net benefit framework. Net benefit and, relative to each intervention, incremental net benefit were calculated at willingness-to-pay of £20,000/QALY and £30,000/QALY. Their mean and 95% CrI were calculated and the treatment with greatest net benefit interpreted as most cost-effective. Cost-effectiveness acceptability curves (CEAC).

A cost-effectiveness plane relative to natalizumab was included but not for natalizumab biosimilar; the high uncertainty and number of treatments give these planes little explanatory value.

A key sensitivity analysis excludes the cost for JCV testing on natalizumab, as a scheme is available whereby the manufacturer pays for this testing (Section 6.4). In this sensitivity, the cost is not excluded for the biosimilar as the scheme does not apply.

While the base case analysis used the cost of primary brands of comparators, a sensitivity analysis used the lowest price generic. This only modifies the price of glatiramer acetate (changing to Brabio manufactured by Viatris UK Healthcare Ltd) and fingolimod (changing to Fingolimod manufactured by Tillomed Laboratories Ltd).

Table 26 generic drug list prices

Drug	Mode	Qty.	Dose	Brand (Manufacturer)	Tariff Price	Indicative Price	delta
Glatiramer acetate	Injection	12	40 mg per 1 ml	Copaxone (Teva UK Ltd)	£513.95	£513.95	
Glatiramer acetate	Injection	12	40 mg per 1 ml	Brabio (Viatris UK Healthcare Ltd)	£513.95	£462.56	10.00%
Fingolimod	Capsule	28	0.5 mg	Gilenya (Novartis Pharmaceuticals UK Ltd)	£1,470.00	£1,470.00	
Fingolimod	Capsule	28	0.25 mg	Fingolimod (Novartis Pharmaceuticals Ltd)		£1,470.00	
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Glenmark Pharmaceuticals Europe Ltd)	£1,470.00	£1,470.00	
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Dr Reddy's Laboratories UK Ltd)	£1,470.00	£1,470.00	
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Amarox UK Ltd)	£1,470.00	NA	
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Sun Pharma UK Ltd)	£1,470.00	£1,470.00	

Drug	Mode	Qty.	Dose	Brand (Manufacturer)	Tariff Price	Indicative Price	delta
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Accord UK Ltd)		£1,469.99	
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Zentiva Pharma UK Ltd)	£1,470.00	£1,396.50	5.00%
Fingolimod	Capsule	28	0.5 mg	Fingolimod (A A H Pharmaceuticals Ltd)		£1,396.50	5.00%
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Teva UK Ltd)	£1,470.00	£1,323.00	10.00%
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Viatris UK Healthcare Ltd)	£1,470.00	£1,250.00	14.97%
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Sandoz Ltd)	£1,470.00	£1,249.50	15.00%
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Tillomed Laboratories Ltd)	£1,470.00	£367.50	75.00%

A summary of the base case and sensitivity cost-effectiveness analyses is provided in Table 27.

Table 27 Description of base case and sensitivity cost-effectiveness analyses

Analysis	Description
Base case	Uses HA RRMS from MS Registry for baseline rates, all RRMS fixed effects from NMA for treatment effects, EDSS starting distribution from MS Registry for HA RRMS. Costs for primary bands are used for comparator drugs.
Scenario 1. Sensitivity using all RRMS and EDSS distribution for all RRMS from MS registry	Changes base case to better match the all RRMS population in the NMA. Uses all RRMS from the MS Registry for both baseline rates and the starting EDSS distribution for all RRMS
Scenario 2. Sensitivity using results of random effects NMAs	Changes base case to use the all RRMS random effects results from the NMA for treatment effects
Scenario 3. Sensitivity including JCV testing	Excludes the one-off cost of £247 associated with JCV testing for the natalizumab IV and SC interventions, but includes it for natalizumab biosimilar IV.
Scenario 4. Sensitivity using lowest price generic	Switches to using lowest price generic for comparators.
Scenario 5. Sensitivity assuming a reduction in Natalizumab-SC administration costs	Reduces administration cost by a factor of 0.5x for Natalizumab-SC to explore the company's assumption of reduced resource use (nurse administration hours per year). Increased capacity for service delivery at home(company funded) or in primary care setting.[34].
Scenario 6. Sensitivity using HA RRMS NMA	HARRMS on ARR only. all RRMS NMA for the other outcomes. Restricted to only the treatments which are included in the HA RRMS NMA for ARR (i.e., alemtuzumab, cladribine, fingolimod, interferon beta 1a, natalizumab IV, ocrelizumab IV)
Scenario 7. Sensitivity using mortality rates stratified by disease severity	Mortality ratios calculated using a Chi square table for MS patients stratified by mild (n=1394), moderate (n=789) and severe (n=165) in analysis by the MS Society of Canada between 1972-1985, by Sadovnik et al 1992 and cited in Pokorski et al 1997.

Analysis	Description
	These ratios are widely used in MS appraisals; TA767, TA699, TA533, TA312, TA254 TA127.

6.6.3 Value of information analysis

Parameter uncertainty was quantified using value of information analysis.[165] The per-person expected value of partial perfect information (EVPPI) was estimated for each parameter or for groups of parameters of interest (e.g., each efficacy and safety treatment effect from the NMA, baseline rates from the MS Registry, utilities, uncertain costs, discontinuation rates, and SAE rates). These constitute a large number of uncertain parameters as, for example, there are 10+ treatments on which we would have treatment effects. We therefore use the Bayesian additive regression trees (BART) method, as implemented in the R package VOI, for EVPPI estimation due to its suitability for EVPPI of many parameters. Alternatives we considered were Generalised additive models (GAM), Gaussian processes (GP), and, if found necessary, Multilevel Monte Carlo (MLMC) simulation were used to estimate EVPPI.[166, 167] This per-person EVPPI was used as the probabilistic decision-theoretic alternative to one-way deterministic sensitivity analysis.

If evidence were available on the incidence of 2nd line highly active RRMS, the population EVPPI could be estimated. However, no evidence on this incidence was identified so only per person EVPPI was included.

6.6.4 Software

The model will be coded in the R programming language.[63, 168, 169] The 'DESCEM package was used for the implementation of DES, 'BCEA' will be used for generating the CEACs and CEAFs, and both 'BCEA' and 'VOI' will be used for value of information analysis.[169]

6.7 Changes from the protocol

The model was changed so that there would be no treatment effects on SPMS progression or mortality. The SLR found no data on SPMS progression. Mortality was not included by the SLR as an outcome of interest, but it was not widely reported. MS may reduce life expectancy, with a recent study estimating life expectancy to be 75.9 years in an MS population compared to 83.4 years in a population matched on sex, age, and region. [9] However, the studies generally included patients in their 30s and 40s so would not be expected to find a great impact on mortality.

The software for model implementation was unchanged but the 'DESCEM' package was used instead of 'simmer' due to its greater focus on health economic modelling.

The targeted search for placebo and standard of care outcomes, and the review of health related quality of life, were not undertaken.

The targeted search on placebo and standard of care outcomes was replaced by an analysis of individual patient data from the UK MS Registry (Section 6.5.2).

The "desirable quested analyses" from the MS Registry were removed as were not conducted. These were to estimated EQ-5D-5L for RRMS and SPMS and to model treatment switching patterns.

We removed the plan to calculate ICERs so as to focus interpretation on the total and incremental net benefits. We kept only one cost-effectiveness plane (for natalizumab-IV) as the uncertainty gave it little explanatory power. We included the CEAC but because of the number of treatments, and that non-natalizumab treatments were coming out with highest probabilities, we decided against including the cost-effectiveness acceptability frontiers.

Only per person EVPPI is calculated as we did not find an estimate of the incidence of HA RRMS that corresponded to our definition.

The ratio of EVPPI to EVPI was not calculated as the number of uncertain parameters in the economic model was 247. We instead calculated the EVPPI of substantial groups of parameters.

Validation was limited to a comparison of EDSS severity over time and not SPMS status, as only evidence on EDSS severity could be found by the literature searches.

6.8 Model Results

6.8.1 Results of the MS Registry analyses

The results of the MS registry analyses exponential survival models are summarised in Table 29 (treatment dependent rates) and Table 31 (treatment independent rates). Samples sizes for the treatment dependent models are in Table 30, while those treatment independent models are in Table 31. These coefficients are on the log scale and the total log rate is calculated by adding the relevant components (i.e., the intercept plus the product of the current EDSS category with EDSS coefficient in all models, plus the coefficient for natalizumab in the treatment dependent models). The covariance matrices for the coefficients are provided in Appendix 7. The economic model was probabilistic so coefficients are sampled from multivariate normal with means in Table 29 and Table 31 and covariance matrices in Appendix 7. The MS Registry found no patients with highly active RRMS who decreased in EDSS so analysis could not be conducted.

Table 28 Number of Highly Active RRMS and RRMS patients by severity state in the MS Registry data set.*

EDSS	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
HARRMS	29	6	56	36	56	26	82	10	0	0
RRMS	50	18	200	188	150	90	214	45	5	0

*301 patients in total in HARRMS and 960 in RRMS.

The results of the multistate model are provided in Appendix 7. Due to the low sample size for the transitions between 9 different EDSS states, the log rates were very extreme between low severity states. For example, the mean rate (i.e., exponent of the log rates) between from EDSS 1 to EDSS 0 was 1041.7, EDSS 0 to EDSS 1 was 434.6 and from EDSS 2 to EDSS 3 was 83.0. It was decided to use only the exponential survival models for EDSS increase and decrease events in the economic model.

Table 29 Log rates and log rate ratios for events with treatment dependence estimated by the MS Registry using exponential survival models*

	Times to EDSS Increase (RRMS Highly Active)	Times to EDSS Increase (All RRMS)	Time to Relapse (RRMS Highly Active)	Time to Relapse (All RMS)
Intercept	-0.93 (-1.94, 0.07)	-2.25 (-2.63, -1.86)	-2.13 (-2.95, -1.3)	-2.63 (-3.08, -2.18)
EDSS	-0.18 (-0.33, -0.03)	-0.17 (-0.25, -0.1)	-0.02 (-0.2, 0.17)	-0.07 (-0.16, 0.01)
Alemtuzumab	-0.34 (-1.49, 0.81)	0.05 (-0.68, 0.78)	0.02 (-2.07, 2.12)	0.18 (-0.58, 0.93)
Cladribine	-3.29 (-5.44, -1.14)	-1.17 (-2.35, 0)	-0.79 (-2.87, 1.29)	0.37 (-1.05, 1.79)
Fingolimod	-2.38 (-3.53, -1.23)	-0.53 (-1.05, -0.01)	-0.21 (-1.1, 0.68)	0.13 (-0.34, 0.6)
Glatiramer Acetate	-1.04 (-2.23, 0.16)	-0.3 (-0.81, 0.2)	-0.52 (-1.49, 0.45)	0.04 (-0.39, 0.48)
Natalizumab	-1.26 (-2.5, -0.02)	0.28 (-0.17, 0.72)	-0.74 (-1.92, 0.43)	0.4 (-0.1, 0.9)
Ocrelizumab	-1.05 (-2.09, 0)	0.37 (-0.06, 0.8)	-0.17 (-1.4, 1.05)	0.29 (-0.36, 0.93)
Ofatumumab	-1.81 (-3.24, -0.38)	-0.02 (-0.72, 0.67)	-1.03 (-3.11, 1.05)	-0.1 (-1.53, 1.32)
Ponesimod	-1.43 (-3.58, 0.72)	-0.51 (-2.49, 1.48)	-0.38 (-2.46, 1.7)	0.23 (-1.76, 2.22)

*The economic model only used the intercept, effect of EDSS, and effect of natalizumab.

Table 30 Samples sizes in MS Registry analyses for treatment dependent events*

Event	N	Alemtuzumab	Cladribine	Fingolimod	Glatiramer acetate	Natalizumab	Ocrelizumab	Ofatumumab	Ponesimod
Time to EDSS Increase (RRMS Highly Active)	224	12	23	65	20	23	43	25	4
Time to EDSS Increase (All RRMS)	1016	41	35	158	158	177	203	69	7
Time to Relapse (RRMS Highly Active)	50	1	1	13	11	7	4	1	1
Time to Relapse (All RRMS)	191	9	2	34	44	28	15	2	1

* The MS Registry found no patients with highly active RRMS who decreased in EDSS so analysis could not be conducted.

Table 31 Log rates and log rate ratios for events with no treatment dependence estimated by the MS Registry using exponential survival models

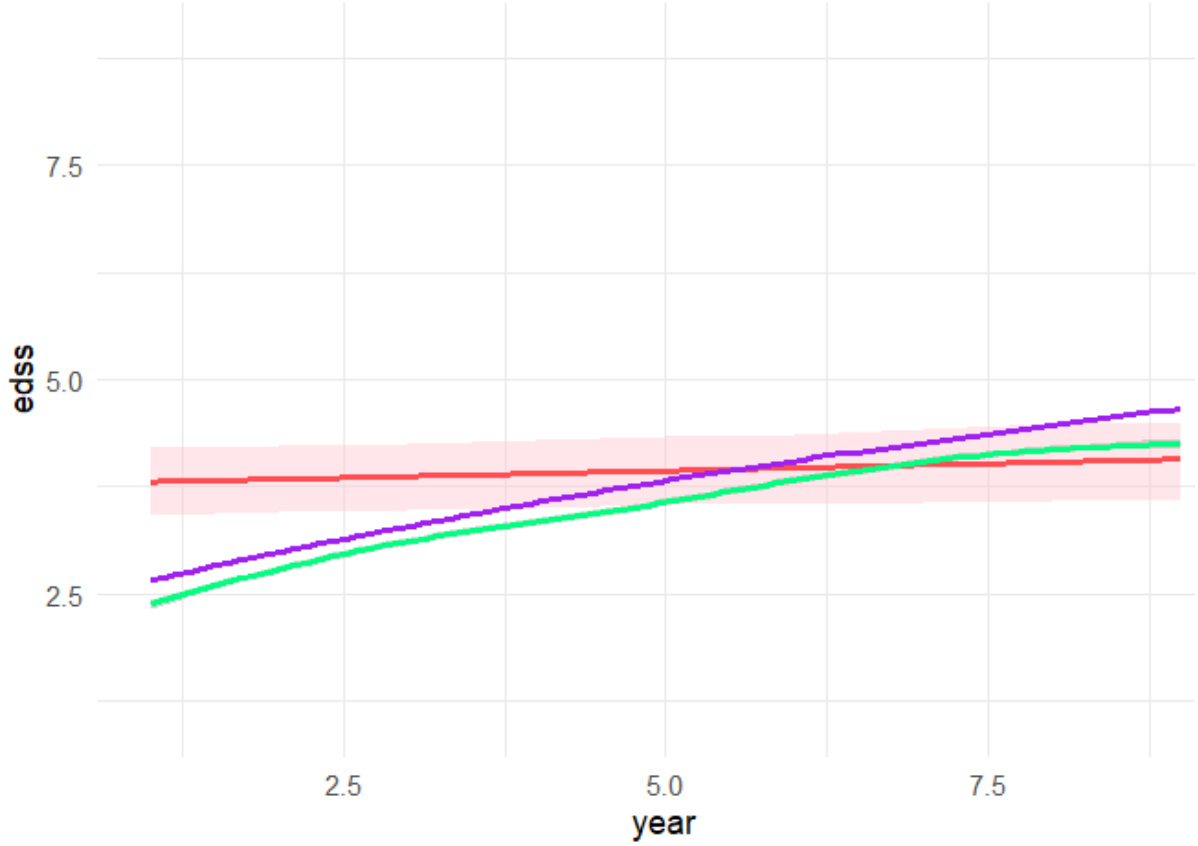
	Time to EDSS Decrease (All RRMS)*	Time to EDSS Increase (SPMS)	Time to Relapse (SPMS)	Time to SPMS Conversion (RRMS Highly Active)	Time to SPMS Conversion (All RRMS)
Sample size	793	181	164	66	222
Rate	-3.51 (-3.94, -3.08)	-1.89 (-3.15, -0.63)	-4.83 (-6.66, -3.01)	-2.58 (-3.89, -1.26)	-2.81 (-3.52, -2.1)
EDSS	0.14 (0.04, 0.23)	-0.2 (-0.42, 0.01)	0.07 (-0.22, 0.36)	0.01 (-0.21, 0.23)	0.04 (-0.08, 0.15)

* The MS Registry found no patients with highly active RRMS who decreased in EDSS so analysis could not be conducted.

6.8.2 Validation

The model code was validated by Javier Sanchez Alvarez at Evidera who found no major issues but suggested some minor improvements to flow and usage of DESCEM.

Figure 25 Validation through comparison of EDSS severity over time from economic model (red line with 95% CrI) and predictions from Palace 2014 (purple and green)



We compare the model's predictions to a continuous-time Markov model fit in to predict EDSS progression in a natural history cohort based on entry demographic and clinical data, but which did not distinguish between RRMS and SPMS, was not specific to highly active RRMS, and only included treatment with beta interferons rather than the latest DMT sequences. The model was fit in a cohort of the UK Risk Sharing Scheme and validated in a closely matched cohort from the British Columbia Canada Data set.[170] The mean (redline) and 95% CrI (shaded area) severity over the first 10 years in our DES model. The purple and green lines are the predicted and observed mean severity over the same time period in the published continuous-time Markov models.[126] The general overlap over this 10 year period is poor and the progression of the DES is less marked. This is likely explained by the comparator model being developed for both RRMS and SPMS and not including the latest DMT sequences.

6.8.3 Base case analysis

The results of the convergence test are in Table 32. This show that the mean and 95% CrI for total costs, QALYs, and net benefits for natalizumab-IV are somewhat stable with only 100 patients and 100 samples. The QALYs are potentially unstable below 500 samples and 250 patients but not to the extent that could affect results. We can therefore use 100 patients and 100 samples for sensitivity analysis as this is sufficient to demonstrate sensitivity or otherwise to the explored assumption.

Table 32 Assessment of convergence of economic model using mean and 95% CrI for natalizumab-IV (publicly available list prices)

		100 samples	250 samples	500 samples	1000 samples
Total costs	**100 patients**	445472.50 (384656.65, 509474.14)	444492.41 (386345.23, 509371.78)	446070.50 (386020.17, 517116.33)	446722.86 (384447.35, 524336.57)
	250 patients	444579.64 (384496.23, 507860.53)	444660.35 (390839.71, 509576.99)	446462.19 (388384.41, 514534.77)	446827.19 (388053.27, 519831.46)
	500 patients	444352.17 (385221.63, 503746.48)	444374.31 (387993.11, 507067.87)	446253.58 (386560.01, 512472.00)	446718.85 (387718.03, 523731.01)
	1000 patients	444033.08 (387382.41, 503238.51)	444304.18 (387987.75, 507098.10)	446291.36 (389490.23, 513545.21)	446764.59 (388187.03, 522503.46)
Total QALYs	**100 patients**	11.17 (6.88, 13.96)	11.14 (7.90, 14.06)	11.23 (7.65, 14.24)	11.24 (7.57, 14.35)
	250 patients	11.22 (7.10, 14.44)	11.17 (7.68, 14.25)	11.24 (7.83, 14.11)	11.24 (7.79, 14.33)
	500 patients	11.19 (7.24, 14.45)	11.16 (7.71, 14.17)	11.24 (7.80, 14.17)	11.24 (7.78, 14.21)
	1000 patients	11.19 (7.37, 14.39)	11.17 (7.77, 14.06)	11.24 (7.80, 14.13)	11.24 (7.82, 14.24)
Net benefit at £20,000/QALY	**100 patients**	-222100.21 (-315910.74, -147473.73)	-221623.97 (-311437.80, -151447.38)	-221445.97 (-321909.96, -142724.31)	-221851.40 (-331455.40, -141065.67)
	250 patients	-220083.86 (-327530.00, -148019.42)	-221256.83 (-313627.18, -155317.50)	-221716.31 (-319519.28, -147883.01)	-222033.01 (-324006.64, -146689.45)
	500 patients	-220558.05 (-322712.11, -146683.00)	-221138.91 (-321733.35, -157801.16)	-221416.46 (-325079.54, -148819.25)	-221925.01 (-325677.31, -148858.02)
	1000 patients	-220193.42 (-316098.78, -148549.24)	-220965.56 (-318089.52, -157068.85)	-221407.43 (-320050.45, -152547.75)	-221930.81 (-325860.27, -150887.39)
Net benefit at £30,000/QALY	**100 patients**	-110414.07 (-245243.77, -17389.21)	-110189.75 (-226669.27, -21420.45)	-109133.71 (-241461.47, -8006.11)	-109415.67 (-245068.55, -7896.10)
	250 patients	-107835.97 (-249433.06, -8308.71)	-109555.07 (-230754.67, -21452.04)	-109343.37 (-233895.66, -10332.30)	-109635.92 (-238812.72, -12210.18)

		100 samples	250 samples	500 samples	1000 samples
	500 patients	-108660.99 (-243280.18, -17087.04)	-109521.20 (-242563.36, -25297.47)	-108997.89 (-246339.94, -16767.23)	-109528.09 (-244229.56, -15209.80)
	1000 patients	-108273.59 (-234743.88, -20799.59)	-109296.25 (-237325.93, -27301.52)	-108965.46 (-240913.49, -20119.42)	-109513.92 (-241330.58, -18726.67)

The results of the base case analysis using the HARRMS population from the MS Registry and base case NMA results (i.e., fixed effects analysis in the All RRMS population) are provided in this section. We used 1000 samples and 1000 patients for this simulation. Uncertainty, as indicated by the 95% CrI is very high but general patterns can be seen.

With the exception of ocrelizumab, all treatments had greater net benefit at £20-30,000/QALY than natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC. The 95% CrI for incremental net benefits relative to natalizumab-IV excluded zero and the 95% CrI for net benefits for natalizumab biosimilar-IV and natalizumab-SC were not overlapping with those of comparators, indicating confidence that the net benefits of the natalizumabs are lower. Ocrelizumab had lower net benefit than any of the natalizumabs. Natalizumab-IV has lower net benefit at £20-30,000/QALY than natalizumab biosimilar-IV, although the 95% CrI overlap with 0.0 indicating no evidence of a difference in net benefits. Natalizumab-SC has very similar mean net benefit to Natalizumab-IV.

Across treatments, glatiramer Acetate 20mg and 40mg have the greatest net monetary benefits at £20-30,000/QALY, followed by interferon-beta-1a SC 44µg and interferon-beta-1b SC 250µg.

Table 33 Net Benefit and incremental net benefit in for treatments in comparison to Natalizumab IV (Public list prices) for the base case (HARRMS)

Treatment	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)	INB at £20,000/QALY (95% CrI)	INB at £30,000/QALY (95% CrI)	CEAC at £20,000/QALY	CEAC at £30,000/QALY
Natalizumab -IV	-221930.81 (-325860.27, -150887.39)	-109513.92 (-241330.58, -18726.67)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0	0
Natalizumab -SC	-221816.85 (-325779.04, -150089.10)	-109261.82 (-242489.08, -12993.23)	113.96 (-19952.71, 20391.27)	252.10 (-22509.33, 23031.01)	0	0
Natalizumab biosimilar-IV	-211500.56 (-316036.43, -141710.58)	-99158.71 (-235407.06, -4747.04)	10430.25 (-9866.37, 33118.11)	10355.21 (-12501.66, 36094.29)	0	0
Fingolimod	-2e+05 (-3e+05, -134564.90)	-94311.01 (-220151.54, 1275.82)	17287.91 (-7082.76, 45155.59)	15202.91 (-12047.99, 45526.85)	0	0

Treatment	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)	INB at £20,000/QALY (95% CrI)	INB at £30,000/QALY (95% CrI)	CEAC at £20,000/QALY	CEAC at £30,000/QALY
Alemtuzumab	-152392.62 (-276918.47, -67219.64)	-38961.07 (-194203.82, 71584.52)	69538.19 (-6695.87, 161476.86)	70552.85 (-9314.54, 164282.34)	0.003	0.005
Cladribine	-150332.71 (-275648.38, -56964.47)	-42513.74 (-2e+05, 74956.72)	71598.10 (4838.93, 154730.42)	67000.17 (-1139.26, 150009.19)	0	0
Ponesimod	-165188.69 (-291888.18, -91638.04)	-55654.88 (-218236.52, 44700.22)	56742.12 (14675.92, 1e+05)	53859.04 (5779.06, 99977.03)	0	0
Ofatumumab	-211098.14 (-316552.83, -141119.09)	-98494.07 (-236561.98, -7018.57)	10832.67 (-10896.15, 31986.99)	11019.85 (-16076.43, 35701.92)	0	0
Ocrelizumab	-223985.21 (-332413.48, -152208.74)	-111270.42 (-239271.93, -18105.73)	-2054.40 (-28173.17, 20457.65)	-1756.50 (-32266.54, 24285.25)	0	0
Peginterferon -β-1 SC 125µg	-106013.63 (-219477.93, -29343.97)	6109.89 (-136070.05, 107045.38)	115917.18 (53804.14, 188910.01)	115623.81 (50564.10, 186451.39)	0.264	0.311
Interferon-beta-1a SC 22µg	-119106.47 (-239882.00, -40586.41)	-7852.16 (-158279.13, 94944.57)	1e+05 (44991.63, 170168.40)	1e+05 (41745.72, 169892.42)	0.02	0.035
Interferon-beta-1a SC 44µg	-112006.15 (-242641.36, -28367.59)	-2203.32 (-162378.25, 108832.39)	109924.66 (44792.20, 180986.40)	107310.59 (40296.34, 181737.90)	0.06	0.077
Interferon-beta-1a IM 30µg	-118921.02 (-247888.19, -34500.47)	-10163.40 (-175931.60, 1e+05)	1e+05 (41729.36, 175767.26)	99350.52 (35020.88, 172631.09)	0.01	0.016
Interferon-beta-1b SC 250µg	-112632.59 (-245651.67, -24389.30)	-4104.95 (-172738.91, 112113.78)	109298.22 (42980.66, 186758.07)	105408.97 (33814.12, 184712.12)	0.092	0.083
Glatiramer Acetate 20mg	-105659.02 (-234955.60, -18835.48)	3875.40 (-161256.44, 119588.55)	116271.79 (49230.69, 189757.44)	113389.31 (43692.80, 187217.79)	0.262	0.233
Glatiramer Acetate 40mg	-106021.95 (-233241.35, -20311.08)	3401.66 (-160842.66, 117148.40)	115908.86 (52235.22, 191921.67)	112915.58 (47344.46, 188242.01)	0.289	0.24

The total costs and QALYs for all included treatments, and their incremental comparison with Natalizumab IV, are provided in Table 34. The 95% CrI for both costs and QALYs are wide, suggesting high uncertainty. All treatments, with the exception of ocrelizumab have lower costs than natalizumab-IV with 95% CrI for incremental costs excluding 0.0 and indicating that costs are lower on the comparators. Except for ocrelizumab, and ofatumumab in comparison with natalizumab biosimilar-IV, all 95% CrI for costs on comparators do not overlap with those for natalizumab biosimilar-IV or natalizumab SC, suggesting costs are also higher. The 95% CrI for QALYs were overlapping suggesting no difference, although the mean QALYs were lower on most treatments than on the

natalizumab. The exceptions were alemtuzumab, ofatumumab, and ocrelizumab, which had higher mean QALYs (although ofatumumab was tied with natalizumab-SC).

The natalizumab biosimilar-IV has lower costs but also lower QALYs than natalizumab-IV. However the differences in costs and QALYs are uncertain with 95% CrI overlapping. The 95% CrI for incremental costs and QALYs of natalizumab biosimilar-IV and natalizumab-IV are overlapping with 0.0 suggesting no evidence of a difference in costs or QALYs. Natalizumab-SC has very similar costs and QALYs to natalizumab-IV.

Across treatments, total costs are lower on fingolimod, alemtuzumab, cladribine, and ponesimod than on the natalizumab treatments with 95% CrI that do not overlap. QALYs appear to be lower on fingolimod, cladribine, and ponesimod but uncertainty is higher and the 95% CrI are overlapping.

We see that alemtuzumab has the greatest mean QALYs, followed by ocrelizumab. Ocrelizumab also has the highest costs, followed by natalizumab-SC, which is almost level with natalizumab-IV. The favourable net benefits for glatiramer Acetate 20mg and 40mg, interferon-beta-1a SC 44µg, and interferon-beta-1b SC 250µg, are seen to be driven by their having the lowest costs, despite their low QALYs.

Table 34 Total and incremental costs and QALYs for treatments in comparison to Natalizumab IV (Public list prices) for the base case (HARRMS)

Treatment	Total costs £ (95% CrI)	Total QALYs (95% CrI)	Incremental costs £ (95% CrI)	Incremental QALYs (95% CrI)
Natalizumab-IV	446764.59 (388187.03, 522503.46)	11.24 (7.82, 14.24)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Natalizumab-SC	446926.92 (389334.27, 525252.77)	11.26 (7.75, 14.24)	162.33 (-17068.04, 17934.54)	0.014 (-0.42, 0.41)
Natalizumab biosimilar-IV	436184.26 (381421.18, 508599.25)	11.23 (7.77, 14.26)	-10580.33 (-30737.92, 6946.76)	-0.0075 (-0.41, 0.43)
Fingolimod	425306.68 (377192.22, 487796.53)	11.03 (7.61, 14.09)	-21457.91 (-46859.83, -1646.99)	-0.21 (-0.68, 0.26)
Alemtuzumab	379255.72 (330988.23, 443641.14)	11.34 (7.71, 14.36)	-67508.87 (-155132.70, 1749.04)	0.10 (-0.41, 0.63)
Cladribine	365970.64 (316216.65, 431692.60)	10.78 (7.11, 13.95)	-80793.95 (-167683.94, -15278.73)	-0.46 (-1.10, 0.088)
Ponesimod	384256.30 (342207.84, 453538.80)	10.95 (7.26, 14.05)	-62508.29 (-105287.10, -28331.84)	-0.29 (-1.06, 0.25)
Ofatumumab	436306.27 (381061.14, 5e+05)	11.26 (7.95, 14.14)	-10458.33 (-27281.97, 3504.06)	0.019 (-0.53, 0.53)

Treatment	Total costs £ (95% CrI)	Total QALYs (95% CrI)	Incremental costs £ (95% CrI)	Incremental QALYs (95% CrI)
Ocrelizumab	449414.79 (386810.14, 525045.39)	11.27 (7.75, 14.11)	2650.19 (-12692.16, 20848.86)	0.03 (-0.54, 0.62)
Peginterferon -β-1 SC 125µg	330260.67 (290256.33, 388923.34)	11.21 (7.80, 14.17)	-116503.92 (-184620.72, -58258.85)	-0.029 (-0.60, 0.56)
Interferon-beta-1a SC 22µg	341615.11 (3e+05, 4e+05)	11.13 (7.71, 14.10)	-105149.49 (-172331.26, -50539.06)	-0.12 (-0.73, 0.42)
Interferon-beta-1a SC 44µg	331611.79 (289797.35, 4e+05)	10.98 (7.49, 14.03)	-115152.80 (-185982.35, -57567.98)	-0.26 (-0.91, 0.26)
Interferon-beta-1a IM 30µg	336436.28 (294318.50, 405345.27)	10.88 (7.13, 13.97)	-110328.31 (-181158.37, -51670.35)	-0.37 (-1.12, 0.20)
Interferon-beta-1b SC 250µg	329687.88 (285495.32, 4e+05)	10.85 (7.18, 14.03)	-117076.71 (-190840.46, -56263.43)	-0.39 (-1.15, 0.20)
Glatiramer Acetate 20mg	324727.86 (280404.33, 389771.40)	10.95 (7.19, 14.10)	-122036.73 (-195613.46, -58804.24)	-0.29 (-0.93, 0.23)
Glatiramer Acetate 40mg	324869.17 (281520.26, 390156.24)	10.94 (7.26, 14.02)	-121895.43 (-196665.10, -61498.05)	-0.30 (-0.98, 0.21)

The cost-effectiveness plane and CEAC are presented in Figure 26 and Figure 27, respectively. The cost-effectiveness plane graphically illustrates the high uncertainty in incremental costs and effects of Table 34. It also makes it clear that natalizumab-IV is very unlikely to be cost-effective at a £30,000/QALY willingness-to-pay threshold compared to any of the treatments. The CEAC confirms the finding that glatiramer Acetate 20mg, glatiramer acetate 40mg, and interferon-beta-1b SC 250µg are most likely to be cost-effective in the £20-30,000/QALY range. These CEAC values at £20,000/QALY and £30,000/QALY are also reported in Table 33. However, the probability that any one of them has the greatest net benefit is below 25%, indicating high uncertainty as to which is most cost-effective. The natalizumabs have close to 0% chance of having highest net benefit (CEAC) at £20,000/QALY and £30,000/QALY.

Figure 26 Cost-Effectiveness Plane for treatments in comparison to Natalizumab IV, WTP £30,000/QALY (Public list prices) for the base case (HARRMS)

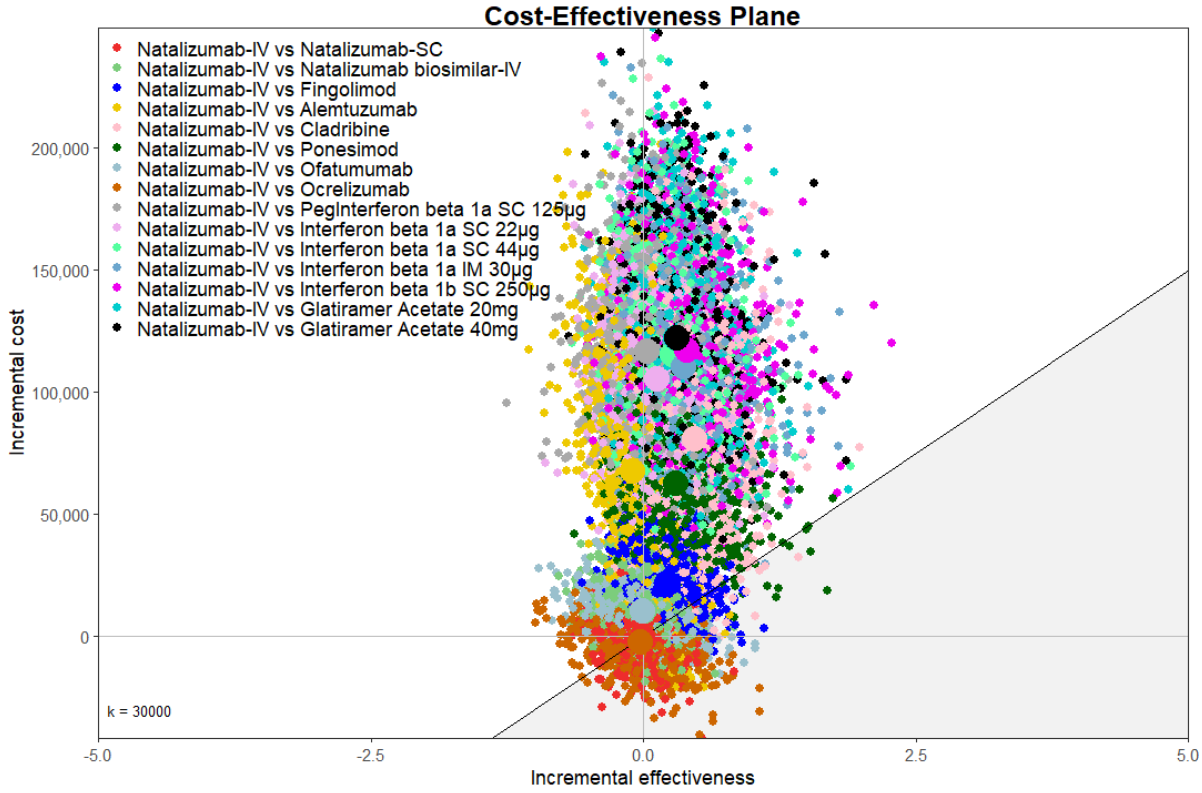
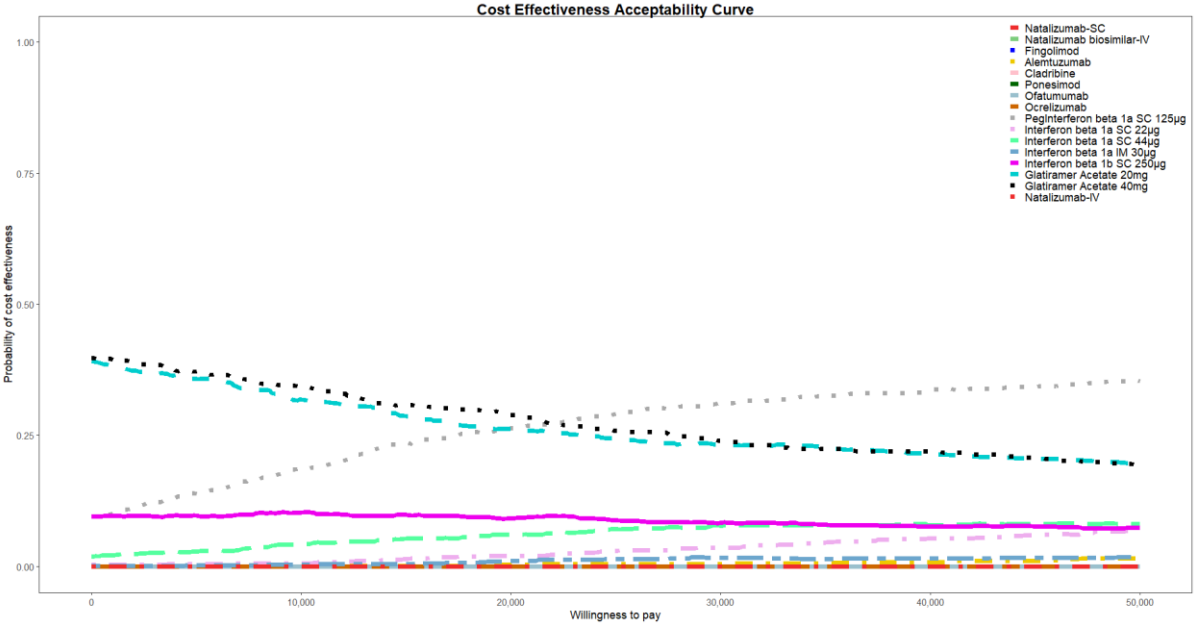


Figure 27 Cost Effectiveness Acceptability Curve for treatments in comparison to Natalizumab IV, WTP £30,000 (Public list prices)



6.8.4 Sensitivity analyses

The incremental net benefits from the sensitivity analyses at £20,000/QALY are presented in Table 35 and at £30,000/QALY in Table 36. We used 100 samples and 100 patients for these simulations.

These sensitivities again find that natalizumab-IV has lower net benefit at £20-30,000/QALY than natalizumab biosimilar-IV with very little impact on the mean results.

Glatiramer Acetate 20mg and 40mg, interferon-beta-1b SC 250µg, and interferon-beta-1a SC 44µg all have the greatest net benefits under all sensitivities except that using the HA RRMS fixed effects NMA which did not include these treatments. In this sensitivity Peginterferon-β-1 SC 125µg was the most cost-effective treatment.

Table 35 Incremental net benefits relative to natalizumab-IV at £20,000/QALY for the base case and sensitivity analyses (publicly available list prices)

Treatment	Base case	Scenario 1 (All RRMS MS Registry population)	Scenario 2 (base-case w/ random effects NMA)	Scenario 3 (base-case & assuming JCV testing provided free of charge by manufacturers)	Scenario 4 (using lowest price generics for comparators)	Scenario 5 (base case & assuming a reduction in Natalizumab-SC administration costs)	Scenario 6 (base-case w/ HA RRMS fixed effects NMA)	Scenario 7 (stratifying mortality by EDSS severity)
Natalizumab-SC	113.96 (-19952.71, 20391.27)	4895.89 (-39205.98, 49241.71)	1328.30 (-43407.17, 50042.28)	301.92 (-54443.94, 42594.90)	290.30 (-54703.54, 43027.00)	29595.30 (-27040.98, 78970.81)	-1446.96 (-46684.75, 44816.42)	-1185.43 (-59638.17, 51227.82)
Natalizumab biosimilar-IV	10430.25 (-9866.37, 33118.11)	8419.56 (-42300.57, 61986.08)	10165.51 (-25734.68, 62974.00)	7491.13 (-36096.45, 47657.00)	9244.85 (-34755.73, 49310.20)	9382.04 (-34051.04, 50103.86)	NA	8876.76 (-40353.52, 59885.62)
Fingolimod	17287.91 (-7082.76, 45155.59)	10953.73 (-39440.55, 70030.22)	21094.72 (-28741.59, 76532.03)	14397.26 (-33316.28, 70273.81)	114805.14 (26396.68, 202734.77)	16193.94 (-32763.50, 72469.58)	13749.84 (-47882.38, 66118.75)	17016.27 (-29082.15, 64385.05)
Alemtuzumab	69538.19 (-6695.87, 161476.86)	66281.33 (-7385.52, 148491.50)	66645.95 (-36459.02, 185053.43)	70322.96 (-30347.06, 164138.11)	72093.83 (-29439.92, 166806.60)	72098.62 (-29906.08, 165748.81)	64895.74 (-22650.54, 154990.93)	68363.73 (-36852.72, 154550.75)
Cladribine	71598.10 (4838.93, 154730.42)	54218.68 (1825.62, 109582.27)	69437.69 (-17083.99, 160907.84)	68491.77 (-19872.07, 144966.82)	70262.12 (-18885.64, 147451.02)	70306.24 (-18928.13, 146517.30)	67090.14 (-21620.01, 141883.97)	67947.25 (-14882.37, 146343.98)
Ponesimod	56742.12 (14675.92, 100225.55)	49249.72 (6668.01, 106365.21)	55898.88 (-11376.28, 116166.09)	55682.28 (-5229.59, 118928.12)	57449.86 (-3895.69, 121424.61)	57409.60 (-3771.59, 120518.98)	NA	53997.48 (-14671.74, 96935.81)
Ofatumumab	10832.67 (-10896.15, 31986.99)	11382.52 (-33304.37, 61448.23)	9759.87 (-65303.87, 61190.89)	5482.83 (-40455.40, 52093.46)	7245.96 (-38857.24, 54118.01)	7387.25 (-37914.90, 55350.90)	NA	6605.59 (-49142.68, 51597.14)

Treatment	Base case	Scenario 1 (All RRMS MS Registry population)	Scenario 2 (base-case w/ random effects NMA)	Scenario 3 (base-case & assuming JCV testing provided free of charge by manufacturers)	Scenario 4 (using lowest price generics for comparators)	Scenario 5 (base case & assuming a reduction in Natalizumab-SC administration costs)	Scenario 6 (base-case w/ HA RRMS fixed effects NMA)	Scenario 7 (stratifying mortality by EDSS severity)
Ocrelizumab	-2054.40 (-28173.17, 20457.65)	4164.11 (-45204.89, 58868.11)	1708.60 (-46988.96, 50625.63)	173.86 (-42704.81, 43363.17)	1947.05 (-41307.01, 45096.64)	1846.71 (-42278.11, 44735.24)	-2009.33 (-47146.53, 54952.96)	-1571.86 (-45018.49, 53735.56)
Peginterfero-beta-1 SC 125µg	115917.18 (53804.14, 188910.01)	106726.98 (56754.96, 156352.89)	114103.51 (39198.21, 191816.07)	112535.34 (37503.05, 183902.04)	114297.43 (38606.47, 186117.59)	114333.26 (38163.78, 186039.19)	111205.44 (49307.15, 188195.60)	113526.59 (32332.44, 188505.75)
Interferon-beta-1a SC 22µg	102824.34 (44991.63, 170168.40)	95157.12 (35795.90, 161703.99)	98413.09 (33653.88, 166618.89)	101087.49 (26832.76, 168413.44)	102862.79 (27804.59, 170745.92)	102762.18 (28027.37, 169978.27)	98865.00 (23759.36, 163764.60)	102264.10 (26814.28, 158608.11)
Interferon-beta-1a SC 44µg	109924.66 (44792.20, 180986.40)	99150.87 (39185.50, 164114.74)	107898.51 (15575.28, 181921.57)	106575.04 (20511.69, 192287.76)	108332.44 (21444.88, 194909.59)	108480.56 (20722.21, 193998.53)	109892.07 (39143.65, 198658.03)	103556.87 (20850.92, 177562.31)
Interferon-beta-1a IM 30µg	103009.79 (41729.36, 175767.26)	92515.34 (33963.26, 152783.19)	96923.71 (10162.06, 168693.98)	99145.04 (23411.19, 187905.73)	100903.52 (24834.30, 190502.16)	100989.74 (23544.30, 189843.94)	103990.45 (15486.56, 172648.50)	102256.18 (21344.63, 179800.06)
Interferon-beta-1b SC 250µg	109298.22 (42980.66, 186758.07)	98342.19 (43882.25, 154030.78)	113495.87 (34404.90, 192017.80)	106228.93 (29844.59, 174330.93)	108000.87 (30736.55, 177233.90)	108086.04 (30784.82, 178134.93)	NA	105714.15 (26192.83, 165685.15)
Glatiramer Acetate 20mg	116271.79 (49230.69, 189757.44)	104948.30 (54206.04, 159494.22)	115594.65 (31042.04, 202626.77)	114316.36 (22861.02, 186364.60)	119723.46 (26230.62, 194240.47)	116067.04 (24066.83, 189715.74)	NA	115586.80 (33579.76, 192430.82)
Glatiramer Acetate 40mg	115908.86 (52235.22, 191921.67)	106969.47 (40479.92, 166503.76)	117613.64 (48215.02, 199974.13)	114998.37 (41676.74, 199230.85)	120378.23 (44910.10, 207373.20)	116760.09 (42665.33, 202742.31)	NA	113011.73 (28420.26, 185119.68)

Table 36 Incremental net benefits relative to natalizumab-IV at £30,000/QALY for the base case and sensitivity analyses (publicly available list prices)

Treatment	Base case	Scenario 1 (All RRMS MS Registry population)	Scenario 2 (base-case w/ random effects NMA)	Scenario 3 (base-case & assuming JCV testing provided free of charge by manufacturers)	Scenario 4 (using lowest price generics for comparators)	Scenario 5 (base case & assuming a reduction in Natalizumab-SC administration costs)	Scenario 6 (base-case w/ HA RRMS fixed effects NMA)	Scenario 7
Natalizumab-SC	252.10 (-22509.33, 23031.01)	5548.49 (-48143.47, 57612.35)	1431.53 (-54958.94, 66479.75)	555.47 (-68423.97, 52051.14)	543.85 (-68683.56, 52260.97)	29848.85 (-40966.08, 88221.33)	-1327.19 (-60521.37, 57139.10)	-1063.34 (-70158.88, 64174.15)
Natalizumab biosimilar-IV	10355.21 (-12501.66, 36094.29)	7535.00 (-54971.50, 68887.44)	9557.75 (-31713.85, 71892.32)	7155.86 (-45802.04, 61464.69)	8909.58 (-44461.32, 63133.78)	9046.77 (-44081.77, 63525.38)	NA	8724.10 (-51873.52, 71749.68)
Fingolimod	15202.91 (-12047.99, 45526.85)	7703.02 (-53853.19, 79591.67)	19660.16 (-42925.26, 80366.48)	11692.17 (-47043.64, 76164.52)	112100.05 (14823.79, 205399.15)	13488.85 (-46429.99, 78461.71)	11320.93 (-69395.06, 76256.01)	15464.42 (-42381.85, 73697.51)
Alemtuzumab	70552.85 (-9314.54, 164282.34)	68569.57 (-18776.49, 154032.06)	66631.58 (-46114.83, 186765.71)	71752.67 (-39818.04, 169711.83)	73523.55 (-38842.81, 172125.37)	73528.34 (-39303.79, 171375.93)	65293.77 (-28120.24, 161792.09)	69583.85 (-51668.33, 159573.24)
Cladribine	67000.17 (-1139.26, 150009.19)	47925.74 (-15758.85, 115144.07)	64038.76 (-32928.61, 166013.22)	63343.28 (-30946.83, 142026.83)	65113.63 (-29954.22, 144216.84)	65157.75 (-29990.66, 143962.06)	61586.01 (-35184.55, 144023.09)	63197.03 (-30339.32, 149319.90)
Ponesimod	53859.04 (5779.06, 99977.03)	45417.84 (-4986.66, 109487.63)	52361.89 (-22244.03, 125652.46)	52914.78 (-21367.68, 127407.75)	54682.36 (-20094.45, 129871.31)	54642.10 (-19989.83, 128998.62)	NA	50485.35 (-34032.96, 103687.64)
Ofatumumab	11019.85 (-16076.43, 35701.92)	11392.17 (-43527.36, 73438.46)	9101.42 (-81547.54, 71661.17)	4542.80 (-50682.42, 61640.90)	6305.94 (-49455.46, 63754.93)	6447.23 (-49272.63, 65224.82)	NA	5965.65 (-64148.91, 66594.07)

Treatment	Base case	Scenario 1 (All RRMS MS Registry population)	Scenario 2 (base-case w/ random effects NMA)	Scenario 3 (base-case & assuming JCV testing provided free of charge by manufacturers)	Scenario 4 (using lowest price generics for comparators)	Scenario 5 (base case & assuming a reduction in Natalizumab-SC administration costs)	Scenario 6 (base-case w/ HA RRMS fixed effects NMA)	Scenario 7
Ocrelizumab	-1756.50 (-32266.54, 24285.25)	6083.57 (-54760.01, 76072.39)	2436.73 (-53964.77, 63208.69)	1182.58 (-54514.66, 54166.99)	2955.77 (-52789.89, 56044.66)	2855.42 (-52497.13, 55773.34)	-1692.38 (-55521.89, 66379.70)	-799.92 (-59031.30, 67011.13)
Peginterferon-beta-1 SC 125µg	115623.81 (50564.10, 186451.39)	105909.53 (44777.06, 162447.26)	113451.30 (33505.51, 196675.44)	111694.15 (25988.13, 194708.74)	113456.24 (27049.32, 196924.29)	113492.07 (25861.49, 196845.89)	109663.65 (32429.07, 196701.79)	113297.31 (26322.42, 206200.06)
Interferon-beta-1a SC 22µg	101661.76 (41745.72, 169892.42)	93804.93 (27077.84, 172572.88)	95988.16 (22092.04, 176099.78)	99565.28 (15283.09, 175195.96)	101340.58 (16254.93, 177498.18)	101239.97 (16481.05, 176715.60)	97066.81 (11614.41, 168362.09)	101543.98 (17951.11, 164857.78)
Interferon-beta-1a SC 44µg	107310.59 (40296.34, 181737.90)	95889.64 (29493.56, 173368.99)	104546.70 (-3285.31, 185018.90)	103305.46 (11909.60, 196222.80)	105062.85 (12899.75, 198502.25)	105210.97 (12585.65, 198123.52)	107545.64 (27665.19, 208223.99)	99881.53 (5734.23, 184926.69)
Interferon-beta-1a IM 30µg	99350.52 (35020.88, 172631.09)	87881.04 (17732.45, 162731.29)	91789.77 (-799.46, 167486.12)	94649.83 (15470.52, 195217.83)	96408.31 (16410.50, 197415.81)	96494.53 (15649.24, 197020.17)	101106.66 (7111.15, 185677.62)	98568.26 (4621.29, 180172.81)
Interferon-beta-1b SC 250µg	105408.97 (33814.12, 184712.12)	93156.95 (27895.51, 156339.77)	110847.20 (19936.40, 199364.12)	102232.50 (21434.50, 171463.58)	104004.44 (22284.72, 173594.21)	104089.61 (22371.04, 175048.28)	NA	101259.94 (5924.89, 172003.94)
Glatiramer Acetate 20mg	113389.31 (43692.80, 187217.79)	101473.55 (40585.57, 165634.60)	111954.69 (15074.72, 204471.72)	111624.42 (8862.28, 187008.85)	117031.53 (12231.88, 194810.43)	113375.10 (10068.09, 189150.07)	NA	112793.31 (16387.07, 193357.11)
Glatiramer Acetate 40mg	112915.58 (47344.46, 188242.01)	103574.85 (25064.64, 167350.25)	115017.85 (34471.32, 208709.69)	111996.24 (29943.39, 205073.47)	117376.09 (33576.76, 212377.89)	113757.96 (30444.69, 207861.01)	NA	109898.14 (15011.62, 191191.23)

6.8.5 Value of information analysis

The results of the value of information analysis are presented in Table 37. These show that the EVPPI is greatest for the NMA treatment effects on efficacy (ARR and CDP6) and safety (SAEs and discontinuation). This indicates that the greatest decision uncertainty is associated with the NMA estimates and RCT data. Utilities have a greater EVPPI than costs but both are important factors with a high EVPPI relative to total EVPI. Baseline rates of EDSS increase/decrease, progression to SPMS, and relapse rates have high and similar EVPPI. Absolute discontinuation rate and SAE rate have low EVPPI and their uncertainty thus has limited impact on the decision.

Table 37 Value of Information analysis results for the HARRMS base case using BART* method (publicly available list prices)

Parameter group	Per-person EVPPI at £20,000/QALY	Per-person EVPPI at £30,000/QALY
Total EVPI	8023.66	8985.47
NMA on CDP6	5966.55	6313.04
NMA on ARR	6005.47	6318.98
NMA on SAEs	5383.41	5629.18
NMA on discontinuation	5854.56	6171.58
Costs	3669.85	3061.73
Utilities	4712.21	4811.31
MS registry EDSS increase/decrease	3330.83	2693.98
MS registry SPMS progression	3051.01	2515.00
MS registry ARR	3089.55	2486.53
Discontinuation rate	1018.96	367.12
SAEs rate	1052.14	417.71

*BART=Bayesian additive regression trees

6.8.6 Summary of findings of economic evaluation

With the exception of ocrelizumab, all treatments had greater net benefit at £20-30,000/QALY than natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC. The natalizumabs also had close to 0% chance of having highest net benefit at £20,000/QALY and £30,000/QALY. Costs were generally higher on natalizumab than other treatments, though there was no difference in QALYs with 95% CrI completely overlapping.

Natalizumab-IV has lower mean net benefit at £20-30,000/QALY than natalizumab biosimilar-IV, although the 95% CrI overlap. Natalizumab-SC has very similar mean net benefit to Natalizumab-IV. The natalizumab biosimilar-IV has lower costs but also lower QALYs than natalizumab-IV but the 95% CrI for both are overlapping suggesting no evidence of a difference. Natalizumab-SC has very similar costs and QALYs to natalizumab-IV, again with no evidence of a difference.

Across all treatments, glatiramer Acetate 20mg and 40mg have the greatest net monetary benefits at £20-30,000/QALY, followed by interferon-beta-1a SC 44µg and interferon-beta-1b SC 250µg. However, the probability that any one of them has the greatest net benefit is below 25%, indicating high uncertainty as to which is most cost-effective.

Results were robust to sensitivity analyses relating to MS registry baseline estimates, use of random effects NMA, use of HA RRMS NMA, excluding the price of JCV testing for branded natalizumab, reducing the natalizumab-SC treatment administration costs, and stratifying mortality by EDSS severity. In the sensitivity using the HA RRMS NMA, glatiramer acetate and Interferon-beta-1b SC 250µg were not included. However, natalizumab-IV and natalizumab-SC were not cost-effective compared to any included treatment and the most cost-effective treatment was peginterferon -β-1 SC 125µg.

Value of information analysis found that the parameters with greatest impact on the results were the NMA hazard ratios on ARR, CDP6, SAEs, and discontinuation. However, many parameters, including costs, utilities, and MS registry rates, had substantial impact on the results indicating high parameter uncertainty.

7 Assessment of factors relevant to the NHS and other parties

New diagnostic criteria for MS reported at the recent ECDMS conference may allow earlier diagnosis, and hence also treatment, of people with MS. This will have implications for the NHS. The lack of a consensus definition on HARRMS make it challenging to introduce treatments for this population. There is a need for a clear and consistent definition of the HARRMS population to allow treatments to be prescribed appropriately.

Evolving formulation availability will affect delivery options and some Trusts may make decisions based on support from pharmaceutical companies. For example, in-home delivery of infusions by nurses supplied by companies. However, this could raise a vulnerability with shifts in demand if these are subsequently withdrawn, particularly if done at relatively short notice.

8 DISCUSSION

8.1 Statement of principal findings

Based on findings from our NMA and SLR, most interventions reduced relapses and the proportion of participants with MRI lesions compared to placebo. Alemtuzumab, ocrelizumab, natalizumab, fingolimod and peginterferon beta 1a also reduced disease progression compared to placebo. There was no differences in any AEs, serious AEs or treatment related AEs for any intervention compared to placebo. Fingolimod, glatiramer acetate, interferon beta 1a, interferon beta 1b and peginterferon beta 1a were associated with increased treatment discontinuation. There was little evidence for a difference in quality of life. There was no evidence of a difference between natalizumab and natalizumab biosimilar for relapse rates, MRI lesions or AEs. Data in HARRMS were available for fingolimod, ocrelizumab, alemtuzumab, cladribine, beta-interferon, AHSCT, and placebo. We also included one study on natalizumab conducted in a population that was close to our definition of HARRMS. All interventions except interferon beta 1a were associated with reduced relapse risk compared to placebo; there were little data for other outcomes.

Compared with natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC, all treatments had greater net benefit at £20-30,000/QALY, with the only exception being ocrelizumab which had lower net benefits. Costs were generally higher on natalizumab than other treatments, though there was no difference in QALYs with 95% CrI completely overlapping. The results and conclusions were unchanged under all sensitivities. Value of information analysis found that the greatest contributor to decision uncertainty was the effectiveness of treatments.

8.1.1 Findings on clinical effectiveness

We identified 42 studies that fulfilled inclusion criteria for our SLR. However, the majority of the evidence was in the general RRMS population rather than those with highly active disease, and most studies evaluated comparator interventions rather than the technologies of interest for this appraisal - natalizumab (Tysabri, Biogen) and natalizumab biosimilar (Tyruko, Sandoz).

ARR was the most frequently reported outcome across studies, with 39 of the 40 trials in the general RRMS population reporting data for this outcome. ARR data generally suggested that newer DMT, such as alemtuzumab, ocrelizumab, and natalizumab, are more effective than older treatments like interferon beta and glatiramer acetate, which showed limited improvements over placebo. Fewer than half the included studies provided data on the proportion of participants who had Gd+ (19 studies) or new or enlarging T2 lesions (17 studies) but data were consistent with the findings for ARR, suggesting a greater effect for newer DMT. Disease progression was also reported in less than half of studies, and we were unable to connect studies of teriflunomide, ponesimod, and ofatumumab to the main network. These studies were therefore not included in the NMA for these outcomes. Data for the remaining interventions were also consistent with the findings for ARR, suggesting a

greater effect of newer DMT on reducing disease progression, with slightly stronger evidence on an effect for CDP3. Disability progression can be highly variable across individuals, with some showing gradual decline followed by periods of improvement rather than consistent decline over relatively short time periods, with decline only becoming evidence over longer time periods. This can make it difficult for patients to meet the criteria for confirmed disability progression, particularly CDP6 which requires sustained progression over 6 months, over shorter follow-up periods (e.g., 6 months). The use of sustained disability metrics, such as 6-month confirmed disability progression (CDP6), offers a more reliable measure of true progression than CDP3, as it reflects long-term changes rather than temporary fluctuations. However, true disability progression often unfolds over years or even decades, making it challenging to observe in standard clinical trials with shorter follow-up periods.[171, 172]

All but two of the trials included in this review provided data on AEs, a further two only reported data on specific AEs of interest and so could not be included in our synthesis as they did not report at least one the AEs measures of interest for this appraisal (incidence of any AEs, SAEs, treatment related AEs, of treatment discontinuation due to AEs). There was no evidence of an increased risk of any AEs or treatment related AEs for any of the interventions evaluated. It may be difficult to determine the true impact of AEs from the outcome “any AE” as this is defined very broadly so that any potential adverse events, including those not thought to be related to the intervention, are recorded as potential AEs. Close to 100% of participants in both groups experienced AEs and so this measure does not distinguish between groups. There were less data on treatment related AEs which were only reported for eight studies. These may be expected to be a more appropriate measure of the true risk of AEs associated with the different interventions, but there was also little evidence of a difference between groups for this measure. There was a suggestion that natalizumab and peginterferon beta 1a were associated with a lower risk of SAEs compared to placebo, but CrIs were wide and included 1. Fingolimod, glatiramer acetate (SC20), interferon beta 1a (SC44) and peginterferon beta 1a were associated with a higher rate of treatment discontinuation than placebo; there was no evidence of a difference between other interventions and placebo. However, SAEs are generally rare and so require large sample sizes to show difference in risk between groups. Analyses of real-world data may be necessary to identify the potential risk of these.[173]

There was limited evidence on the technologies of interest for this appraisal - natalizumab and natalizumab biosimilar. We identified only four studies of these interventions. This included two placebo control trials of natalizumab – AFFIRM, a large multinational trial (n=943) with 24 months follow-up, and Saida 2017 which only included 94 participants, had a short follow-up period of 6 months and only included Japanese participants. An additional trial (REVEAL) compared natalizumab with fingolimod. This phase 4 randomised study, with a planned overall duration of 68 weeks was terminated prematurely due to slow enrolment and so data were only available for 12 months follow-up. The fourth trial was a direct comparison between natalizumab and natalizumab biosimilar – the only randomised

evidence available for this intervention. This trial also had a short follow-up period (24 weeks) and its primary outcomes were MRI findings (new gadolinium-enhancing T1-weighted lesions and new/enlarging T2-weighted lesions). However, two previous meta-analyses [174, 175] have found a correlation between the effect of MS drugs on relapses and MRI activity, with the magnitude of the benefit on MRI lesions predicting the magnitude of the effect on relapse rates. All four trials were conducted in the general RRMS population and did not provide any data specifically in patients with HARRMS. However, the Saida 2017 study included a very high proportion (88%) of previously treated participants and required that participants had experienced at least one relapse in the preceding year, and so was close to our definition of at least 90% of participants having HARRMS. Overall, the available data suggested no evidence of a difference between natalizumab and its biosimilar in terms of annualized relapse rate (ARR), the proportion of participants with MRI-detected lesions or AEs. There were no data on disease progression for patients treated with natalizumab biosimilar, although natalizumab was associated with a greater reduction in CDP3 and CDP6 compared to placebo.

All trials of natalizumab evaluated natalizumab administered intravenously - there were no studies of natalizumab administered subcutaneously. We did not identify any studies that compared subcutaneous administration of natalizumab with another intervention of interest for this appraisal. We are aware of a small number of trials that have compared different modes of administration of natalizumab, but none met inclusion criteria for our review. DELIVER[176] compared the pharmacokinetics and pharmacodynamics of single subcutaneous or intramuscular 300 mg doses of natalizumab with IV 300 mg doses in patients with MS with a short follow-up duration of 24 weeks and REFINE[177] compared switching to different dosing regimens in stable patients with RRMS who were treated with natalizumab. This study did not meet inclusion criteria for our review as all participants were already receiving natalizumab. These two studies found that natalizumab administered as a 300 mg SC injection every 4 weeks was comparable to 300 mg IV infusion natalizumab every 4 weeks in terms of ARR and CDP3 at week 60 as well as for pharmacokinetics, pharmacodynamics, and safety outcomes.

We only identified 6 trials that provided data on people with HARRMS. Two studies (MIST, and CARE-MS II) were conducted exclusively in people with HARRMS, and four reported data for a subgroup of participants with HARRMS – this included two sets of related trials that provided pooled results for the highly active subgroup. We also included the Saida 2017 trial in our synthesis of data on people with HARRMS as it was close to fulfilling our criteria of a "highly active population". However, it should be noted that this study was restricted to Japanese patients and so results may not be generalisable to the UK population. Comparison of baseline characteristics between these populations suggested that those with highly active disease had fewer relapses as baseline, possibly as they had all been treated with DMTs in the previous year, and generally slightly worse EDSS scores. The only outcome with sufficient data to conduct an NMA for this population was ARR. To enable us to connect the network for this analysis we had to assume a class effect for interferon beta

1a (Interferon beta 1a IM30 and interferon beta 1a SC44). The findings from this analysis were very similar to the findings in the overall RRMS population. To allow direct comparison of findings between these two populations we conducted an NMA for the general RRMS population restricted to the interventions for which data were available in the HARRMS population (alemtuzumab, ocrelizumab, fingolimod, cladribine and natalizumab). Results were very similar across the two populations, although with wider credible intervals for the HARRMS population. This would be expected as there were less studies and less patients contributing to this analysis. Although we could not carry out an NMA for disease progression, we presented results for the highly active and general RRMS populations in a table to allow direct comparison between populations. This suggested that estimates were similar, with HRs generally slightly lower (i.e. suggesting a greater effect) in the highly active population, but again with wider confidence intervals. Data on adverse events and quality of life were only reported in the CARE-MS I study and so it was difficult to draw conclusions regarding the impact of DMT on these measures in the HARRMS population.

In addition to the data from RCTs in people with HARRMS, there is some evidence from non-randomised studies on the effectiveness of natalizumab in people with HARRMS; these studies were not included in our SLR and NMA as our inclusion criteria specified that only RCTs were eligible. A recent targeted literature review and meta-analysis of natalizumab for the treatment of highly active RRMS[178] included studies in adults (≥ 18 years) with a confirmed diagnosis of RRMS who had an unchanged or increased relapse rate compared with the previous year, failed to respond to a full and adequate course of disease modifying therapy (DMT), and had experienced at least one relapse in the previous year while on therapy. They included 16 non-randomised studies that compared natalizumab to interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate and fingolimod and 11 case series of people treated with natalizumab. Data in the HARRMS population are also available for the TOP study, the largest real world study of natalizumab, that evaluated the long-term safety and efficacy of natalizumab in 6321 patients (134 UK patients) with RRMS with a follow-up pf 15 years. [151] A post-hoc subgroup analysis in a subset of patients with HARRMS, defined as those who had received prior treatment with ≥1 DMT and had experienced 1 relapse reported similar findings to the findings in the general RRMS population of a reduction of over 90% compared to the year before starting natalizumab. These findings support natalizumab improving outcomes for patients with RRMS and HARRMS, but do not provide a comparison with other interventions.

Overall, the very limited data suggest that interventions evaluated in people with HARRMS are at least as effective in this population as they are in the general RRMS population, but this should be interpreted with some caution due to the very small number of studies for which data were available in patients with HARRMS.

8.1.2 Findings on cost-effectiveness

Our systematic review of existing cost-effectiveness evaluations found seven studies for inclusion. None of these answered our decision problem of evaluating the cost-effectiveness

of natalizumab and natalizumab biosimilar relative to standard of care in our target population of HARRMS after at least one disease modifying therapy. We therefore undertook an independent economic assessment.

To design the model we reviewed models used in previous relevant TAs. These were essentially the same Markov multistate model based on EDSS severity level with baseline transition rates informed by the British Columbia Multiple Sclerosis registry and London Ontario MS databases and treatment effects by individual trials and NMA. Primary criticisms of these models were that they did not capture treatment sequencing and that they were unable to accurately reflect the course of the condition. We aimed to overcome these limitations by using a DES microsimulation that allowed the modelling of treatment sequences, similar to a recent microsimulation for the Dutch RRMS guidelines. [138-141] Our model included attributes for age, sex, EDSS, SPMS status and current treatment. It modelled the events EDSS increase, EDSS decrease, progression to SPMS, relapse, SAEs, treatment discontinuation, and death. Patients could switch treatment twice, meaning that up to 4th line therapy was included in the model. It furthermore modelled patients who progressed to SPMS with events of EDSS increase, relapse, SAEs, and death.

Event rates were a combination of natural history informed by analyses conducted by the UK MS Registry and treatment effects of ARR and CDP6 informed by the NMA. The clinical review found no evidence on AHSCT so this was not included in the economic model. Baseline SAEs and discontinuation came from AFFIRM and ANTELOPE with treatment effects from the NMA. Event rates in the SPMS population were informed purely by the MS Registry analyses as no treatment effects were assumed. Our approach to costs and utilities were aligned with previous TAs. The economic model was implemented in the R programming language using the DESCEM package.[179] The code was validated by the DESCEM develop Javier Sanchez Alvarez at Evidera.

A validation against EDSS progression over time from an earlier Markov model found that the trend predicted by the economic model was for lower increase in severity.[126] However, the earlier model was in a mixture of RRMS and SPMS and did not include the latest DMT sequences, so would be expected to have a worse prognosis. Convergence tests found the model to give stable results with greater than 100 patients and 100 samples.

Compared with natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC, all treatments had greater net benefit at £20-30,000/QALY, with the exception of ocrelizumab. The natalizumabs also had close to 0% chance of having highest net benefit at £20,000/QALY and £30,000/QALY. Costs were generally higher on natalizumab than other treatments, though there was no difference in QALYs with 95% CrI completely overlapping. Natalizumab-IV has lower mean net benefit at £20-30,000/QALY than natalizumab biosimilar-IV, although the 95% CrI overlap. Natalizumab-SC has very similar mean net benefit to Natalizumab-IV. The natalizumab biosimilar-IV has lower costs but also lower QALYs than natalizumab-IV but the 95% CrI for both are overlapping suggesting no evidence

of a difference. Natalizumab-SC has very similar costs and QALYs to natalizumab-IV, again with no evidence of a difference.

We conducted sensitivity analyses testing robustness switching to All RRMS estimates from the MS Registry, switching to use of random effects NMA, using the HA RRMS NMA, excluding the price of JCV testing for branded natalizumab, reducing the natalizumab-SC treatment administration costs, and using mortality stratified by EDSS severity. The results and conclusions were unchanged under all sensitivities. Our estimates of the EVPPI in value of information analysis found that the parameters with greatest impact on the results were the NMA treatment effects on ARR, CDP6, SAEs, and discontinuation. However, many parameters, including costs, utilities, and MS registry rates, had substantial impact on the results indicating high parameter uncertainty.

8.2 Strengths and limitations of the assessment

8.2.1 Systematic review and NMA strengths and limitations

Our systematic review followed published guidance on the conduct of systematic reviews,[46, 47] and network meta-analysis[47] and is reported according to PRISMA-2020[48] and PRISMA guidance for NMA[49] making our review processes transparent and robust. The protocol was pre-registered on the PROSPERO database (PROSPERO 2024 CRD42024556838).[180] Changes to the protocol are clearly described in Section 4.4. Protocol changes were either to clarify issues that were ambiguous in the original protocol or to focus the review to make this manageable within the resources and time available. We clarified the inclusion criteria in relation to interventions, limiting inclusion so that only those evaluated at doses currently licensed in the UK were eligible for inclusion. This ensured that findings would be directly relevant to the UK population. Due to time and resource constraints, we focused on the following outcomes: relapse rates, proportion of participants with Gd+ and T2 weighted lesions on MRI scans, disability progression, adverse events and health-related quality of life measured using EQ-5D or SF-36. This means that we did not consider severity of relapses or symptoms of multiple sclerosis (such as fatigue , cognition, and visual disturbance) that had been specified as eligible in our protocol. These outcomes were reported inconsistently across included studies using a variety of different outcome measures and so it is unlikely that sufficient data would have been available in a consistent format to allow us to conduct an NMA for these outcome measures. Focusing on our two specific MRI measures (proportion of participants with Gd+ or new or enlarging T2 lesions) means that we were not able to considered other MRI measures such as brain lesion volume which has been proposed as a better marker of disease progression than clinical measures such as CDP6.[181]

We conducted extensive literature searches designed to maximise retrieval of relevant studies and did not apply any language, date or publication restrictions to these searches or to inclusion in the review. Four reports considered potentially relevant for inclusion and reviewed at the full text stage were reported in non-English language. We used Google Translate to assess these against our inclusion criteria and determined that none met our eligibility criteria. We pre-specified clearly defined, objective inclusion criteria. Although the

population of interest for our appraisal was those with HARRMS, we defined broad inclusion criteria so that studies in any RRMS population were eligible for inclusion. We also applied a broad definition for highly active disease to include any "unchanged or increased clinical or radiological evidence of disease activity despite treatment with at least one Disease Modifying Therapy (DMT)" – this broad definition ensured that any data in a population that could be considered to have highly active disease based on definitions used in trials would be eligible for inclusion. As no data were available for natalizumab for this population, we further broadened eligibility criteria to include the Saida 2017 study that had a high proportion of patients who had been previously treated and used this as a proxy for highly active disease. This allowed us to include natalizumab in our NMA for ARR for people with HARRMS. We screened TAs that had evaluated any of the interventions or comparators of interest for this appraisal to identify additional studies and data that were relevant to the review but were not reported in publications of the trials. This allowed us to include additional data than had we only included data available in publications or clinical trial registries. We clearly report all publications and TAs related to each included study in Appendix 2, and document whether data were extracted from each report. Some of the TAs included redacted information that appeared relevant to our review but could not be included as we did not have access to this information. Data that could not be accessed that may have been informative to our review were:

- TRANSFORMS (TA254): baseline data on relapses and EDSS scores and hazard ratios for HARRMS, and EQ-5D data for general population.[40]
- CAMMS 223 (TA312): redacted QoL data – unclear what measures were reported.[39]
- OPTIMUM (TA767) – some data in HARRMS but unclear exactly what outcomes reported as full table redacted.[42]
- ASCLEOPIOS I and II (TA699) – ARR, CDP3 and CDP6 for HARRMS.[41]

These data may have allowed us to include TRANSFORMS in the analysis for disease progression in the HARRMS population – this study was included for the ARR synthesis in people with HARRMS. OPTIMUM and ASCLEPIOS I & II did not report data for the HARRMS subgroup and so these data may have allowed us to include these studies for this population. However, both studies were only included to connect the network as teriflunomide was not listed as a comparator for this appraisal and so these data would only have been helpful if their inclusion created additional connected networks for the HARRMS population. In addition, the definition of HARRMS for the ASCLEPIOS studies differed from our definition as it included people previously treated with DMT who discontinued DMT due to lack of efficacy – relapses were not part of the definition. The data on QoL for TRANSFORMS and CAMMS 223 could have provided additional useful data on QoL that was rarely reported in studies included in our review.

We conducted a formal assessment of the risk of bias of included studies using the RoB 2 tool for RCTs,[55] the only tool for the assessment of risk of bias in RCTs recommended as a key tool by the LATITUDES Network.[182] Risk of bias was performed at the outcome level as recommended, the importance of following this approach was shown by the fact that for

some trials risk of bias judgements differed for the different outcomes. We incorporated the risk of bias into the synthesis for ARR, the only outcome for which sufficient data were available, by conducting a sensitivity analysis restricting the analysis to studies at low risk of bias. This produced very similar results to the overall analysis suggesting that risk of bias did not impact on findings for this outcome. For all outcomes, we included the risk of bias in results tables to allow readers to qualitatively judge whether risk of bias may have impacted on study findings.

We used a new software package, Nested Knowledge, to manage the different stages of the review process. We found that this improved the efficiency of the review process and management of the review, and facilitated creation of tables for analysis and inclusion in the report. This reduced the risk of errors when exporting and manipulating data.

We employed Bayesian Network Meta-Analyses (NMA) to compare the efficacy and safety of treatment options using trial data, enabling simultaneous evaluation of multiple interventions. NMA strengthens inferences by combining direct and indirect comparisons while maintaining randomisation, making it especially useful for reviews such as our when most treatments lack head-to-head RCT comparisons. This systematic review assessed key outcomes to evaluate disease-modifying therapies (DMTs) for multiple sclerosis (MS), offering a comprehensive comparison across various domains of safety and effectiveness. Unlike previous reviews, we included studies with follow-up durations under 12 months, expanding the scope of data analysed and integrating follow-up time into calculations to account for treatment exposure. Unlike prior pooling by timepoint, all timepoints were included in a single analysis allowing us to create a more comprehensive network, as evidence from previous reviews has suggested no significant variation in rates across timepoints. [183, 184] Additional analyses on confirmed disability progression (CDP) utilised both the CDP3 and CDP6 networks, facilitating broader comparisons between interventions. The inclusion of recently published studies ensured up-to-date data on several treatments, while analysing drugs and doses as individual nodes allowed for precise comparisons. Model selection (random- or fixed-effects) was determined based on heterogeneity and Deviance Information Criterion (DIC) values to ensure optimal fit for each analysis. Minimal heterogeneity was observed for key outcomes, including annualised relapse rate (ARR), CDP3, adverse events (AEs), and MRI outcomes, with fixed-effect models providing better data fits in these cases. The exception was CDP6 where the random effects-model provided a better fit to the data.

Our network meta-analysis (NMA) focused on interventions identified by NICE as being within the scope of this appraisal. This may have excluded some relevant treatments that are recommended for the general RRMS population but not for the HARRMS population, including dimethyl fumarate, diroximel fumarate and teriflunomide. Whilst we included studies that compared teriflunomide with interventions and comparators in scope for this appraisal, we did not expand our searches to identify studies that compared teriflunomide against other treatments such as placebo due to time and resource constraints. As

teriflunomide was not identified as a comparator for this appraisal as it is not recommended for people with HARRMS, we were not aiming to provide recommendations on its effectiveness. Results for teriflunomide should therefore be interpreted with caution.

Where we calculated hazard ratios (HRs) for confirmed disability progression (CDP3 and CDP6), proportion of participants with lesions on MRI scans, and adverse events, we assumed constant HRs over time. This may not be a valid assumption, but data were not available to allow other methods of estimation. Variability across studies in definitions, follow-up times, and baseline characteristics posed challenges, though clinicians confirmed these differences were reasonably comparable. The analysis of the HARRMS population was further constrained by inconsistent definitions and data gaps for several interventions, introducing potential heterogeneity. Finally, the limited number of studies for each individual intervention restricted sensitivity analyses, potentially impacting the robustness of certain conclusions.

Many reviews have evaluated the safety and/or efficacy of treatments for MS in the past 5 years.[183-194] We did not include existing reviews in our review, but we screened the included trials from recent reviews (published in past 3 years) against our review inclusion criteria to ensure that we had not missed any relevant studies. The only study included in an existing review that met our inclusion criteria but had not been included in our review was reported only in a conference abstract – we were unable to retrieve the full text of this study.[66] Most previous reviews focus only on one or two specific outcomes, for example ARR and CDP[192, 195] for adverse events,[193] or on specific interventions such as cladribine[191] or ocrelizumab.[183] The results of our review are consistent with those from other recent reviews that have included a broadly similar set of interventions, with very similar estimates of effect for ARR.[192, 195] The exception was for teriflunomide, with estimates from our review suggesting that this is less effective than found by other reviews. This may be because they differed in eligibility criteria for interventions, including all studies of teriflunomide including those compared to placebo. In contrast, we only included studies of teriflunomide to allow us to fully include ocrelizumab in our network. Teriflunomide itself was not specified as a comparator for our review. Previous reviews[183-194] have mostly focused on interventions for people with RRMS. We are only aware of one previous systematic review [196] in the HARRMS population. This review only included 2 studies comparing fingolimod and dimethyl fumarate with placebo. Our review is therefore the first to provide a comprehensive overall assessment of the effectiveness of our specified interventions and comparators in this population.

Limitations of the evidence base

The risk of bias (ROB) varied across studies and outcomes, with around half of studies judged at low ROB overall. No studies were classified as high ROB for the randomisation domain, although 14 studies were rated as having "some concerns" due to insufficient information on randomisation or allocation concealment but with no evidence of baseline imbalance. Five studies were at high ROB due to participants being aware of interventions

and evidence of differential withdrawal across treatment groups. Another five unblinded studies showed no deviations from intended interventions and were judged at "some concerns." High ROB was observed in several trials due to a high proportion of withdrawals potentially linked to the intervention as worse outcomes could be associated with a greater likelihood of withdrawing. Six studies were rated as high ROB for missing outcome data for relapse rates with an additional eight rated high ROB for missing MRI data. There was little suggestion of missing data for adverse events, which were reported for most participants in the included trials. Although most studies used an ITT or modified ITT analysis to include all randomised participants in the analysis, few detailed the methods used for estimating outcomes for participants without follow-up data. Two studies were rated high ROB for outcome measurement due to unblinded assessors, and 14 studies had "some concerns" for selective outcome reporting, as protocols were unavailable or outcomes were inconsistently reported. We conducted a separate ROB assessment for the trials that reported data in people with highly active disease. We did not consider this to change the risk of bias for the randomisation domain, as whether or not participants had highly active disease was determined at baseline and so could not be influenced by treatment. This means that we would expect randomisation to result in equivalent groups in this sub-population.

8.2.2 Economic model strengths and limitations

We developed a novel economic model for highly active RRMS that built on the evidence and assumptions of previous NICE TAs but extended to a flexible DES approach that enabled the modelling of treatment sequences. The baseline rates of EDSS increase, EDSS decrease, relapse, and progression to SPMS were informed by a new analyses of the UK MS Registry, aligning with our target UK highly active RRMS population. Treatment effects on disability progression, relapse, adverse events and discontinuation were estimated using the high quality NMA on randomised controlled trial evidence, although it was necessary to use the all RRMS population as few trials were identified for highly active RRMS. The DES modelled disease that has progressed to SPMS, capturing the disease course beyond RRMS. A large number of treatment comparators were included, representing possible standard of care in highly active RRMS. The model was fully probabilistic with parameter uncertainty propagated from the input evidence to the final results, and considered in interpretations. Validation against published data found differences in EDSS trend over time that could be explained by the comparator model mixing RRMS and SPMS patients and not including patients on the latest DMT sequences. Convergence tests found that results became stable with only a low number of patients and samples. Finally, value of information analysis was used instead of deterministic one-way sensitivity analysis. This considers the uncertainty in all parameters simultaneously, rather than varying parameters one at a time. Unlike deterministic sensitivity analysis, it measures a parameter as important if its uncertainty can change the decision (i.e., switch an incremental net benefit from positive to negative and vice versa) rather than only changing the net benefit or ICER themselves.

Despite the novelty and strength of evidence, the economic model also had substantial limitations. A key limitation is that treatment effects were informed by the NMA in all

RRMS, rather than being based on trials in highly active RRMS. Furthermore, there was no evidence identified on autologous haematopoietic stem cell transplantation so this was not included in the economic model.

Although we used new analyses of the MS Registry to inform baseline rates of events, these were based on small sample sizes which gave uncertainty estimates. The MS Registry found no patients with highly active RRMS who decreased in EDSS so analysis could not be conducted and EDSS decrease from the all RRMS population had to be used in all analyses. It was also not possible to use the multistate modelling approach due to unstable estimates of transition rates between low EDSS states.

Our model used constant SMRs rather than varying these with EDSS states. Previous appraisals (e.g., TA767) have modelled relative risk of death being applied to each EDSS health state, taken from Pokorski (1997) but these data are considerably out of date and no replacement was identified.[42] Despite it being possible using discrete event simulation, we did not consider capacity constraints, for example with limited availability of MRI machines. Treatment stopping rates were assumed constant over time, rather than being higher in the first year of treatment than in subsequent years, which was recommended by the EAG in TA616.[38] This flexibility is possible but the NMA on discontinuation due to AE did not have sufficient data to vary rates by year since treatment initiation. The validation was limited to EDSS change over time. No suitable data were identified for a deeper validation of relapse rates and EDSS distributions.

8.3 Uncertainties

The key uncertainty remaining is whether treatment effects vary between those with RRMS and those with HA disease. There were insufficient data in people with highly active disease to fully answer this question. There was also very limited data on natalizumab biosimilar and so there is also some uncertainty in whether this is equivalent in effectiveness to natalizumab, and on whether either of these interventions is effective in those with highly active disease. This uncertainty is also key to the cost-effectiveness conclusions as the model assumed that treatment effects would not vary between those with RRMS and those with HA disease.

There were differences across studies in how outcomes, particularly relapse rates and disease progression were defined. There were insufficient data to investigate whether these differences affected estimates of treatment effect. Previous research has suggested that different ways of measuring disability may affect estimates of treatment effect.[197] There was also inconsistency in how studies defined “highly active disease”. Future studies should also adopt a consistent definition.

Another key uncertainty is whether it is reasonable to assume that treatment effects remain stable over time. The economic model assumed that treatment effect were stable long-

term, despite this uncertainty. For our analysis, we combined data from studies with different durations of follow-up ranging from 6 to 24 months, although most studies reported outcomes at 24 months follow-up. We had intended to conduct a sensitivity analysis to investigate whether results were different when analysed at different time points, but there were insufficient studies that reported results at 6 and 12 months follow-up for this to be possible. Three studies (AFFIRM, IFNB study and PRISMS) reported data at both 12 and 24 months follow-up. These studies reported similar estimates of ARR at the different follow-up times suggesting no difference in effect, but it was unclear whether those with 6 months follow-up would have different findings. Five studies only reported short duration of follow-up of less than 12 months (range 4 to 9 months). It may not be reasonable to expect consistency over time in MRI outcomes – our clinicians advised us that they would be less concerned about new lesions that develop within the first 6 to 12 months of treatment but would be more concerned with lesions after longer treatment duration. AEs may also differ in effects and timing depending on the specific interventions. For example, for some drugs like alemtuzumab and cladribine effects may be expected to be front loaded whereas for others a more cumulative effect may be expected. These potential differential effects were not assessed in our review and so this remains an uncertainty of our findings.

The MS Registry analyses that were used to inform the economic model had low sample size for some events. Relapse rates in the highly active RRMS were based on only 50 patients while the rate of progression to SPMS was based on only 66 patients. Furthermore, it was not possible to estimate reliable multistate transition matrix so only exponential survival models could be used for EDSS increase and decrease events.

The results themselves are highly uncertain, in particular the total and incremental QALYs. The 95% CrI are completely overlapping for all treatments, meaning that differences in effectiveness cannot be established. These are themselves due to uncertainty in the clinical evidence from the MS Registry and NMA on trials in all RRMS. However, cost differences are large and 95% CrI more rarely overlap, which leads to the observed differences in net benefit. Value of information analysis ranked the parameters on their impact on decision uncertainty, from highest to lowest, as NMA treatment effects, MS Registry baseline rates, costs, utilities, rates of discontinuation, and rates of SAEs.

8.4 Patient and Public Involvement

We involved one patient representative with lived experience of MS in this project. They attended team meetings (one at the beginning of the project and one closer to the end of the project), gave feedback on the plain language summary report, and wrote the section below about the impact that these interventions may have on people with MS.

8.5 Impact on patients

Receiving a diagnosis of highly active relapsing-remitting multiple sclerosis (RRMS) can be a challenging and emotionally taxing experience. The nature of RRMS, with its unpredictable

relapses and potential for significant disability, often makes the journey to diagnosis complex and uncertain. While timely diagnosis is crucial, particularly for highly active cases, accuracy and careful tailoring of treatment plans are even more critical to ensure the best outcomes for patients. The period of waiting for a diagnosis or treatment can be overwhelming, highlighting the need for transparent communication and support throughout this process.

Advances in disease-modifying therapies (DMTs) have transformed the landscape of RRMS treatment, yet identifying the most effective and tolerable option for each individual remains a nuanced and sometimes lengthy process. Patients frequently report feeling underserved when it comes to monitoring treatment effectiveness or managing side effects. Improvements in these areas, supported by robust evidence and innovative tools, could significantly enhance care. Holistic, patient-centred approaches that prioritise early intervention, personalised treatment and psychosocial support are essential to improving quality of life for those living with RRMS.

8.6 Equality, Diversity and Inclusion

Our research was based on existing literature and so we had no control over the participants enrolled. We were broad in our inclusion criteria such that studies from any country and in any language of publication were eligible.

Our team included researchers with a broad range of experience and expertise. The lead authors are junior researchers within Bristol TAG, who were given the opportunity to lead on the writing of this report to help develop their research skills and portfolio. They were supported by the two senior authors, who provided advice and mentorship to the junior researchers leading on the reviews and health economic modelling. The team included those with expertise in systematic reviews, health economics, and medical statistics.

8.7 Implications for decision makers

There are insufficient data on natalizumab and natalizumab biosimilar in people with HARRMS. Limited evidence suggests that there is no difference in treatment effect between these interventions in people with RRMS. There is also a suggestion that other DMT have at least equivalent efficacy in people with highly active disease to that in people with RRMS. It may be reasonable to assume that this would also be the case for natalizumab and natalizumab biosimilar. The economic model made this assumption of equivalent efficacy in HARRMS as in the general RRMS and found that natalizumab and natalizumab biosimilar are unlikely to be cost-effective. These should therefore not be recommended for people with HARRMS.

8.8 Research recommendations

There is a clear need for more studies in people with highly active disease to determine optimum treatment recommendations. There is a lack of data on the efficacy of natalizumab

and natalizumab biosimilar, particularly in people with highly active disease. This was a key uncertainty in the economic model, as indicated by the value of information analysis. Further studies are needed of these interventions in people with highly active disease. Future studies should include at least 24 months follow-up to determine whether effects are sustained over a reasonable time frame. This is particularly important for assessment of disease progression, especially over longer periods of time such as CDP6. There is also a need for accepted definitions of HARRMS, relapses, and disease progression with MS. Future studies should use the same definitions to allow comparison across studies. Understanding of disease progression in HARRMS is also limited, as indicated by value of information analysis and low sample size in the MS Registry analyses. Further studies should additionally record utilities by EDSS severity and the disutilities associated of relapse and adverse events.

9 CONCLUSIONS

There were no data on the effectiveness of natalizumab or natalizumab biosimilar in patients with highly active disease. Limited data suggest that natalizumab and natalizumab biosimilar have similar effectiveness for people with RRMS population. Comparison of data on the effectiveness of DMT in people with highly active disease and those with RRMS suggest that DMTs evaluated are at least as effective in this population. However, this is based on very limited data. Assuming that natalizumab and natalizumab biosimilar follow this same pattern, it may be reasonable to assume that these interventions would also be effective in those with highly active disease. However, trials in this specific population are needed to confirm whether this is the case.

Based on the findings from the clinical review, the economic model made the assumption that treatment effects in the general RRMS population would apply to the HARRMS population and used these data and baseline rates from the MS Registry in highly active RRMS. All treatment had greater net benefit at £20-30,000/QALY than natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC, with the exception of ocrelizumab which had lower net benefits. The natalizumabs also had very low probability of having highest net benefit at £20,000/QALY and £30,000/QALY. There were no differences in costs, QALYs, or net benefit between the natalizumabs, with the 95% CrI overlapping. Analyses were robust to sensitivities and the greatest decision uncertainty was found in the treatment effects as estimated by the NMA. These findings suggests that natalizumab and natalizumab biosimilar are not cost-effective compared to standard of care in highly active RRMS but that further research is needed on the treatment effects.

10 Additional Information

10.1 Declaration of competing interests

Dr Claire Rice declares the following interests:

- Regular prescriber of Multiple Sclerosis (MS) disease modifying therapies in National Health Service (NHS) MS clinics.
- Work with the MS Society as an expert panel reviewer on grant applications.
- Research grant funded by Sanofi looking at blood biomarkers of people with MS.
- Routinely involved in clinical trials other clinical studies of people on disease modifying therapies for MS including natalizumab but these are investigator-led and are not commercial studies.

Dr Emma Tallantyre declares the following interests:

- Honorarium from Roche / Novartis for consulting work in the last 12m.
- Expenses for attending educational meetings from Merck.
- Biogen honorarium for speaker fees but not in the last 24m.

Howard Thom owns shares in Clifton Insight which has received consulting fees from Amicus, Argenx, Baxter, Bayer, Daiichi-Sankyo, Eisai, Janssen, Lundbeck, Merck, Novartis, Novo Nordisk, Pfizer, and Roche.

10.2 Contributions of authors

Catalina Lopez Manzano- Conceptualisation; data extraction and risk of bias assessment; network meta-analysis; project administration; writing – original draft; writing – reviewing and editing
Ayman Sadek- Conceptualisation; health economic modelling; project administration; visualisation; writing – original draft; writing – reviewing and editing
Chris Cooper – Literature searches and health economics review; writing – original draft
Eve Tomlinson – Data extraction; writing – reviewing and editing
Hanyu Wang – Data extraction; writing – reviewing and editing
Claire Rice - Writing – reviewing and editing; other – clinical advice
Emma Tallantyre - Writing – reviewing and editing; other – clinical advice
Ananya Rao-Middleton - Writing – reviewing and editing; other – PPI contributions
Penny Whiting – Conceptualisation; formal analysis; funding acquisition; methodology; investigation; project administration; supervision of systematic review; visualisation; writing – original draft; writing – reviewing and editing
Howard Thom - Conceptualisation; formal analysis; funding acquisition; methodology; investigation; project administration; supervision of network meta-analysis and economic modelling; visualisation; writing – original draft; writing – reviewing and editing

10.3 Acknowledgements

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application on the RoB 2 tool. We would also like to thank Nicola Horler, Bristol TAG, for providing administrative support.

10.4 Data-sharing statement

All data extracted for the systematic review and the results of the risk of bias assessments are provided in full in the appendices to this report. The economic model can be obtained from the corresponding author and will be shared upon reasonable request for academic collaboration.

10.5 Ethics Statement

The MS Registry analyses worked with primary data. This was approved by the 21/SW/0085 Southwest central Bristol ethics committee. The remainder of the research included in this report is secondary research and as such did not require ethical approval.

10.6 Information Governance Statement

There were no personal data involved in the production of this report.

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Appendix 1
Literature search strategies
Clinical effectiveness searches

Database: Ovid (MEDALL)
Host: Ovid
Data parameters: 1946 to April 130, 2024
Date of search: 1 May 2024

#	Search terms	Results
1	Multiple Sclerosis, Relapsing-Remitting/ or ((("multiple sclerosis*" or MS) and (relap* or remit*)) or RRMS).ti,ab,kf,kw.	22740
2	Natalizumab/ or (natalizumab* or antegren* or tyruko* or tysabri* or "AN-100226*" or "AN 100226*" or AN100226* or "bg-0002" or "bg 0002" or bg0002 or "dst-356a1" or "dst 356a1" or dst356a1 or "pb-006" or "pb 006" or pb006 or "pbp-2002" or "pbp 2002" or pbp2002 or L04AA23 or 3JB47N2Q2P or "189261−10−7").ti,ab,kf,kw.	3358
3	(glatiramer* or copaxobene* or copaxone* or copemyl* or copolymer* or glatect* or galtipex* or glataxon* or glatimyl* or glatopa* or glaxaton* or marcyto* or myeloxen* or perscleran* or remurel* or sclerthon* or "tv 5010" or "tv-5010" or tv5010 or "COP 1" or "COP-1" or COP1 or "Copolymer-1" or (tv adj "5010") or u782c039qp or L03AX13 or U782C039QP or "28704-27-0" or "147245−92−9").ti,ab,kf,kw.	52890
4	*INTERFERON-BETA/ or ((INTERFERON adj2 (BETA* or fibroblast)) or avonex* or extavia* or feron* or fiblaferon* or fibrolast* or frone* or hemeferon* or naferon* or "bm 532" or "bm-532" or bm532 or "SNG 001" or "SNG-001" or SNG001 or "mr 21" or "mr-21" or mr21 or V9GU1EM8SF or "74899-71-1").ti,ab,kf,kf.	15774
5	ALEMTUZUMAB/ or (alemtuzumab* or campath* or lemtrada* or mabcambath* or mabkampat* or remniq* or "bxt 1523" or "bxt-1523" or bxt1523 or "gz 402673" or "gz-402673" or gz402673 or "ldp 03" or "ldp 103" or "ldp-103" or ldp103 or L04AA34 or 3A189DH42V or "216503-57-0").ti,ab,kf,kw.	4050
6	cladribine/ or (cladribine* or biodribin* or intocel* or leustat* or leustatin* or litak* or mavenclad* or movectro* or mylinax* or "RWJ 26251" or "RWJ-26251" or RWJ26251 or L04AA40 or 47M74X9YT5 or "4291-63-8").ti,ab,kf,kw.	2634
7	Fingolimod Hydrochloride/ or (fingolimod* or bonaxon* or chantico* or efigalo* or fenoxa* or fimodigo* or fingod* or "fty 720" or "fty-720" or fty720 or gilenia* or gilenya* or golpimec* or imusera* or inzolfi* or lognif* or "ro 7079904" or "ro-7079904" or ro7079904 or tascenso* or "tdi 132" or "tdi-132" or tdi132 or L04AA27 or 3QN8BYN5QF or "162359-55-9").ti,ab,kf,kw.	4682
8	(ocrelizumab* or ocrevus* or rhumba* or "PR 070769" or "PR-070769" or PR070769 or "R 1594" or "R-1594" or R1594 or "RG 1594" or "RG-1594" or RG1594 or "RO 4964913" or "RO-4964913" or RO4964913 or L04AA36 or A10SJL62JY or "637334-45-3").ti,ab,kf,kw.	980
9	(ofatumumab* or arzerra* or kesimpta* or "HuMax CD20" or "HuMax-CD20" or HuMaxCD20 or "humac CD20" or "humac-CD20" or humacCD20 or "GSK 1841157" or "GSK-1841157" or GSK1841157 or "HSDB 8170" or "HSDB-8170" or HSDB8170 or "OMB 157" or "OMB-157" or OMB157 or L01FA02 or M95KG522R0 or "679818-59-8").ti,ab,kf,kw.	777

#	Search terms	Results
10	(ponesimod* or ponvory* or "ACT 128800" or "ACT-128800" or ACT128800 or "r 3477" or "r-3477" or r3477 or "rg 3477" or "rg-3477" or rg3477 or L04AA50 or 5G7AKV2MKP or "854107-55-4").ti,ab,kf,kw.	122
11	HEMATOPOIETIC STEM CELL TRANSPLANTATION/ or ((haematopoietic and stem and cell and transplant*) or (haematopoietic and stem and cell and therap*) or (hematopoietic and stem and cell and transplant*) or (hematopoietic and stem and cell and therap*) or (HSC adj1 (therap* or transplant*))).ti,ab,kf,kw.	79877
12	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	159934
13	randomized controlled trial.pt.	612247
14	controlled clinical trial.pt.	95537
15	random*.ti,ab,kf,kw.	1517590
16	placebo.ab.	247945
17	("Phase 3*" or "phase3*" or "phase III*" or P3* or "PIII*" or "Phase 2*" or "phase2*" or "phase II*" or P2* or "PII*").ti,ab,kw,kf.	407300
18	(trial or trail).ti,ab,kw,kf.	835874
19	13 or 14 or 15 or 16 or 17 or 18	2430396
20	1 and 12 and 19	2022

Database: Embase
Host: Ovid
Data parameters: 1974 to 2024 April 30
Date of search: 1 May 2024

#	Search terms	Results
1	*relapsing remitting multiple sclerosis/ or ((("multiple sclerosis*" or MS) and (relap* or remit*)) or RRMS).ti,ab,kf,kw.	45210
2	natalizumab/ or (natalizumab* or antegren* or tyruko* or tysabri* or "AN-100226*" or "AN 100226*" or AN100226* or "bg-0002" or "bg 0002" or bg0002 or "dst-356a1" or "dst 356a1" or dst356a1 or "pb-006" or "pb 006" or pb006 or "pbp-2002" or "pbp 2002" or pbp2002 or L04AA23 or 3JB47N2Q2P or "189261−10−7").ti,ab,kf,kw.	14696
3	*glatiramer/ or (glatiramer* or copaxobene* or copaxone* or copemyl* or copolymer* or glatect* or galtipex* or glataxon* or glatimyl* or glatopa* or glaxaton* or marcyto* or myeloxen* or perscleran* or remurel* or sclerthon* or "tv 5010" or "tv-5010" or tv5010 or "COP 1" or "COP-1" or COP1 or "Copolymer-1" or (tv adj "5010") or u782c039qp or L03AX13 or U782C039QP or "28704-27-0" or "147245−92−9").ti,ab,kf,kw.	55546
4	*beta interferon/ or ((INTERFERON adj2 (BETA* or fibroblast)) or avonex* or extavia* or feron* or fiblaferon* or fibrolast* or frone* or hemeferon* or naferon* or "bm 532" or "bm-532" or bm532 or "SNG 001" or "SNG-001" or SNG001 or "mr 21" or "mr-21" or mr21 or V9GU1EM8SF or "74899-71-1").ti,ab,kf,kf.	23719
5	*alemtuzumab/ or (alemtuzumab* or campath* or lemtrada* or mabcambath* or mabkampat* or remniq* or "bxt 1523" or "bxt-1523" or bxt1523 or "gz 402673" or "gz-402673" or gz402673 or "ldp 03" or "ldp 103" or "ldp-103" or ldp103 or L04AA34 or 3A189DH42V or "216503-57-0").ti,ab,kf,kw.	9493
6	*cladribine/ or (cladribine* or biodribin* or intocel* or leustat* or leustatin* or litak* or mavenclad* or movectro* or mylinax* or "RWJ 26251" or "RWJ-26251" or RWJ26251 or L04AA40 or 47M74X9YT5 or "4291-63-8").ti,ab,kf,kw.	4644

#	Search terms	Results
7	*fingolimod/ or (fingolimod* or bonaxon* or chantico* or efigalo* or fenoxa* or fimodigo* or fingod* or "fty 720" or "fty-720" or fty720 or gilenia* or gilenya* or golpimec* or imusera* or inzolfi* or lognif* or "ro 7079904" or "ro-7079904" or ro7079904 or tascenso* or "tdi 132" or "tdi-132" or tdi132 or L04AA27 or 3QN8BYN5QF or "162359-55-9").ti,ab,kf,kw	9012
8	*ocrelizumab/ or (ocrelizumab* or ocrevus* or rhumba* or "PR 070769" or "PR-070769" or PR070769 or "R 1594" or "R-1594" or R1594 or "RG 1594" or "RG-1594" or RG1594 or "RO 4964913" or "RO-4964913" or RO4964913 or L04AA36 or A10SJL62JY or "637334-45-3").ti,ab,kf,kw.	2587
9	*ofatumumab/ or (ofatumumab* or arzerra* or kesimpta* or "HuMax CD20" or "HuMax-CD20" or HuMaxCD20 or "humac CD20" or "humac-CD20" or humacCD20 or "GSK 1841157" or "GSK-1841157" or GSK1841157 or "HSDB 8170" or "HSDB-8170" or HSDB8170 or "OMB 157" or "OMB-157" or OMB157 or L01FA02 or M95KG522R0 or "679818-59-8").ti,ab,kf,kw.	1932
10	*ponesimod/ or (ponesimod* or ponvory* or "ACT 128800" or "ACT-128800" or ACT128800 or "r 3477" or "r-3477" or r3477 or "rg 3477" or "rg-3477" or rg3477 or L04AA50 or 5G7AKV2MKP or "854107-55-4").ti,ab,kf,kw.	257
11	*autologous hematopoietic stem cell transplantation/ or ((haematopoietic and stem and cell and transplant*) or (haematopoietic and stem and cell and therap*) or (hematopoietic and stem and cell and transplant*) or (hematopoietic and stem and cell and therap*) or (HSC adj1 (therap* or transplant*))).ti,ab,kf,kw.	983369
12	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	206490
13	randomized controlled trial/	818976
14	controlled clinical trial/	473299
15	random*.ti,ab,kf,kw.	2068701
16	placebo.ab.	366592
17	("Phase 3*" or "phase3*" or "phase III*" or P3* or "PIII*" or "Phase 2*" or "phase2*" or "phase II*" or P2* or "PII*").ti,ab,kw,kf.	638979
18	(trial or trail).ti,ab,kw,kf.	1218800
19	13 or 14 or 15 or 16 or 17 or 18	5332
20	1 and 12 and 19	2194

Clinical Trials.gov
Date of search: 8 May 2024
URL: https://classic.clinicaltrials.gov/ct2/results/refine?show_xprt=Y
Searcher location: London, UK

344 Studies found for: (Relapsing AND Remitting AND multiple sclerosis OR RRMS) AND ((natalizumab OR Tysabri OR antegren OR tyruko) OR (glatiramer OR copaxone OR brabio OR glatopa OR copolymer) OR (INTERFERON-BETA OR IFN-beta) OR (alemtuzumab OR campath OR lemtrada) OR (cladribine OR leustatin OR mavenclad) OR (fingolimod OR gilenya) OR (ocrelizumab OR ocrevus) AND OR AND (ofatumumab ORarzerra OR kesimpta OR HuMax-CD20) OR (ponesimod OR ponvory) OR autologous AND haematopoietic AND stem AND cell AND transplantation)

WHO ICTRP
Date of search: 8 May 2024
URL: https://trialsearch.who.int/Default.aspx
Searcher location: London, UK

(((Relapsing AND Remitting AND multiple sclerosis) OR (RRMS)) AND ((natalizumab OR Tysabri OR antegren OR tyruko) OR (glatiramer OR copaxone OR brabio OR glatopa OR copolymer) OR (INTERFERON-BETA OR IFN-beta) OR (alemtuzumab OR campath OR lemtrada) OR (cladribine OR leustatin OR mavenclad) OR (fingolimod OR gilenya) OR (ocrelizumab OR ocrevus) OR (ofatumumab ORarzerra OR kesimpta OR HuMax-CD20) OR (ponesimod OR ponvory) OR (autologous AND haematopoietic AND stem AND cell AND transplantation)))

Cost effectiveness and economics searches

Database: Ovid (MEDALL)
Host: Ovid
Data parameters: 1946 to May 14, 2024
Date of search: 15 May 2024

#	Search terms	Results
1	Multiple Sclerosis, Relapsing-Remitting/ or *Multiple Sclerosis, Chronic Progressive/ or (RRMS or RMS or SPMS or (("multiple sclerosis*" or MS) adj5 (relap* or remit* or secondary or progres*))).ti,ab,kf,kw.	44865
2	exp "Costs and Cost Analysis"/	270448
3	exp Economics, Hospital/ or Financial management, hospital/	33116
4	Economics, Medical/	9280
5	economics, nursing/	4013
6	economics, pharmaceutical/	3134
7	(economic* or cost or costs or costly or costing or expense or expenses or financial or price or prices or pricing or pharmacoeconomic* or "pharmaco-economic*" or CEA or CUA or CBA or CMA).ti,ab,kf,kw.	1293465
8	exp "fees and charges"/	31446
9	exp budgets/	14209
10	(resource*1 and (allocation or utili* or usage or use*1)).ti,ab,kf,kw.	289137
11	(expenditure* not energy).ti,ab,kw.	38946
12	(value adj1 (money or monetary)).ti,ab,kw.	922
13	(budget* or fiscal or funding or financial or finance*).ti,ab,kw.	252168
14	("decision tree" or Markov or "semi Markov" or "partitioned adj2 survival" or "discrete event" or "conceptual* adj2 model*" or (decision adj2 model*) or "outcome model*" or "causal model*" or (simulat* adj2 model*) or "monte carlo" or "decision tree" or QALY*).ti,ab,kf.	170283
15	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	1864162
16	1 and 15	2164
17	(2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021* or 2022* or 2023* or 2024*).dt,dp,ed,ep,yr.	14514910
18	16 and 17	1492

Database: Embase
Host: Ovid
Data parameters: 1974 to 2024 May 14
Date of search: 15 May 2024

#	Search terms	Results
1	*relapsing remitting multiple sclerosis/ or *progressive multiple sclerosis/ or (RRMS or RMS or SPMS or (("multiple sclerosis*" or MS) adj5 (relap* or remit* or secondary or progres*))).ti,ab,kf,kw.	68614
2	health-economics/	36483
3	exp economic-evaluation/	367967
4	exp health-care-cost/	352578
5	exp pharmacoeconomics/	241926
6	economics, pharmaceutical/	3134
7	(economic* or cost or costs or costly or costing or expense or expenses or financial or price or prices or pricing or pharmacoeconomic* or "pharmaco-economic*" or CEA or CUA or CBA or CMA).ti,ab,kf,kw.	1658860
8	(resource*1 and (allocation or utili* or usage or use*1)).ti,ab,kf,kw.	380346
9	(expenditure* not energy).ti,ab,kw.	52598
10	(value adj1 (money or monetary)).ti,ab,kw.	3114
11	(budget* or fiscal or funding or financial or finance*).ti,ab,kw.	372153
12	("decision tree" or Markov or "semi Markov" or "partitioned adj2 survival" or "discrete event" or "conceptual* adj2 model*" or (decision adj2 model*) or "outcome model*" or "causal model*" or (simulat* adj2 model*) or "monte carlo" or "decision tree" or QALY*).ti,ab,kf.	206543
13	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	2592681
14	(2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021* or 2022* or 2023* or 2024*).yr.	17479900
15	1 and 12 and 13	2907
16	limit 14 to embase	1229

Database: Econlit
Host: EBSCOhost
Data parameters: 1981-current
Date of search: 15 May 2024

#	Search terms	Results
1	AB (("RRMS" or "SPMS" or (("multiple sclerosis*" or MS) N5 (relap* or remit* or secondary or progres*)))) OR TI (("RRMS" or "SPMS" or (("multiple sclerosis*" or MS) N5 (relap* or remit* or secondary or progres*))))	17

Database: NHS EED (via CRD Databases)
Host: https://www.crd.york.ac.uk/CRDWeb/HomePage.asp
Data parameters: unreported
Date of search: 15 May 2024

#	Search terms	Results
1	AB (("RRMS" or "SPMS" or (("multiple sclerosis*" or MS) AND (relap* or remit* or secondary or progres*)))) OR TI (("RRMS" or "SPMS" or (("multiple sclerosis*" or MS) N5 (relap* or remit* or secondary or progres*))))	6

Appendix 2
Tables of ongoing, or excluded studies

On-going studies

Table 38 On-going studies that appear to meet inclusion criteria

Citation	Interventions of interest for this appraisal
Brittain G, Petrie J, Duffy K, et al. Efficacy and safety of autologous haematopoietic stem cell transplantation versus alemtuzumab, ocrelizumab, ofatumumab or cladribine in relapsing remitting multiple sclerosis (StarMS): protocol for a randomised controlled trial. BMJ open. 2024;14(2):e083582. doi:10.1136/bmjopen-2023-083582.	Autologous haematopoietic stem cell transplantation versus alemtuzumab, ocrelizumab, ofatumumab or cladribine
NCT03477500. *Randomized Autologous Hematopoetic Stem Cell Transplantation Versus Alemtuzumab, Cladribine or Ocrelizumab for RRMS (RAM-MS)*. URL: https://classic.clinicaltrials.gov/show/NCT03477500 (Accessed 8 May 2024).	
NCT05906992. *A Study to Compare Efficacy, Pharmacokinetics, Pharmacodynamics and Safety of CT-P53 and Ocrevus in Patients With Relapsing-remitting Multiple Sclerosis*.2023. URL: https://clinicaltrials.gov/show/NCT05906992 (Accessed 8 May 2024).	Ocrelizumab
NCT04047628. *Best Available Therapy Versus Autologous Hematopoetic Stem Cell Transplant for Multiple Sclerosis (BEAT-MS)*. URL: https://classic.clinicaltrials.gov/show/NCT04047628 (Accessed 8 May 2024).	Autologous Hematopoetic Stem Cell Transplantation
NCT04788615. *Open Label Randomized Multicenter to Assess Efficacy & Tolerability of Ofatumumab 20mg vs. First Line DMT in RMS*. URL: https://classic.clinicaltrials.gov/show/NCT04788615 (Accessed 8 May 2024).	Ofatumumab
NCT00176592. *Phase IV Study, Betaseron Versus Copaxone for Relapsing Remitting or CIS Forms of MS Using Triple Dose Gad 3 T MRI*. URL: https://classic.clinicaltrials.gov/show/NCT00176592 (Accessed 8 May 2024).	interferon beta-1b and glatiramer acetate
NCT01058005. *Study Evaluating Rebif, Copaxone, and Tysabri for Active Multiple Sclerosis*. URL: https://classic.clinicaltrials.gov/show/NCT01058005 (Accessed 8 May 2024).	interferon beta-1a and glatiramer acetate and Natilziumab
2019-001549-42. *Stem cell transplantation versus disease modifying therapy (alemtuzumab or ocrelizumab) for patients with highly active relapsing remitting MS*.2020. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2019-001549-42 (Accessed 8 May 2024).	Stem cell transplantation versus disease modifying therapy (alemtuzumab or ocrelizumab)
2010-023560-40. *Blood stem cell transplantation for patients with relapsing-remitting multiple sclerosis, in whom standard treatment has failed*.2010. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-023560-40 (Accessed 8 May 2024).	Stem cell transplantation versus disease modifying therapy (alemtuzumab or ocrelizumab)

Studies included in manufacturers' submissions

Below we tabulate decisions made and reasons for exclusion, where applicable, for studies reported in submissions from manfuacturers.

Table 39 Studies included in submission from BIOGEN

Study Name	Reference	Decision
AFFIRM	Polman CH, O'Connor PW, Havrdova E, *et al.* A Randomized, Placebo-Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis. *N Engl J Med*. 2006;354(9):899–910. https://doi.org/10.1056/NEJMoa044397.	Included
	Hutchinson M, Kappos L, Calabresi PA, *et al.* The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL. *J Neurol*. 2009;256(3):405–415. https://doi.org/10.1007/s00415-009-0093-1.	Included
DELIVER	Plavina T, Fox EJ, Lucas N, Muralidharan KK, Mikol D. A Randomized Trial Evaluating Various Administration Routes of Natalizumab in Multiple Sclerosis. *J Clin Pharmacol*. 2016;56(10):1254–1262. https://doi.org/10.1002/jcph.707.	Excluded - Comparison of different administration routes
NOVA	Foley JF, Defer G, Ryerson LZ, *et al.* Comparison of switching to 6-week dosing of natalizumab versus continuing with 4-week dosing in patients with relapsing-remitting multiple sclerosis (NOVA): a randomised, controlled, open-label, phase 3b trial. *Lancet Neurol*. 2022;21(7):608–619. https://doi.org/10.1016/S1474-4422(22)00143-0.	Excluded - Comparison of different dosing schedules
REFINE	Trojano M, Ramió-Torrentà L, Grimaldi LM, *et al.* A randomized study of natalizumab dosing regimens for relapsing-remitting multiple sclerosis. *Mult Scler Houndmills Basingstoke Engl*. 2021;27(14):2240–2253.	Excluded - Comparison of different doses
TOP	Trojano M, Wiendl H, Kappos L, *et al.* TYSABRI Observational Program: Long-term Safety and Effectiveness in Relapsing-Remitting Multiple Sclerosis over 15 Years. EPO-658. Presented at European Academy of Neurology 9th Congress, 1-4 July. 2023.	Excluded - Observational Study
	Nicholas R, Harrower T, Sun Z, Davies H. Long-term Effectiveness of Natalizumab for RRMS: UK and Global 2022 Results from TYSABRI Observational Program. P184. Presented at Association of British Neurologists. 9-12 May. 2023.	

Table 40 Studies included in submission from Sandoz

Study name	Study Details	Decision
AFFIRM	Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006;354:899-910.	Included
ANTELOPE	Hemmer B, Wiendl H, Roth K, et al. Efficacy and Safety of Proposed Biosimilar Natalizumab (PB006) in Patients With Relapsing-Remitting Multiple Sclerosis: The Antelope Phase 3 Randomized Clinical Trial. JAMA Neurol 2023;80:298-307.	Included
DELIVER	Plavina T, Fox EJ, Lucas N, et al. A Randomized Trial Evaluating Various Administration Routes of Natalizumab in Multiple Sclerosis. J Clin Pharmacol 2016;56:1254-62.	Excluded – not informative to the network: compares different protocols [Report excluded in Nested but no reason was given]
NEXT-MS	Toorop AA, van Kempen ZLE, Steenhuis M, et al. Decrease of natalizumab drug levels after switching from intravenous to subcutaneous administration in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry 2023;94:482-486.	Excluded – not an RCT
REFINE	Trojano M, Ramió-Torrentà L, Grimaldi LM, et al. A randomized study of natalizumab dosing regimens for relapsing-remitting multiple sclerosis. Mult Scler 2021;27:2240-2253.	Excluded - Comparison of different doses
	ClinicalTrials.gov. Exploratory Study of the Safety, Tolerability and Efficacy of Multiple Regimens of Natalizumab in Adult Participants With Relapsing Multiple Sclerosis (MS) (REFINE). Available from: https://classic.clinicaltrials.gov/ct2/show/NCT01405820. [Last Accessed: 13th February 2024].	
TOP	Butzkueven H, Kappos L, Wiendl H, et al. Long-term safety and effectiveness of natalizumab treatment in clinical practice: 10 years of real-world data from the Tysabri Observational Program (TOP). Journal of Neurology, Neurosurgery & Psychiatry 2020;91:660-668.	Excluded - Observational Study
	Butzkueven H, Kappos L, Spelman T, et al. No evidence for loss of natalizumab effectiveness with every-6-week dosing: a propensity score-matched comparison with every-4-week dosing in patients enrolled in the Tysabri Observational Program (TOP). Ther Adv Neurol Disord 2021;14:17562864211042458.	
NR	Samjoo IA, Drudge C, Walsh S, et al. Comparative efficacy of therapies for relapsing multiple sclerosis: a systematic review and network meta-analysis. J Comp Eff Res 2023;12:e230016.	Excluded – Review (references screened)
NR	Filippi M, Danesi R, Derfuss T, et al. Early and unrestricted access to high-efficacy disease-modifying therapies: a consensus to optimize benefits for people living with multiple sclerosis. J Neurol 2022;269:1670-1677.	Excluded – Commentary
NR	Pfeuffer S, Ruck T, Pul R, et al. Impact of previous disease-modifying treatment on effectiveness and safety outcomes, among patients with multiple sclerosis treated with alemtuzumab. J Neurol Neurosurg Psychiatry 2021;92:1007-1013.	Excluded - Observational Study

Study name	Study Details	Decision
NR	Killestein J, van Oosten B. Emerging safety issues in alemtuzumab-treated MS patients. Multiple Sclerosis Journal 2019;25:1206-1208.	Excluded - Editorial
NR	ClinicalTrials.gov. Safety Study of Natalizumab to Treat Multiple Sclerosis (MS). Available from: https://classic.clinicaltrials.gov/ct2/show/NCT00559702. [Last Accessed: 13th February 2024].	Excluded – Not informative to the network – compares different protocols
NR	ClinicalTrials.gov. A Study to Evaluate Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of Natalizumab (BG00002) Administered Subcutaneously to Japanese Participants With Relapsing-Remitting Multiple Sclerosis. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05265728. [Last Accessed: 12th February 2024].	Excluded – Not an RCT
NR	ClinicalTrials.gov. A Study to Investigate the Radiological Onset of Action After Treatment Initiation With Subcutaneous (SC) Natalizumab in Participants With Relapsing-Remitting Multiple Sclerosis (RRMS). Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05532163. [Last Accessed: 12th Februrary 2024].	Excluded – Not an RCT (& terminated)
NR	Gelissen LMY, Loveless S, Toorop AA, et al. Subcutaneous administration of natalizumab can lead to lower drug concentrations compared to intravenous administration. Mult Scler Relat Disord 2024;90:105796.	Excluded – Not an RCT
NR	Pelle J, Briant AR, Branger P, et al. Real-World Effectiveness of Natalizumab Extended Interval Dosing in a French Cohort. Neurol Ther 2023;12:529-542.	Excluded – Observational study
NR	Perncezky J, Sellner J. Natalizumab extended-interval dosing in multiple sclerosis to mitigate progressive multifocal leukoencephalopathy risk: initial study evidence and real-world experience. J Cent Nerv Syst Dis 2022;14:11795735221135485.	Excluded – Review
NR	Achtnichts L, Zecca C, Findling O, et al. Correlation of disability with quality of life in patients with multiple sclerosis treated with natalizumab: primary results and post hoc analysis of the TYSabri ImPROvement study (PROTYS). BMJ Neurol Open. 2023;5(1):e000304.	Excluded – Observational study

Studies excluded at full-text screening

Table 41 Reports excluded at full-text screening

Citation	Reason for exclusion
Abbasi Kasbi N, Ghadiri F, Sahraian M, et al. Comparing infusion-related reactions of the first full dose (600 mg) biosimilar ocrelizumab administration with the standard divided protocol in multiple sclerosis patients: a randomized controlled trial study. Acta neurologica Belgica. 2024;124(1):205-212. doi:10.1007/s13760-023-02366-z.	MS but not >90% RRMS
Abdar M, Ebrahimifar P, Etemadifar M. The outbreak fingolimod cardiovascular side effects in relapsing-remitting multiple sclerosis patient: A longitudinal study in an Iranian population. ARYA atherosclerosis. 2016;12(6):274-280.	Does not report on one of the outcomes of interest
Abdelgaied M, Rashad M, El-Tayebi H, Solayman M. Correction to: The impact of metformin use on the outcomes of relapse-remitting multiple sclerosis patients receiving interferon beta 1a: an exploratory prospective phase II open-label randomized controlled trial. Journal of neurology. 2024;271(5):2925. doi:10.1007/s00415-024-12249-9.	Not informative to the network - non DMT add on
Abdelgaied M, Rashad M, El-Tayebi H, Solayman M. The impact of metformin use on the outcomes of relapse-remitting multiple sclerosis patients receiving interferon beta 1a: an exploratory prospective phase II open-label randomized controlled trial. Journal of neurology. 2024;271(3):1124-1132. doi:10.1007/s00415-023-12113-2.	Not informative to the network - non DMT add on
Abramowicz M. Glatiramer acetate for relapsing multiple sclerosis. Medical Letter on Drugs and Therapeutics. 1997;39(1004):61-64.	Not a primary study
Irct2013020812398N. *The Effectiveness, Safety and Tolerability of Actovex® Compared to Avonex® in Subjects with Relapsing Remitting Multiple Sclerosis (RRMS)*.2014. URL: http://en.irct.ir/trial/12461 (Accessed 8 May 2024).	Not informative to the network - compares brands
Aivo J, Lindsrom B, Soilu-Hanninen M. A Randomised, Double-Blind, Placebo-Controlled Trial with Vitamin D3 in MS: Subgroup Analysis of Patients with Baseline Disease Activity Despite Interferon Treatment. Multiple sclerosis international. 2012;2012:802796. doi:10.1155/2012/802796.	Not informative to the network - non DMT add on
Albert C, Mikolajczak J, Liekfeld A, et al. Fingolimod after a first unilateral episode of acute optic neuritis (MOVING) - preliminary results from a randomized, rater-blind, active-controlled, phase 2 trial. BMC neurology. 2020;20(1):75. doi:10.1186/s12883-020-01645-z.	MS but not >90% RRMS
Irct20170128032241N. *Effect of oral curcuden on multiple sclerosis patients*.2018. URL: http://en.irct.ir/trial/25165 (Accessed 8 May 2024).	Did not evaluate intervention of interest
ACTRN12619000348156. *Autologous Haematopoietic Stem Cell Transplantation for highly active treatment resistant multiple sclerosis*.2019. URL: https://anzctr.org.au/ACTRN12619000348156.aspx (Accessed 8 May 2024).	Not an RCT
jRCT2051210146. *Phase 3 Study to Evaluate Efficacy, Safety, PK, and PD of SC Natalizumab in Japanese Participants With RRMS*.2021. URL: https://jrct.niph.go.jp/latest-detail/jRCT2051210146 (Accessed 8 May 2024).	Not an RCT

Citation	Reason for exclusion
NCT05296161. B Cell Tailored Ocrelizumab Versus Standard Ocrelizumab in Relapsing Remitting Multiple Sclerosis.2022. URL: https://clinicaltrials.gov/show/NCT05296161 (Accessed 8 May 2024).	Not informative to the network - DMT add on
Anderson G, Meyer D, Herrman C, et al. Tolerability and safety of novel half milliliter formulation of glatiramer acetate for subcutaneous injection: an open-label, multicenter, randomized comparative study. Journal of neurology. 2010;257(11):1917-23. doi:10.1007/s00415-010-5779-x.	Not informative to the network - compares different protocols
Anonymous. Alemtuzumab (Campath) off-label for relapsing multiple sclerosis. Medical Letter on Drugs and Therapeutics. 2009;51(1307):17-18.	Not a primary study
Anonymous. Avonex 30 mug i.m. once a week is the correct dose for the therapy of relapsing-remitting multiple sclerosis. Deutsche Apotheker Zeitung. 2000;140(50):38.	Not a primary study
Anonymous. Erratum to Daclizumab in active relapsing multiple sclerosis (CHOICE study): A phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta [Lancet Neurol, (2010), 9, 381-90]. The Lancet Neurology. 2010;9(8):759. doi:10.1016/s1474-4422(10)70172-1.	Not informative to the network - non DMT add on
Anonymous. Erratum to Methylprednisolone in combination with interferon beta-1a for relapsing-remitting multiple sclerosis (MECOMBIN study): A multicentre, double-blind, randomised, placebo controlled, parallel-group trial [Lancet Neurol, (2010), 9, 672-80]. The Lancet Neurology. 2010;9(8):759. doi:10.1016/s1474-4422(10)70171-x.	Not informative to the network - non DMT add on
Anonymous. Evidence of interferon beta-1a dose response in relapsing-remitting MS: the OWIMS Study. The Once Weekly Interferon for MS Study Group. Neurology. 1999;53(4):679-86. doi:10.1212/wnl.53.4.679.	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
Anonymous. Glatiramer acetate for multiple sclerosis. Drug and Therapeutics Bulletin. 2001;39(6):41-43. doi:10.1136/dtb.2001.39641.	Not a primary study
Anonymous. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. European Study Group on interferon beta-1b in secondary progressive MS. Lancet (London, England). 1998;352(9139):1491-7.	MS but not >90% RRMS
Anonymous. PRISMS-4: Long-term efficacy of interferon-beta-1a in relapsing MS. Neurology. 2001;56(12):1628-36. doi:10.1212/wnl.56.12.1628.	Extension/expansion study
Anonymous. Promising outcomes from Phase III CLARITY study for the treatment of multiple sclerosis announced. Expert review of pharmacoeconomics & outcomes research. 2009;9(3):198. doi:10.1586/erp.09.25.	Not a primary study
Anonymous. Randomized controlled trial of interferon- beta-1a in secondary progressive MS: Clinical results. Neurology. 2001;56(11):1496-504. doi:10.1212/wnl.56.11.1496.	MS but not >90% RRMS

Citation	Reason for exclusion
Arnold D, Calabresi P, Kieseier B, et al. 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 neurology. 2017;17(1):29. doi:10.1186/s12883-017-0799-0.	Extension/expansion study
Arnold D, Campagnolo D, Panitch H, et al. Glatiramer acetate after mitoxantrone induction improves MRI markers of lesion volume and permanent tissue injury in MS. Journal of neurology. 2008;255(10):1473-8. doi:10.1007/s00415-008-0911-x.	Not informative to the network - non DMT add on
Arnold D, Narayanan S, Antel S. Neuroprotection with glatiramer acetate: evidence from the PreCISe trial. Journal of neurology. 2013;260(7):1901-6. doi:10.1007/s00415-013-6903-5.	MS but not >90% RRMS
Ashtari F, Savoj M. Effects of low dose methotrexate on relapsing-remitting multiple sclerosis in comparison to Interferon beta-1alpha: A randomized controlled trial. Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences. 2011;16(4):457-62.	Not informative to the network - non DMT add on
Ashtari F, Toghianifar N, Zarkesh-Esfahani S, Mansourian M. High dose Vitamin D intake and quality of life in relapsing-remitting multiple sclerosis: a randomized, double-blind, placebo-controlled clinical trial. Neurological research. 2016;38(10):888-92. doi:10.1080/01616412.2016.1227913.	Not informative to the network - non DMT add on
Atkins H, Bowman M, Allan D, et al. Immunoablation and autologous haemopoietic stem-cell transplantation for aggressive multiple sclerosis: a multicentre single-group phase 2 trial. Lancet (London, England). 2016;388(10044):576-85. doi:10.1016/s0140-6736(16)30169-6.	Not an RCT
ACTRN12616000151437. *A Phase II study:
Haematopoietic Stem Cell Transplantation for highly active
treatment resistant multiple sclerosis .
*.2016. URL: https://anzctr.org.au/ACTRN12616000151437.aspx (Accessed 8 May 2024).	Not an RCT
Bandari D, Wynn D, Miller T, et al. Rebif(R) Quality of Life (RebiQoL): A randomized, multicenter, Phase IIIb study evaluating quality-of-life measures in patients receiving the serum-free formulation of subcutaneous interferon beta-1a for the treatment of relapsing forms of multiple sclerosis. Multiple sclerosis and related disorders. 2013;2(1):45-56. doi:10.1016/j.msard.2012.07.005.	Not informative to the network - compares different protocols
Barbero P, Verdun E, Bergui M, et al. High-dose, frequently administered interferon beta therapy for relapsing-remitting multiple sclerosis must be maintained over the long term: the interferon beta dose-reduction study. Journal of the neurological sciences. 2004;222(1-2):13-9. doi:10.1016/j.jns.2004.03.023.	Not informative to the network - compares different protocols
Bar-Or A, Grove R, Austin D, et al. Subcutaneous ofatumumab in patients with relapsing-remitting multiple sclerosis: The MIRROR study. Neurology. 2018;90(20):e1805-e1814. doi:10.1212/wnl.0000000000005516.	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
Bar-Or A, Wiendl H, Montalban X, et al. Rapid and sustained B-cell depletion with subcutaneous ofatumumab in relapsing multiple sclerosis: APLIOS, a randomized phase-2 study. Multiple sclerosis (Houndmills, Basingstoke, England). 2022;28(6):910-924. doi:10.1177/13524585211044479.	Not informative to the network - compares different protocols

Citation	Reason for exclusion
Barroso-Rodriguez N, Nunez-Orozco L, Santos-Caballero N, et al. Comparative study with random assignment and blind assessor to determine the effect on the soluble Vascular Cell Adhesion Molecules (sVCAM-1) of the Interferon Beta 1a biogeneric of Mexican production against an Interferon Beta 1a of international production in patients with Relapsing-Remitting Multiple Sclerosis (RRMS). Revista Mexicana de Neurociencia. 2008;9(4):268-272.	Not informative to the network - compares brands
Bartosik-Psujek H, Mitosek-Szewczyk K, Belniak E, Stelmasiak Z. [Development of binding antibodies to interferon-beta during treatment of multiple sclerosis with different types of interferon-beta]. Powstawanie przeciwcial wiazacych interferon beta w trakcie leczenia stwardnienia rozsianego roznymi preparatami interferonu beta. 2004;17(97):28-32.	Not an RCT
Bates D, Bartholome E. Treatment effect of natalizumab on relapse outcomes in multiple sclerosis patients despite ongoing MRI activity. Journal of neurology, neurosurgery, and psychiatry. 2012;83(1):55-60. doi:10.1136/jnnp-2011-300279.	Not an RCT
Baum K. Safety and tolerability of a 'refrigeration-free' formulation of interferon beta-1b--results of a double-blind, multicentre, comparative study in patients with relapsing-remitting or secondary progressive multiple sclerosis. The Journal of international medical research. 2006;34(1):1-12. doi:10.1177/147323000603400101.	MS but not >90% RRMS
Bell Gorrod H, Latimer N, Damian D, Hettle R, Harty G, Wong S. Assessing the Long-Term Effectiveness of Cladribine vs. Placebo in the Relapsing-Remitting Multiple Sclerosis CLARITY Randomized Controlled Trial and CLARITY Extension Using Treatment Switching Adjustment Methods. Advances in therapy. 2020;37(1):225-239. doi:10.1007/s12325-019-01140-z.	Not a primary study
Bellmann-Strobl J, Paul F, Wuerfel J, et al. Epigallocatechin Gallate in Relapsing-Remitting Multiple Sclerosis: A Randomized, Placebo-Controlled Trial. Neurology(R) neuroimmunology & neuroinflammation. 2021;8(3). doi:10.1212/nxi.0000000000000981.	Not informative to the network - non DMT add on
Benedict R, Cohan S, Lynch S, et al. Improved cognitive outcomes in patients with relapsing-remitting multiple sclerosis treated with daclizumab beta: Results from the DECIDE study. Multiple sclerosis (Houndmills, Basingstoke, England). 2018;24(6):795-804. doi:10.1177/1352458517707345.	Comparator not informative to the network
Berkovich R, Bakshi R, Amezcua L, et al. Adrenocorticotropic hormone versus methylprednisolone added to interferon beta in patients with multiple sclerosis experiencing breakthrough disease: a randomized, rater-blinded trial. Therapeutic advances in neurological disorders. 2017;10(1):3-17. doi:10.1177/1756285616670060.	Did not evaluate intervention of interest
Bermel R, Weinstock-Guttman B, Bourdette D, Foulds P, You X, Rudick R. Intramuscular interferon beta-1a therapy in patients with relapsing-remitting multiple sclerosis: a 15-year follow-up study. Multiple sclerosis (Houndmills, Basingstoke, England). 2010;16(5):588-96. doi:10.1177/1352458509360549.	Extension/expansion study
Biernacki T, Bencsik K, Sandi D, Vecsei L. [Alemtuzumab therapy 2017]. Alemtuzumabterapia, 2017. 2017;70(11-12):371-380. doi:10.18071/isz.70.0371.	Not a primary study
2005-003930-16. *A Multi-centre, Double Blind, Randomised, Placebo Controlled, Parallel Group Study Investigating Simvastatin as an Add-on Treatment to Interferon-beta-1a for the Treatment of Relapsing-Remitting Multiple Sclerosis - SIMCOMBIN*.2005. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2005-003930-16 (Accessed 8 May 2024).	Not informative to the network - non DMT add on

Citation	Reason for exclusion
2010-024000-10. A Study to Evaluate the Effect of Different Doses of TYSABRI on Safety and Efficacy in Relapsing Multiple Sclerosis.2011. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-024000-10 (Accessed 8 May 2024).	Not informative to the network - compares different protocols
2009-012500-11. Comparison of Daclizumab HYP and Avonex® in Multiple Sclerosis.2010. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-012500-11 (Accessed 8 May 2024).	Comparator not informative to the network
Ctri 380. A clinical trial to determine the efficacy and safety of BG00012 in patients with relapsing remitting multiple sclerosis.2009. URL: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=380 (Accessed 8 May 2024).	Can't locate
ISRCTN68218781. A Multi-center, Double Blind, Randomized, Placebo Controlled, Parallel Group Trial Investigating Methylprednisolone in Combination with Interferon-beta-1a for the Treatment of Relapsing-Remitting Multiple Sclerosis.2004. URL: http://isrctn.com/ISRCTN68218781 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
2018-003008-38. A Study to Evaluate the Safety, Tolerability, and Efficacy of BIIB017 (Peginterferon beta-1a) in Paediatric Participants for the Treatment of Relapsing-Remitting Multiple Sclerosis.2019. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-003008-38 (Accessed 8 May 2024).	RRMS but not in adults
2018-000516-22. Study to Evaluate the Efficacy and Safety of BG00012 and BIIB017 for the Treatment of Relapsing-Remitting Multiple Sclerosis in Paediatric Participants.2018. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-000516-22 (Accessed 8 May 2024).	RRMS but not in adults
2013-002318-11. Phase 3 Efficacy and Safety Study of BG00012 in Subjects With Relapsing-Remitting Multiple Sclerosis (RRMs).2014. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-002318-11 (Accessed 8 May 2024).	RRMS but not in adults
34882. *A Multicenter, Randomized, Rater-Blind, Parallel-Group, Active Controlled Study to Evaluate the Benefits of Switching Therapy (Glatiramer Acetate or Interferon β-1a) to Natalizumab in Subjects with Relapsing Remitting Multiple Sclerosis*.2010. URL: https://onderzoekmetmensen.nl/en/trial/34882 (Accessed 8 May 2024).	Terminated study
2016-000434-21. *PLENO – Open-label, Randomized, 2-arm, Active Comparator Study to Evaluate Safety and Tolerability in Portuguese Patients with Relapsing Remitting Multiple Sclerosis (MS) Transitioning from Current Subcutaneous Interferon Therapy to Peginterferon Beta 1a (PLEGRIDY™)*.2016. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-000434-21 (Accessed 8 May 2024).	Not informative to the network - compares against switch to chosen iDMT
Irct2013030512398N. The Effectiveness, Safety and Tolerability of Actoferon® Compared to Betaferon® in Subjects with Relapsing Remitting Multiple Sclerosis (RRMS).2014. URL: http://en.irct.ir/trial/12462 (Accessed 8 May 2024).	Not informative to the network - compares brands
Birnbaum G, Cree B, Altafullah I, Zinser M, Reder A. Combining beta interferon and atorvastatin may increase disease activity in multiple sclerosis. Neurology. 2008;71(18):1390-5. doi:10.1212/01.wnl.0000319698.40024.1c.	Not informative to the network - non DMT add on

Citation	Reason for exclusion
Boiko A, Bosenko L, Vasilovskii V, et al. A Comparative Placebo-Controlled Clinical Trial of the Efficacy and Safety of Interferon beta-1a Formulations for S.C. Administration in Patients with Remitting Multiple Sclerosis: First-Year Results. Neuroscience and Behavioral Physiology. 2018;48(7):883-889. doi:10.1007/s11055-018-0643-z.	Not informative to the network - compares brands
Boiko A, Lashch N, Sharanova S, 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. Neuroscience and Behavioral Physiology. 2018;48(3):351-357. doi:10.1007/s11055-018-0570-z.	Not informative to the network - compares brands
Bonavita S, Dinacci D, Lavorgna L, et al. Treatment of multiple sclerosis with interferon beta in clinical practice: 2-year follow-up data from the South Italy Mobile MRI Project. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2006;27 Suppl 5:S365-8. doi:10.1007/s10072-006-0696-6.	Not a RCT
Bornstein M, Miller A, Slagle S. A pilot trial of cop 1 in exacerbating-remitting multiple sclerosis. New England Journal of Medicine. 1987;317(7):408-414. doi:10.1056/nejm198708133170703.	Did not evaluate intervention of interest
Boyko A, Bakhtiyarova K, Boyko O, et al. [Long-term Efficacy and Safety of Sampeginterferon-beta1a in the Treatment of Relapsing Remitting Multiple Sclerosis: a Randomized, Double-Blind Clinical Trial 104-Week Results]. Dolgosrochnye dannye po effektivnosti i bezopasnosti preparata sampeginterferon-beta1a u patsientov s remittiruyushchim rasseyannym sklerozom: rezul'taty 104-nedel'nogo randomizirovannogo dvoinogo slepogo klinicheskogo issledovaniya. 2023;123(2):52-59. doi:10.17116/jnevro202312302152.	Comparator not informative to the network
Boyko A, Bakhtiyarova K, Dudin V, et al. [The new pegylated interferon beta-1a (sampeginterferon beta-1a, BCD-054) in the treatment of remitting multiple sclerosis]. Novyi pegilirovannyi interferon beta-1a (sampeginterferon beta-1a, BCD-054) v terapii remittiruiushchego rasseiannogo skleroza. 2019;119(10. Vyp. 2):100-109. doi:10.17116/jnevro201911910100.	Comparator not informative to the network
Boyko A, Bosenko L, Vasilovskiy V, et al. [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]. Sravnitel'noe platsebo-kontroliruemoe klinicheskoe issledovanie effektivnosti i bezopasnosti preparatov interferona beta-1a dlia podkozhnogo vvedeniia u patsientov s remittiruiushchim rasseiannym sklerozom: rezul'taty pervogo goda nabliudeniia. 2017;117(2. Vyp. 2):107-113. doi:10.17116/jnevro201711722107-113.	Not informative to the network - compares brands
Boyko A, Bosenko L, Vasilovskiy V, et al. Efficacy, tolerability and safety of the treatment with teberif: The results of a 2-year randomized clinical trial of treatment naive patients with remitting multiple sclerosis, who have not received dmt, after switching from other interferon beta-1a. Zhurnal Nevrologii i Psihiatrii imeni S.S. Korsakova. 2019;119(2):73-85. doi:10.17116/jnevro20191192273.	Not informative to the network - compares brands
Boyko A, Boyko O, Bakhtiyarova K, et al. [Efficacy and safety of sampeginterferon beta-1a in the treatment of relapsing remitting multiple sclerosis: results of 52 weeks of therapy in a randomized, double-blind clinical trial]. Effektivnost' i bezopasnost' sampeginterferona beta-1a dlya lecheniya remittiruyushchego rasseyannogo skleroza: rezul'taty 52-nedel'nogo randomizirovannogo dvoinogo slepogo klinicheskogo issledovaniya. 2022;122(1):62-71. doi:10.17116/jnevro202212201162.	Comparator not informative to the network

Citation	Reason for exclusion
Boyko A, Lashch N, Sharanova S, et al. [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]. Sravnitel'noe platsebo-kontroliruemoe klinicheskoe issledovanie effektivnosti i bezopasnosti preparatov glatiramera atsetata 20 mg u patsientov s remittiruyushchim rasseyannym sklerozom: rezul'taty pervogo goda nablyudeniya. 2016;116(10 Pt 2):61-67. doi:10.17116/jnevro201611610261-67.	Not informative to the network - compares brands
Boyko A. [Comments on the GLIMPSE study on evaluating the efficacy of the drug cladribine in tablets in routine clinical practice in comparison with other tablet drugs for the pathogenetic treatment of multiple sclerosis]. Kommentarii k issledovaniyu GLIMPSE po otsenke effektivnosti preparata kladribin v tabletkakh v usloviyakh rutinnoi klinicheskoi praktiki v sravnenii s drugimi tabletirovannymi preparatami dlya patogeneticheskogo lecheniya rasseyannogo skleroza. 2022;122(7. Vyp. 2):73-77. doi:10.17116/jnevro202212207273.	Not a primary study
Brown R, Narayanan S, Stikov N, et al. MTR recovery in brain lesions in the BECOME study of glatiramer acetate vs interferon beta-1b. Neurology. 2016;87(9):905-11. doi:10.1212/wnl.0000000000003043.	Does not report on one of the outcomes of interest
Cabrera-Gomez J, Echazabal-Santana N, Porrero-Martin P, et al. Interferon alpha-2b recombinant improved the cognitive dysfunction in patients with relapsing-remitting multiple sclerosis. Revista de Neurologia. 2003;37(3):214-220. doi:10.33588/rn.3703.2003078.	Did not evaluate intervention of interest
Cadavid D, Kim S, Peng B, et al. Clinical consequences of MRI activity in treated multiple sclerosis. Multiple sclerosis (Houndmills, Basingstoke, England). 2011;17(9):1113-21. doi:10.1177/1352458511405375.	MS but not >90% RRMS
Cadavid D, Mellion M, Hupperts R, et al. Safety and efficacy of opicinumab in patients with relapsing multiple sclerosis (SYNERGY): a randomised, placebo-controlled, phase 2 trial. The Lancet. Neurology. 2019;18(9):845-856. doi:10.1016/s1474-4422(19)30137-1.	Comparator not informative to the network
Cadavid D, Wolansky L, Skurnick J, 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:10.1212/01.wnl.0000345970.73354.17.	MS but not >90% RRMS
Calkwood J, Cree B, Crayton H, et al. Impact of a switch to fingolimod versus staying on glatiramer acetate or beta interferons on patient- and physician-reported outcomes in relapsing multiple sclerosis: post hoc analyses of the EPOC trial. BMC neurology. 2014;14:220. doi:10.1186/s12883-014-0220-1.	Not informative to the network - compares against switch to chosen iDMT
Camu W, Hadjout K, Latour S, Pohlau D, Masri S. Patient satisfaction following transition from the original to the new formulation of subcutaneous interferon beta-1a in relapsing multiple sclerosis: a randomized, two-arm, open-label, Phase IIIb study. Patient preference and adherence. 2010;4:127-33. doi:10.2147/ppa.s10468.	Did not evaluate intervention of interest
Camu W, Lehert P, Pierrot-Deseilligny C, et al. Cholecalciferol in relapsing-remitting MS: A randomized clinical trial (CHOLINE). Neurology(R) neuroimmunology & neuroinflammation. 2019;6(5). doi:10.1212/nxi.0000000000000597.	Not informative to the network - non DMT add on

Citation	Reason for exclusion
Caon C, Namey M, Meyer C, et al. Prevention and Management of Infusion-Associated Reactions in the Comparison of Alemtuzumab and Rebif(R) Efficacy in Multiple Sclerosis (CARE-MS) Program. International journal of MS care. 2015;17(4):191-8. doi:10.7224/1537-2073.2014-030.	Did not evaluate intervention of interest
Cascione M, Tenenbaum N, Wendt J, Meng X, Schofield L, Cree B. Treatment retention on fingolimod compared with injectable multiple sclerosis therapies in African-American patients: A subgroup analysis of a randomized phase 4 study. Multiple sclerosis and related disorders. 2018;25:50-56. doi:10.1016/j.msard.2018.07.014.	Comparator not informative to the network
Cascione M, Wynn D, Barbato L, Pestreich L, Schofield L, McCague K. Randomized, open-label study to evaluate patient-reported outcomes with fingolimod after changing from prior disease-modifying therapy for relapsing multiple sclerosis: EPOC study rationale and design. Journal of medical economics. 2013;16(7):859-65. doi:10.3111/13696998.2013.802239.	Not informative to the network - compares against switch to chosen iDMT
Chaplin S. Ocrelizumab for relapsing or primary progressive MS. Prescriber. 2018;29(9):35-37. doi:10.1002/psb.1705.	Not a primary study
Chitnis T, Arnold D, Banwell B, et al. Trial of Fingolimod versus Interferon Beta-1a in Pediatric Multiple Sclerosis. The New England journal of medicine. 2018;379(11):1017-1027. doi:10.1056/nejmoa1800149.	MS but not >90% RRMS
Chitnis T, Banwell B, Krupp L, et al. Temporal profile of lymphocyte counts and relationship with infections with fingolimod therapy in paediatric patients with multiple sclerosis: Results from the PARADIGMS study. Multiple sclerosis (Houndmills, Basingstoke, England). 2021;27(6):922-932. doi:10.1177/1352458520936934.	MS but not >90% RRMS
Cinar B, Kosehasanogullari 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):337-342. doi:10.1007/s10072-016-2775-7.	Not a RCT
Irct138711281696N. Cinnovex versus Avonex clinica Trial.2009. URL: http://en.irct.ir/trial/1189 (Accessed 8 May 2024).	Not informative to the network - compares different protocols
NCT04966338. *Efficacy and Safety of Xacrel® (Ocrelizumab) in Participants With Relapsing Remitting Multiple Sclerosis*.2021. URL: https://clinicaltrials.gov/show/NCT04966338(Accessed 8 May 2024).	Not informative to the network - compares brands
Clanet M, Kappos L, Hartung H, Hohlfeld R. Interferon beta-1a in relapsing multiple sclerosis: four-year extension of the European IFNbeta-1a Dose-Comparison Study. Multiple sclerosis (Houndmills, Basingstoke, England). 2004;10(2):139-44. doi:10.1191/1352458504ms990oa.	Extension/expansion study
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Filippi M, Wolinsky J, Comi G. Effects of oral glatiramer acetate on clinical and MRI-monitored disease activity in patients with relapsing multiple sclerosis: a multicentre, double-blind, randomised, placebo-controlled study. The Lancet. Neurology. 2006;5(3):213-20. doi:10.1016/s1474-4422(06)70327-1.	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
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Francis G, Panitich H, Weinshenker B, Monaghan E, O'Connor P. Re: Vartanian T. An examination of the results of the EVIDENCE, INCOMIN, and phase III studies of interferon beta products in the treatment of multiple sclerosis. Clin Ther. 2003;25:105-118. Clinical therapeutics. 2003;25(6):1888-90. doi:10.1016/s0149-2918(03)90030-0.	Not a primary study
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Citation	Reason for exclusion
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Freedman M, Wolinsky J, Wamil B, et al. Teriflunomide added to interferon-beta in relapsing multiple sclerosis: a randomized phase II trial. Neurology. 2012;78(23):1877-85. doi:10.1212/wnl.0b013e318258f7d4.	Not informative to the network - DMT add on
Freedman M. Evidence of interferon beta-1a dose response in relapsing-remitting MS: The OWIMS study. Neurology. 1999;53(4):679-686. doi:10.1212/wnl.53.4.679.	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
Frohman E, Cutter G, Remington G, et al. A randomized, blinded, parallel-group, pilot trial of mycophenolate mofetil (CellCept) compared with interferon beta-1a (Avonex) in patients with relapsing-remitting multiple sclerosis. Therapeutic advances in neurological disorders. 2010;3(1):15-28. doi:10.1177/1756285609353354.	Not informative to the network - non DMT add on
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Citation	Reason for exclusion
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Ghiasian M, Nafisi H, Ranjbar A, Mohammadi Y, Ataei S. Antioxidative effects of silymarin on the reduction of liver complications of fingolimod in patients with relapsing-remitting multiple sclerosis: A clinical trial study. Journal of biochemical and molecular toxicology. 2021;35(8):e22800. doi:10.1002/jbt.22800.	Does not report on one of the outcomes of interest
Giovannoni G, Boyko A, Correale J, et al. Long-term follow-up of patients with relapsing multiple sclerosis from the CLARITY/CLARITY Extension cohort of CLASSIC-MS: An ambispective study. Multiple sclerosis (Houndmills, Basingstoke, England). 2023;29(6):719-730. doi:10.1177/13524585231161494.	Extension/expansion study
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Gold R, Arnold D, Bar-Or A, et al. 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):253-265. doi:10.1177/1352458516649037.	Extension/expansion study
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Gold R, Hartung H. Long-term therapy with fingolimod for relapsing MS: 5-year safety and efficacy data of a phase II extension study. Aktuelle Neurologie. 2013;40(2):79-84. doi:10.1055/s-0033-1333778.	Extension/expansion study

Citation	Reason for exclusion
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Goodin D. A randomized study of two interferon-beta treatments in relapsing-remitting multiple sclerosis. Neurology. 2006;67(7):1313-4. doi:10.1212/01.wnl.0000243810.20687.51.	Not a primary study
Goodman A, Rossman H, Bar-Or A, et al. GLANCE: results of a phase 2, randomized, double-blind, placebo-controlled study. Neurology. 2009;72(9):806-12. doi:10.1212/01.wnl.0000343880.13764.69.	Not informative to the network - DMT add on
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Guger M, Enzinger C, Leutmezer F, et al. Real-life clinical use of natalizumab and fingolimod in Austria. Acta neurologica Scandinavica. 2018;137(2):181-187. doi:10.1111/ane.12864.	Not a RCT
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Hartung H, Berger T, Bermel R, et al. Shorter infusion time of ocrelizumab: Results from the randomized, double-blind ENSEMBLE PLUS substudy in patients with relapsing-remitting multiple sclerosis. Multiple sclerosis and related disorders. 2020;46:102492. doi:10.1016/j.msard.2020.102492.	Not informative to the network - compares different protocols
Hartung H, Freedman M, Polman C, et al. Interferon beta-1b-neutralizing antibodies 5 years after clinically isolated syndrome. Neurology. 2011;77(9):835-43. doi:10.1212/wnl.0b013e31822c90d7.	MS but not >90% RRMS

Citation	Reason for exclusion
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Jacobs L, Salazar A, Herndon R. Multicentre double-blind study of effect of intrathecally administered natural human fibroblast interferon on exacerbations of multiple sclerosis. Lancet. 1986;2(8521):1411-1413. doi:10.1016/s0140-6736(86)92730-3.	Did not evaluate intervention of interest
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Kamm C, El-Koussy M, Humpert S, et al. Atorvastatin added to interferon beta for relapsing multiple sclerosis: a randomized controlled trial. Journal of neurology. 2012;259(11):2401-13. doi:10.1007/s00415-012-6513-7.	Not informative to the network - non DMT add on
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Citation	Reason for exclusion
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Kappos L, Wiendl H, Selmaj K, et al. Daclizumab HYP versus Interferon Beta-1a in Relapsing Multiple Sclerosis. The New England journal of medicine. 2015;373(15):1418-28. doi:10.1056/nejmoa1501481.	Comparator not informative to the network
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Khoury S, Healy B, Kivisakk P, et al. A randomized controlled double-masked trial of albuterol add-on therapy in patients with multiple sclerosis. Archives of neurology. 2010;67(9):1055-61. doi:10.1001/archneurol.2010.222.	Not informative to the network - non DMT add on
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Klotz L, Meuth S, Kieseier B, Wiendl H. [Alemtuzumab for relapsing-remitting multiple sclerosis. Results of two randomized controlled phase III studies]. Alemtuzumab bei schubformig-remittierender multipler Sklerose. Ergebnisse von 2 randomisierten kontrollierten Phase-III-Studien. 2013;84(8):984-94. doi:10.1007/s00115-013-3814-8.	Not a primary study
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Knobler R, Greenstein J, Johnson K, et al. Systemic recombinant human interferon-beta treatment of relapsing-remitting multiple sclerosis: pilot study analysis and six-year follow-up. Journal of interferon research. 1993;13(5):333-40. doi:10.1089/jir.1993.13.333.	Did not evaluate intervention of interest
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Citation	Reason for exclusion
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Kolind S, Abel S, Taylor C, et al. Myelin water imaging in relapsing multiple sclerosis treated with ocrelizumab and interferon beta-1a. NeuroImage. Clinical. 2022;35:103109. doi:10.1016/j.nicl.2022.103109.	Does not report on one of the outcomes of interest
Kondo T, Kawachi I, Onizuka Y, et al. Efficacy of dimethyl fumarate in Japanese multiple sclerosis patients: interim analysis of randomized, double-blind APEX study and its open-label extension. Multiple Sclerosis Journal - Experimental, Translational and Clinical. 2019;5(3). doi:10.1177/2055217319864974.	Did not evaluate intervention of interest
Koscielny V. Phase III SUNBEAM and RADIANCE PART B trials for Ozanimod in relapsing multiple sclerosis demonstrate superiority versus interferon-beta-1a (Avonex R) in reducing annualized relapse rates and MRI brain lesions. Neurodegenerative disease management. 2018;8(3):141-142. doi:10.2217/nmt-2018-0012.	Not a primary study
Kristoferitsch W, Seeldrayers P, Kyriallis K, et al. Double-blind randomized multicenter dose-comparison study of interferon-beta-1a (AVONEX): Rationale, design and baseline data. Multiple Sclerosis. 2001;7(3):179-183. doi:10.1191/135245801678438410.	Not informative to the network - drug of interest but not in a licensed dose
Krueger J, Kircik L, Hougeir F, et al. 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. Advances in therapy. 2016;33(7):1231-45. doi:10.1007/s12325-016-0353-2.	Comparator not informative to the network
Krupp L, Banwell B, Chitnis T, et al. Effect of fingolimod on health-related quality of life in paediatric patients with multiple sclerosis: results from the phase 3 PARADIGMS Study. BMJ neurology open. 2022;4(1):e000215. doi:10.1136/bmjno-2021-000215.	MS but not >90% RRMS
La Mantia L, Munari L, Lovati R. Glatiramer acetate for multiple sclerosis. The Cochrane database of systematic reviews. 2010;(5):CD004678. doi:10.1002/14651858.cd004678.pub2.	Review
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Langdon D, Tomic D, Penner I, et al. Baseline characteristics and effects of fingolimod on cognitive performance in patients with relapsing-remitting multiple sclerosis. European journal of neurology. 2021;28(12):4135-4145. doi:10.1111/ene.15081.	Not a RCT
Lanzillo R, Quarantelli M, Pozzilli C, et al. No evidence for an effect on brain atrophy rate of atorvastatin add-on to interferon beta1b therapy in relapsing-remitting multiple sclerosis (the ARIANNA study). Multiple sclerosis (Houndmills, Basingstoke, England). 2016;22(9):1163-73. doi:10.1177/1352458515611222.	Not informative to the network - non DMT add on
Leist T, Cook S, Comi G, et al. Long-term safety data from the cladribine tablets clinical development program in multiple sclerosis. Multiple sclerosis and related disorders. 2020;46:102572. doi:10.1016/j.msard.2020.102572.	Not a RCT

Citation	Reason for exclusion
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Liu Y, Vollmer T, Havrdova E, et al. Impact of daclizumab versus interferon beta-1a on patient-reported outcomes in relapsing-remitting multiple sclerosis. Multiple sclerosis and related disorders. 2017;11:18-24. doi:10.1016/j.msard.2016.11.005.	Comparator not informative to the network
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Maciejowski M. Anti-CD20 monoclonal antibody in multiple sclerosis therapy: The results of phase 3 clinical studies on relapsing and primary progressive multiple sclerosis. Aktualnosci Neurologiczne. 2015;15(3):150-154. doi:10.15557/an.2015.0022.	Not a primary study
Mancardi G, Sormani M, Gualandi F, et al. Autologous hematopoietic stem cell transplantation in multiple sclerosis: a phase II trial. Neurology. 2015;84(10):981-8. doi:10.1212/wnl.0000000000001329.	MS but not >90% RRMS
2018-000284-93. A multinational, multicenter, randomized, Phase III, double blind, parallel group, placebo controlled study in subjects with Relapsing forms of Multiple Sclerosis (RMS) to assess the efficacy, safety and tolerability of GA Depot, a long acting IM injection of glatiramer acetate, administered once every four weeks.2019. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-000284-93 (Accessed 8 May 2024).	Not informative to the network - drug of interest but not in a licensed dose
Irct20170604034325N. Effects of fingolimod in treatment of multiple sclerosis.2018. URL: http://en.irct.ir/trial/33624 (Accessed 8 May 2024).	Not a RCT
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Massacesi L, Tramacere I, Amoroso S, et al. Azathioprine versus beta interferons for relapsing-remitting multiple sclerosis: a multicentre randomized non-inferiority trial. PloS one. 2014;9(11):e113371. doi:10.1371/journal.pone.0113371.	Did not evaluate intervention of interest
Mealli F, Mattei A, Mariottini A, Massacesi L. Non-inferiority analysis of subcutaneous versus intravenous 300 mg monthly natalizumab administration: A post hoc analysis of the REFINE study. Multiple sclerosis (Houndmills, Basingstoke, England). 2024;:13524585241238136. doi:10.1177/13524585241238136.	Not informative to the network - compares different protocols
2005-004289-18. A Multi-centre, Double Blind, Randomized, Placebo Controlled, Parallel Group Trial Investigating Minocycline versus placebo as add-on therapy in patients who are on treatment with Interferon-beta-1a 44mcg tiw (Rebif®) for the Treatment	Not informative to the network - non DMT add on

Citation	Reason for exclusion
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with Relapsing-Remitting MS receiving Rebif® treatment.2010. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-020328-23 (Accessed 8 May 2024).	Not informative to the network - DMT add on
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Citation	Reason for exclusion
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Montalban X, Comi G, O'Connor P, et al. Oral fingolimod (FTY720) in relapsing multiple sclerosis: impact on health-related quality of life in a phase II study. Multiple sclerosis (Houndmills, Basingstoke, England). 2011;17(11):1341-50. doi:10.1177/1352458511411061.	Extension/expansion study
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NCT00451204. A Combination Trial of Copaxone Plus Estriol in Relapsing Remitting Multiple Sclerosis (RRMS). URL: https://classic.clinicaltrials.gov/show/NCT00451204 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT01198132. A Multicentre Study of the Efficacy and Safety of Supplementary Treatment With Cholecalciferol in Patients With Relapsing Multiple Sclerosis Treated With Subcutaneous Interferon Beta-1a 44 µg 3 Times Weekly. URL: https://classic.clinicaltrials.gov/show/NCT01198132 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT01404117. A Multinational, Randomized, Double-blind, Parallel-group, Placebo-controlled Study Assessing the Safety and Tolerability. URL: https://classic.clinicaltrials.gov/show/NCT01404117 (Accessed 8 May 2024).	Not informative to the network - DMT add on

Citation	Reason for exclusion
NCT03283397. A Phase IIIb, Multicenter, International Study to Evaluate the Efficacy, Safety and Tolerability of EK-12 in Patients With RRMS. URL: https://classic.clinicaltrials.gov/show/NCT03283397 (Accessed 8 May 2024).	Comparator not informative to the network
NCT01142466. A Phase IV Study of Rebif ® 44mcg Administered Three Times Per Week by Subcutaneous Injection Compared With no Treatment in the Therapy of Relapsing Multiple Sclerosis After Mitoxantrone. URL: https://classic.clinicaltrials.gov/show/NCT01142466 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT03387046. A Pilot Study in Participants With Relapsing Remitting Multiple Sclerosis (RR-MS). URL: https://classic.clinicaltrials.gov/show/NCT03387046 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
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NCT02064816. A Study of Rebif® in Subjects With Relapsing Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT02064816 (Accessed 8 May 2024).	Not informative to the network - compares different protocols
NCT04121221. A Study to Asses Efficacy, Safety and Tolerability of Monthly Long-acting IM Injection of GA Depot in Subjects With RMS. URL: https://classic.clinicaltrials.gov/show/NCT04121221 (Accessed 8 May 2024).	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
NCT01975298. A Study to Evaluate 2 Doses Of Oral Administration Of Laquinimod Compared to Interferon ß-1a Administered by Injection in Participants With Relapsing Remitting Multiple Sclerosis (RRMS). URL: https://classic.clinicaltrials.gov/show/NCT01975298 (Accessed 8 May 2024).	Comparator not informative to the network
NCT03368664. A Study to Evaluate Efficacy, Safety, and Tolerability of Alemtuzumab in Pediatric Patients With RRMS With Disease Activity on Prior DMT. URL: https://classic.clinicaltrials.gov/show/NCT03368664 (Accessed 8 May 2024).	RRMS but not in adults
NCT03689972. A Study to Evaluate Efficacy, Safety, and Tolerability of EID of Natalizumab (BG00002) in Participants With RRMS Switching From Treatment With Natalizumab SID in Relation to Continued SID Treatment- Followed by Extension Study Comprising SC and IV Natalizumab Administration. URL: https://classic.clinicaltrials.gov/show/NCT03689972 (Accessed 8 May 2024).	Not informative to the network - compares different protocols
NCT05265728. A Study to Evaluate Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of Natalizumab (BG00002) Administered Subcutaneously to Japanese Participants With Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT05265728 (Accessed 8 May 2024).	Not a RCT
NCT05123703. A Study To Evaluate Safety And Efficacy Of Ocrelizumab In Comparison With Fingolimod In Children And Adolescents With Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT05123703 (Accessed 8 May 2024).	RRMS but not in adults
NCT00203086. A Study to Evaluate the Long Term Safety and Effectiveness of Novantrone Therapy Followed by Copaxone Treatment for Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00203086 (Accessed 8 May 2024).	Not a RCT

Citation	Reason for exclusion
NCT00203073. A Study to Evaluate the Safety and Effectiveness of Novantrone Therapy Followed by Copaxone for Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00203073 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT03958877. A Study to Evaluate the Safety, Tolerability, and Efficacy of BIIB017 (Peginterferon Beta-1a) in Pediatric Participants for the Treatment of Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT03958877 (Accessed 8 May 2024).	RRMS but not in adults
NCT00202982. A Study to Test the Effectiveness and Safety of a New Higher 40mg Dose of Copaxone® Compared to Copaxone® 20mg, the Currently Approved Dose. URL: https://classic.clinicaltrials.gov/show/NCT00202982 (Accessed 8 May 2024).	Not informative to the network - drug of interest but not in a licensed dose
NCT00883337. A Study Comparing the Effectiveness and Safety of Teriflunomide and Interferon Beta-1a in Patients With Relapsing Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00883337 (Accessed 8 May 2024).	Comparator not informative to the network
NCT01395316. Alemtuzumab on Surrogate Markers of Disease Activity and Repair Using Advanced MRI Measures in Subjects With Relapsing Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01395316 (Accessed 8 May 2024).	Not a RCT
NCT00206648. An Efficacy and Safety Comparison Study of Two Marketed Drugs in Patients With Relapsing-remitting MS. URL: https://classic.clinicaltrials.gov/show/NCT00206648 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT01578785. An Efficacy, Safety and Tolerability Study of Glatiramer Acetate (GA) 20 mg/0.5 ml New Formulation Administered Daily by Subcutaneous (SC) Injection in Subjects With Relapsing-Remitting Multiple Sclerosis (RRMS). URL: https://classic.clinicaltrials.gov/show/NCT01578785 (Accessed 8 May 2024).	Terminated study
NCT00930553. An Extension Protocol for Multiple Sclerosis Patients Who Participated in Genzyme-Sponsored Studies of Alemtuzumab. URL: https://classic.clinicaltrials.gov/show/NCT00930553 (Accessed 8 May 2024).	Extension/expansion study
NCT06228781. Autologous Hematopoietic Stem Cell Transplantation for Refractory Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT06228781 (Accessed 8 May 2024).	Not a RCT
NCT00168766. Avonex (Interferon-beta-1a) and Avonex Plus Methylprednisolone for the Treatment of Relapsing-remitting MS. URL: https://classic.clinicaltrials.gov/show/NCT00168766 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00459667. BEYOND Follow-up: Betaferon®/Betaseron® Efficacy Yielding Outcomes of a New Dose. URL: https://classic.clinicaltrials.gov/show/NCT00459667 (Accessed 8 May 2024).	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
NCT00893217. BEYOND Pilot Study. URL: https://classic.clinicaltrials.gov/show/NCT00893217 (Accessed 8 May 2024).	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed

Citation	Reason for exclusion
NCT00099502. BEYOND: Betaferon/Betaseron Efficacy Yielding Outcomes of a New Dose in Multiple Sclerosis (MS) Patients. URL: https://classic.clinicaltrials.gov/show/NCT00099502 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT01156311. BG00012 Phase 2 Combination Study in Participants With Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01156311 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00605215. BRAVO Study: Laquinimod Double-blind Placebo-controlled Study in Participants With Relapsing-Remitting Multiple Sclerosis (RRMS) With a Rater Blinded Reference Arm of Interferon β-1a (Avonex®). URL: https://classic.clinicaltrials.gov/show/NCT00605215 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00641537. *CLARITY Extension Study*. URL: https://classic.clinicaltrials.gov/show/NCT00641537 (Accessed 8 May 2024).	Extension/expansion study
NCT01006265. Clinical Study to Evaluate the Efficacy, Safety, and Tolerability of ACT-128800 in Patients With Relapsing-remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01006265 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT01093326. Clinical Study to Investigate the Long-term Safety, Tolerability, and Efficacy of Ponesimod in Patients With Relapsing-remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01093326 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00337779. Clinical Trial Comparing Treatment of Relapsing-Remitting Multiple Sclerosis (RR-MS) With Two Doses of Glatiramer Acetate (GA). URL: https://classic.clinicaltrials.gov/show/NCT00337779 (Accessed 8 May 2024).	Not informative to the network - drug of interest but not in a licensed dose
NCT00211887. Combination Therapy in Patients With Relapsing-Remitting Multiple Sclerosis (MS)CombiRx. URL: https://classic.clinicaltrials.gov/show/NCT00211887 (Accessed 8 May 2024).	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
NCT00298662. Combination Therapy of Betaseron-Prograf in Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00298662 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00618527. Combination Therapy Using Cellcept and Rebif in RRMS. URL: https://classic.clinicaltrials.gov/show/NCT00618527 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT02744222. Comparative Clinical Trial to Evaluate Efficacy, Safety and Tolerance of BCD-054 and Avonex® for Treatment of Patients With Remitting-relapsing Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT02744222 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT03535298. Determining the Effectiveness of early Intensive Versus Escalation Approaches for RRMS. URL: https://classic.clinicaltrials.gov/show/NCT03535298 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT05902429. Effects of Oral Cladribine on Remyelination and Inflammation in Multiple Sclerosis Patients. URL: https://classic.clinicaltrials.gov/show/NCT05902429 (Accessed 8 May 2024).	Not a RCT

Citation	Reason for exclusion
NCT02753088. Efficacy and Safety of BCD-063 and Copaxone-Teva in Patients With Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT02753088 (Accessed 8 May 2024).	Not informative to the network - compares brands
NCT01064401. Efficacy and Safety of BIIB019 (Daclizumab High Yield Process) Versus Interferon β 1a in Participants With Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01064401 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT02881567. Efficacy and Safety of Daclizumab in Participants With RRMS Switching From Natalizumab. URL: https://classic.clinicaltrials.gov/show/NCT02881567 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00333138. Efficacy and Safety of FTY720 in Patients With Relapsing Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00333138 (Accessed 8 May 2024).	MS but not >90% RRMS
NCT05242133. Efficacy and Safety of Peginterferon Beta-1a (CinnaGen) in Participants With Relapsing Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT05242133 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT04115488. Efficacy and Safety of the Biosimilar Natalizumab PB006 in Comparison to Tysabri®. URL: https://classic.clinicaltrials.gov/show/NCT04115488 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00451451. Efficacy and Safety Study of Oral BG00012 With Active Reference in Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00451451 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT01111656. Efficacy, Safety and Tolerability of Atorvastatin 40 mg in Patients With Relapsing-remitting Multiple Sclerosis Treated With Interferon-beta-1b. URL: https://classic.clinicaltrials.gov/show/NCT01111656 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT01963611. Efficacy, Safety, and Tolerability of Plovamer Acetate (Pathway 1). URL: https://classic.clinicaltrials.gov/show/NCT01963611 (Accessed 8 May 2024	Did not evaluate intervention of interest
NCT03177083. Evaluate Safety/Tolerability in Portuguese Participants With RRMS Transitioning From Current Therapy. URL: https://classic.clinicaltrials.gov/show/NCT03177083 (Accessed 8 May 2024).	Comparator not informative to the network
NCT01333358. Evaluating Alemtuzumab as a Treatment in Stabilizing Neurocognitive Function In Relapsing Remitting Multiple Sclerosis Patients. URL: https://classic.clinicaltrials.gov/show/NCT01333358 (Accessed 8 May 2024).	Does not report on one of the outcomes of interest
NCT02939079. Evaluating of the Effect of Fingolimod With Fish Oil on Relapsing-Remitting Multiple Sclerosis Patients. URL: https://classic.clinicaltrials.gov/show/NCT02939079 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT00219908. Evaluation of a New Therapeutic Strategy in Early and Active Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00219908 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT01534182. Evaluation of Patient Reported Outcomes in RRMS Patients Candidates for MS Therapy Change and Transitioned to Fingolimod 0.5 mg (EPOC). URL: https://classic.clinicaltrials.gov/show/NCT01534182 (Accessed 8 May 2024).	Extension/expansion study
NCT01623596. Evaluation of Patient Retention of Fingolimod vs. Currently Approved Disease Modifying Therapy in Patients With Relapsing Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01623596 (Accessed 8 May 2024).	Not a RCT

Citation	Reason for exclusion
NCT01167426. Evaluation of Two Glatiramer Acetate (GA) Formulations in Relapsing-Remitting Multiple Sclerosis (RRMS) Patients. URL: https://classic.clinicaltrials.gov/show/NCT01167426 (Accessed 8 May 2024).	Not a RCT
NCT01405820. Exploratory Study of the Safety, Tolerability and Efficacy of Multiple Regimens of Natalizumab in Adult Participants With Relapsing Multiple Sclerosis (MS). URL: https://classic.clinicaltrials.gov/show/NCT01405820 (Accessed 8 May 2024).	Not informative to the network - drug of interest but not in a licensed dose
NCT01020370. Exploratory Study to Investigate the Reparative and Regenerative Potential of Alemtuzumab in Relapsing-Remitting Multiple Sclerosis Patients Participating in the CARE MS I and MS II Studies. URL: https://classic.clinicaltrials.gov/show/NCT01020370 (Accessed 8 May 2024).	Not a RCT
NCT00235989. Extension of Prior Study Evaluating Safety and Tolerability of Two Doses of Betaseron® to Treat Relapsing-remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00235989 (Accessed 8 May 2024).	Not a RCT
NCT01416155. Extension Study to Evaluate Safety and Efficacy of Natalizumab in Japanese Participants With Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01416155 (Accessed 8 May 2024).	Extension/expansion study
NCT03345940. Fingolimod Versus Dimethyl-fumarate in Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT03345940 (Accessed 8 May 2024).	Comparator not informative to the network
NCT00623415. Flupirtine as Oral Treatment in Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00623415 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00203021. Glatiramer Acetate (Copaxone®) Study to Follow Participants From the First Original Study for Safety and Effectiveness. URL: https://classic.clinicaltrials.gov/show/NCT00203021 (Accessed 8 May 2024).	Not a RCT
NCT01456416. Glatiramer Acetate for Multiple Sclerosis With Autoimmune Comorbidities. URL: https://classic.clinicaltrials.gov/show/NCT01456416 (Accessed 8 May 2024).	Not a RCT
NCT00939549. High Dose Cyclophosphamide Followed by Glatiramer Acetate in the Treatment of Relapsing Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00939549 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT00288626. High-Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis (HALT MS) Study. URL: https://classic.clinicaltrials.gov/show/NCT00288626 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT00662649. Long-term Efficacy and Safety of Fingolimod (FTY720) in Patients With Relapsing-remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00662649 (Accessed 8 May 2024).	Extension/expansion study
NCT01797965. Long-Term Extension Study in Participants With Multiple Sclerosis Who Have Completed Study 205MS301 (NCT01064401) to Evaluate the Safety and Efficacy of BIIB019. URL: https://classic.clinicaltrials.gov/show/NCT01797965 (Accessed 8 May 2024).	Extension/expansion study
NCT02307838. Long-term Follow-up of Fingolimod Phase II Study Patients. URL: https://classic.clinicaltrials.gov/show/NCT02307838 (Accessed 8 May 2024).	Not a RCT

Citation	Reason for exclusion
NCT03961204. Long-Term Outcomes and Durability of Effect Following Treatment With Cladribine Tablets for MS (CLASSIC-MS). URL: https://classic.clinicaltrials.gov/show/NCT03961204 (Accessed 8 May 2024).	Not a RCT
NCT01134627. Minocycline as add-on to Interferon Beta-1a IFN Beta-1a (Rebif®) in Relapsing-Remitting Multiple Sclerosis RRMS. URL: https://classic.clinicaltrials.gov/show/NCT01134627 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT00097760. Natalizumab in Combination With Glatiramer Acetate (GA) in Patients With Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00097760 (Accessed 8 May 2024).	Not informative to the network - DMT add on
NCT04971005. Ocrelizumab or Alemtuzumab Compared With Autologous Hematopoietic Stem Cell Transplantation in Multiple Sclerosis - a Phase-2 Randomised Controlled Trial. URL: https://classic.clinicaltrials.gov/show/NCT04971005 (Accessed 8 May 2024).	Terminated study
NCT00473213. Optimizing IFN Beta - 1B Dose. URL: https://classic.clinicaltrials.gov/show/NCT00473213 (Accessed 8 May 2024).	Not informative to the network - compares different protocols
NCT01317004. Patients With Relapse Remitting Multiple Sclerosis (RRMS): Candidates for MS Therapy Change. URL: https://classic.clinicaltrials.gov/show/NCT01317004 (Accessed 8 May 2024).	Not informative to the network - compares against switch to chosen iDMT
NCT01464905. Phase 3 Study to Evaluate Efficacy and Safety of NU100 in Patients With Relapsing Remitting Multiple Sclerosis (RRMS). URL: https://classic.clinicaltrials.gov/show/NCT01464905 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT02255656. Phase IIIB-IV Long-Term Follow-up Study for Patients Who Participated in CAMMS03409. URL: https://classic.clinicaltrials.gov/show/NCT02255656 (Accessed 8 May 2024).	Not a RCT
NCT00202995. Randomized Study Designed to Look at Disease Progression Using 2 Currently FDA Approved Drugs for the Treatment of RRMS. URL: https://classic.clinicaltrials.gov/show/NCT00202995 (Accessed 8 May 2024).	No results found
NCT00428584. RNF and Betaseron® Tolerability Study. URL: https://classic.clinicaltrials.gov/show/NCT00428584 (Accessed 8 May 2024).	Does not report on one of the outcomes of interest
NCT05423769. Safety and Effectiveness of Generic Fingolimod (Sphingomod®, Hikma) in Patients With Relapsing-Remitting Multiple Sclerosis in Egypt. URL: https://classic.clinicaltrials.gov/show/NCT05423769 (Accessed 8 May 2024).	Not a RCT
NCT00324506. Safety and Efficacy of Cellcept and Avonex as Combination Treatment in Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00324506 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT01941004. Safety and Efficacy of Fingolimod in MS Patients in China. URL: https://classic.clinicaltrials.gov/show/NCT01941004 (Accessed 8 May 2024).	Withdrawn study
NCT02142205. Safety and Efficacy of Natalizumab (BG00002, Tysabri®) in Russian Participants With Relapsing Remitting Multiple Sclerosis (RRMS). URL: https://classic.clinicaltrials.gov/show/NCT02142205 (Accessed 8 May 2024).	Not a RCT

Citation	Reason for exclusion
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NCT01497262. Safety and Tolerability of Fingolimod in Patients With Relapsing-remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01497262 (Accessed 8 May 2024).	Not a RCT
NCT01874145. Safety and Tolerability of Glatiramer Acetate. URL: https://classic.clinicaltrials.gov/show/NCT01874145 (Accessed 8 May 2024).	Not informative to the network - compares different protocols
NCT00151801. Safety and Tolerability of Interferon-Beta-1a and Estroprogestins Association in MS Patients. URL: https://classic.clinicaltrials.gov/show/NCT00151801 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT00947752. Safety of New Formulation of Glatiramer Acetate. URL: https://classic.clinicaltrials.gov/show/NCT00947752 (Accessed 8 May 2024).	Not informative to the network - compares different protocols
NCT00317941. Safety Study in Relapsing-remitting Multiple Sclerosis (RRMS) Patients Receiving Betaferon or Rebif. URL: https://classic.clinicaltrials.gov/show/NCT00317941 (Accessed 8 May 2024).	Not informative to the network - compares brands
NCT00559702. Safety Study of Natalizumab to Treat Multiple Sclerosis (MS). URL: https://classic.clinicaltrials.gov/show/NCT00559702 (Accessed 8 May 2024).	Not informative to the network - compares different protocols
NCT01808885. Safety Study of Olesoxime in Patients With Stable Relapsing Remitting Multiple Sclerosis Treated With Interferon Beta. URL: https://classic.clinicaltrials.gov/show/NCT01808885 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00429442. Simvastatin as an add-on Treatment to Copaxone for the Treatment of Relapsing Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00429442 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT00492765. Simvastatin as an Add-on Treatment to Interferon-beta-1a for the Treatment of Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00492765 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
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Citation	Reason for exclusion
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NCT00525668. Sunphenon Epigallocatechin-gallate (EGCg) in Relapsing-remitting Multiple Sclerosis (SuniMS Study). URL: https://classic.clinicaltrials.gov/show/NCT00525668 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT01285401. Supplementation of VigantOL® Oil Versus Placebo as Add-on in Patients With Relapsing Remitting Multiple Sclerosis Receiving Rebif® Treatment. URL: https://classic.clinicaltrials.gov/show/NCT01285401 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT01005095. The Effects of Interferon Beta Combined With Vitamin D on Relapsing Remitting Multiple Sclerosis Patients. URL: https://classic.clinicaltrials.gov/show/NCT01005095 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT03500328. Traditional Versus Early Aggressive Therapy for Multiple Sclerosis Trial. URL: https://classic.clinicaltrials.gov/show/NCT03500328 (Accessed 8 May 2024).	Did not evaluate intervention of interest
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Newsome S, Kieseier B, Arnold D, et al. 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. Journal of neurology. 2016;263(9):1778-87. doi:10.1007/s00415-016-8182-4.	Extension/expansion study
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Citation	Reason for exclusion
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Per-002-12. *A 4-Month, Open-Label, Multicenter Study To Explore The Safety And Tolerability Of Fingolimod 0.5 Mg In Patients With Relapsing-Remitting Multiple Sclerosis*.2012. URL: https://www.ins.gob.pe/ensayosclinicos/rpec/recuperarECPBNuevoEN.asp?numec=002-12 (Accessed 8 May 2024).	Not a RCT
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Citation	Reason for exclusion
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O'Connor P, Goodman A, Willmer-Hulme A, et al. Randomized multicenter trial of natalizumab in acute MS relapses: clinical and MRI effects. Neurology. 2004;62(11):2038-43. doi:10.1212/01.wnl.0000128136.79044.d6.	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
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Popova E, Boiko A, Vasil'ev A, et al. [Results of a comparative clinical trial of the Russian Beta - interferon-1b bioanalogue (infibeta)]. Zhurnal nevrologii i psikhiatrii imeni S.S. Korsakova. 2012;112(5):56-61.	Not informative to the network - compares brands
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Citation	Reason for exclusion
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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. Multiple sclerosis international. 2015;2015:369348. doi:10.1155/2015/369348.	Extension/expansion study
Rivera V. [The treatment of multiple sclerosis with beta-interferon 1a]. Tratamiento de la esclerosis multiple con interferon-beta 1a. 2000;31(5):470-1.	MS but not >90% RRMS
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Citation	Reason for exclusion
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Siger-Zajdel M, Lewanska M, Zaleski K, et al. [Open trial of the effectiveness of interferon beta 1a (Avonex) in the treatment of multiple sclerosis in Poland: MRI results]. Badanie otwarte oceny skutecznosci dzialania interferonu beta 1A (Avonexu) w leczeniu stwardnienia rozsianego w Polsce. Wyniki analizy badania rezonansu magnetycznego. 2003;37(6):1185-97.	Can't locate
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Singer B, Bandari D, Cascione M, et al. Comparative injection-site pain and tolerability of subcutaneous serum-free formulation of interferonbeta-1a versus subcutaneous interferonbeta-1b: results of the randomized, multicenter, Phase IIIb REFORMS study. BMC neurology. 2012;12:154. doi:10.1186/1471-2377-12-154.	Does not report on one of the outcomes of interest
Soilu-Hanninen M, Aivo J, Lindstrom B, et al. A randomised, double blind, placebo controlled trial with vitamin D3 as an add on treatment to interferon beta-1b in patients with multiple sclerosis. Journal of neurology, neurosurgery, and psychiatry. 2012;83(5):565-71. doi:10.1136/jnnp-2011-301876.	Not informative to the network - non DMT add on
Sorensen P, Lisby S, Grove R, et al. Safety and efficacy of ofatumumab in relapsing-remitting multiple sclerosis: a phase 2 study. Neurology. 2014;82(7):573-81. doi:10.1212/wnl.0000000000000125.	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
Sorensen P, Lycke J, Eralinna J, et al. Simvastatin as add-on therapy to interferon beta-1a for relapsing-remitting multiple sclerosis (SIMCOMBIN study): a placebo-controlled randomised phase 4 trial. The Lancet. Neurology. 2011;10(8):691-701. doi:10.1016/s1474-4422(11)70144-2.	Not informative to the network - non DMT add on
Sorensen P, Mellgren S, Svenningsson A, et al. NORdic trial of oral Methylprednisolone as add-on therapy to Interferon beta-1a for treatment of relapsing-remitting Multiple Sclerosis (NORMIMS study): a randomised, placebo-controlled trial. The Lancet. Neurology. 2009;8(6):519-29. doi:10.1016/s1474-4422(09)70085-7.	Not informative to the network - non DMT add on

Citation	Reason for exclusion
Sorensen P, Sellebjerg F, Lycke J, et al. Minocycline added to subcutaneous interferon beta-1a in multiple sclerosis: randomized RECYCLINE study. European journal of neurology. 2016;23(5):861-70. doi:10.1111/ene.12953.	Not informative to the network - non DMT add on
Steingo B, Al Malik Y, Bass A, et al. Long-term efficacy and safety of alemtuzumab in patients with RRMS: 12-year follow-up of CAMMS223. Journal of neurology. 2020;267(11):3343-3353. doi:10.1007/s00415-020-09983-1.	Extension/expansion study
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. Multiple sclerosis (Houndmills, Basingstoke, England). 2009;15(6):767-70. doi:10.1177/1352458509103610.	MS but not >90% RRMS
Stepien A, Chalimoniuk M, Lubina-Dabrowska N, Chrapusta S, Galbo H, Langfort J. Effects of interferon beta-1a and interferon beta-1b monotherapies on selected serum cytokines and nitrite levels in patients with relapsing-remitting multiple sclerosis: a 3-year longitudinal study. Neuroimmunomodulation. 2013;20(4):213-22. doi:10.1159/000348701.	Not a RCT
NCT05834855. *Non-inferiority Study of Rituximab Compared to Ocrelizumab in Relapsing MS*.2023. URL: https://clinicaltrials.gov/show/NCT05834855 (Accessed 8 May 2024).	Did not evaluate intervention of interest
jRCT2031210175. *Protocol Number; COMB157G1401*.2021. URL: https://jrct.niph.go.jp/latest-detail/jRCT2031210175 (Accessed 8 May 2024).	Extension/expansion study
Svenningsson A, Frisell T, Burman J, et al. Safety and efficacy of rituximab versus dimethyl fumarate in patients with relapsing-remitting multiple sclerosis or clinically isolated syndrome in Sweden: a rater-blinded, phase 3, randomised controlled trial. The Lancet. Neurology. 2022;21(8):693-703. doi:10.1016/s1474-4422(22)00209-5.	Did not evaluate intervention of interest
2011-000888-27. *A clinical trial comparing the efficacy, and safety and tolerability of two disease modifying MS drugs (GTR and Copaxone®) in patients with relapsing remitting multiple sclerosis for 9 months followed by a 15 month GTR treatment part to evaluate efficacy and safety of long-term GTR treatment*.2011. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-000888-27 (Accessed 8 May 2024).	Not informative to the network - compares brands
2013-002082-19. *A clinical study in subjects with relapsing-remitting multiple sclerosis (RRMS) to assess the efficacy, safety and tolerability of two oral doses of laquinimod either of 0.6 mg/day or 1.2mg/day (experimental drug) as compared to Interferon ß-1a (Avonex, authorised drug) administered once weekly*.2013. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-002082-19 (Accessed 8 May 2024).	Comparator not informative to the network
2006-002037-20. *A multi-national, multi-centre, randomized, parallel-group, double-blind study to compare the efficacy, tolerability and safety of Glatiramer Acetate Injection 40 mg/ml to that of Glatiramer Acetate Injection 20 mg/ml administered once daily by subcutaneous injection in subjects with relapsing remitting (RR) Multiple Sclerosis (MS) - FORTE*.2006. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-002037-20 (Accessed 8 May 2024).	Not informative to the network - compares different protocols
2011-005550-57. *A clinical study in patients with multiple sclerosis to assess the efficacy, safety and tolerability of Glatiramer Acetate (GA) 20 mg/0.5 ml (experimental drug)*.2012. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-005550-57 (Accessed 8 May 2024).	Terminated study

Citation	Reason for exclusion
Togha M, Karvigh S, Nabavi M, et al. Simvastatin treatment in patients with relapsing-remitting multiple sclerosis receiving interferon beta 1a: a double-blind randomized controlled trial. Multiple sclerosis (Houndmills, Basingstoke, England). 2010;16(7):848-54. doi:10.1177/1352458510369147.	Not informative to the network - non DMT add on
Toghianifar N, Ashtari F, Zarkesh-Esfahani S, Mansourian M. Effect of high dose vitamin D intake on interleukin-17 levels in multiple sclerosis: a randomized, double-blind, placebo-controlled clinical trial. Journal of neuroimmunology. 2015;285:125-8. doi:10.1016/j.jneuroim.2015.05.022.	Not informative to the network - non DMT add on
Toorop A, van Lierop Z, Gelissen L, et al. Prospective trial of natalizumab personalised extended interval dosing by therapeutic drug monitoring in relapsing-remitting multiple sclerosis (NEXT-MS). Journal of neurology, neurosurgery, and psychiatry. 2024;95(5):392-400. doi:10.1136/jnnp-2023-332119.	Not a primary study
Tremlett H. Randomized multicenter trial of natalizumab in acute MS relapses: clinical and MRI effects. Neurology. 2005;64(1):174-5. doi:10.1212/wnl.64.1.174.	Not a primary study
Trojano M, Ramio-Torrenta L, Grimaldi L, et al. A randomized study of natalizumab dosing regimens for relapsing-remitting multiple sclerosis. Multiple sclerosis (Houndmills, Basingstoke, England). 2021;27(14):2240-2253. doi:10.1177/13524585211003020.	Did not evaluate intervention of interest
2006-004937-13. *multicentee randomized controlled study of azathioprine versus iterferon beta in relapsing remitting multiple sclerosis - M.A.I.N. trial*.2007. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-004937-13 (Accessed 8 May 2024).	Not a primary study
2017-005129-18. *Clinical trial to evaluate the effectiveness and safety of IFN beta-1a (IFN beta-1a), injected once a week via intramuscolar (i.m.), and glatiramer-acetate (GA) in children/adolescent patients with multiple sclerosis*.2018. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-005129-18 (Accessed 8 May 2024).	RRMS but not in adults
2014-000709-10. *Investigation on how alemtuzumab acts in patients with relapsing remitting multiple sclerosis*.2014. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-000709-10 (Accessed 8 May 2024).	Not a RCT
NCT04578639. *Ocrelizumab VErsus Rituximab Off-Label at the Onset of Relapsing MS Disease*.2020. URL: https://clinicaltrials.gov/ct2/show/NCT04578639 (Accessed 8 May 2024).	Did not evaluate intervention of interest
2016-001166-29. *A randomised controlled trial to compare ocrelizumab or alemtuzumab with autologous hematopoietic stem cell transplantation (aHSCT) in high inflammatory multiple sclerosis (COAST)*.2019. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-001166-29 (Accessed 8 May 2024).	Terminated study
2013-002378-26. *Switch To RItuXimab in MS extension An extension study of an ongoing clinical trial where people with multiple sclerosis switch therapy from interferon or glatiramere injections to rituximab, a monoclonal antibody that eliminate B lymphocytes*.2013. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-002378-26 (Accessed 8 May 2024).	Did not evaluate intervention of interest

Citation	Reason for exclusion
Valenzuela B, Olsson Gisleskog P, Poggesi I, et al. An exposure-response analysis of ponesimod clinical efficacy in a randomized phase III study in patients with relapsing multiple sclerosis. CPT: pharmacometrics & systems pharmacology. 2022;11(10):1294-1304. doi:10.1002/psp4.12778.	Does not report on one of the outcomes of interest
Van Wijmeersch B, Singer B, Boster A, et al. Efficacy of alemtuzumab over 6 years in relapsing-remitting multiple sclerosis patients who relapsed between courses 1 and 2: Post hoc analysis of the CARE-MS studies. Multiple Sclerosis Journal. 2020;26(13):1719-1728. doi:10.1177/1352458519881759.	Extension/expansion study
Vermersch P, Czlonkowska A, Grimaldi L, et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. Multiple sclerosis (Houndmills, Basingstoke, England). 2014;20(6):705-16. doi:10.1177/1352458513507821.	Comparator not informative to the network
Vermersch P, Scaramozza M, Levin S, et al. Effect of Dimethyl Fumarate vs Interferon beta-1a in Patients With Pediatric-Onset Multiple Sclerosis: The CONNECT Randomized Clinical Trial. JAMA network open. 2022;5(9):e2230439. doi:10.1001/jamanetworkopen.2022.30439.	MS but not >90% RRMS
Irct201705108323N. *Evaluating the efficacy and side effects fingolimod in 3 -year follow-up of patients with recurrent forms of multiple sclerosis*.2017. URL: http://en.irct.ir/trial/8804 (Accessed 8 May 2024).	Not a RCT
Irct201112267419N. *Randomized, open labeled, multicenter study evaluating safety Fingolide® in patients with Relapsing-Remitting Multiple Sclerosis*.2012. URL: http://en.irct.ir/trial/7881 (Accessed 8 May 2024).	Not a RCT
Irct201406018323N. *The evaluation of the efficacy and safety of oral fingolimod in relapsing remitting multiple sclerosis*.2015. URL: http://en.irct.ir/trial/8799 (Accessed 8 May 2024).	Not a RCT
Vollmer T, Cohen J, Alvarez E, et al. Safety results of administering ocrelizumab per a shorter infusion protocol in patients with primary progressive and relapsing multiple sclerosis. Multiple sclerosis and related disorders. 2020;46:102454. doi:10.1016/j.msard.2020.102454.	Comparator not informative to the network
Vollmer T, Panitch H, Bar-Or A, et al. Glatiramer acetate after induction therapy with mitoxantrone in relapsing multiple sclerosis. Multiple sclerosis (Houndmills, Basingstoke, England). 2008;14(5):663-70. doi:10.1177/1352458507085759.	Did not evaluate intervention of interest
Vollmer T, Sorensen P, Selmaj K, et al. A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. Journal of neurology. 2014;261(4):773-83. doi:10.1007/s00415-014-7264-4.	Comparator not informative to the network
Voskuhl R, Wang H, Wu T, et al. 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. doi:10.1016/s1474-4422(15)00322-1.	Not informative to the network - non DMT add on
NCT04458688. *Investigating the Effect of Ocrelizumab in African Americans and Caucasians With Relapsing Multiple Sclerosis*.2020. URL: https://clinicaltrials.gov/show/NCT04458688 (Accessed 8 May 2024).	Not a RCT

Citation	Reason for exclusion
Wolinsky J, Borresen T, Dietrich D, et al. 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. doi:10.1016/j.msard.2015.06.005.	Did not evaluate intervention of interest
Wray S, Then Bergh F, Wundes A, et al. Efficacy and Safety Outcomes with Diroximel Fumarate After Switching from Prior Therapies or Continuing on DRF: Results from the Phase 3 EVOLVE-MS-1 Study. Advances in therapy. 2022;39(4):1810-1831. doi:10.1007/s12325-022-02068-7.	Did not evaluate intervention of interest
Wroe S. Effects of dose titration on tolerability and efficacy of interferon beta-1b in people with multiple sclerosis. The Journal of international medical research. 2005;33(3):309-18. doi:10.1177/147323000503300306.	Not informative to the network - compares different protocols
Wynn D, Kaufman M, Montalban X, et al. Daclizumab in active relapsing multiple sclerosis (CHOICE study): a phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta. The Lancet. Neurology. 2010;9(4):381-90. doi:10.1016/s1474-4422(10)70033-8.	Not informative to the network - non DMT add on
Wynn D, Meyer C, Allen N, O'Brien D. Optimal dosing of immunomodulating drugs: A dose-comparison study of GA in RRMS. Progress in Neurotherapeutics and Neuropsychopharmacology. 2008;3(1):137-151. doi:10.1017/s1748232107000110.	Not informative to the network - drug of interest but not in a licensed dose
2012-003735-32. *Study to compare the efficacy and/or safety of masitinib to interferon beta-1a, interferon beta-1b, peginterferon beta-1a or glatiramer acetate in patients with relapsing remitting multiple sclerosis with unsatisfactory response to these first line treatments*.2015. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-003735-32 (Accessed 8 May 2024).	Terminated study
2021-005746-15. *A Rollover Study to Evaluate the Long-Term Safety and Efficacy of Ocrelizumab In Patients with Multiple Sclerosis*.2022. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2021-005746-15 (Accessed 8 May 2024).	Not a RCT
2020-004128-41. *A Study to Evaluate Safety and Efficacy of Ocrelizumab in Comparison with Fingolimod in Children and Adolescents with Relapsing-Remitting Multiple Sclerosis*.2021. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-004128-41 (Accessed 8 May 2024).	RRMS but not in adults
2015-005597-38. *A Study to Evaluate the Efficacy and Safety of Ocrelizumab in Patients With Relapsing Remitting Multiple Sclerosis*.2016. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-005597-38 (Accessed 8 May 2024).	Not an RCT
2020-000893-69. *A Study to Evaluate the Efficacy, Safety and Pharmacokinetics of a Higher Dose of Ocrelizumab in Adults with Relapsing Multiple Sclerosis*.2020. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-000893-69 (Accessed 8 May 2024).	Not informative to the network - compares different protocols

Citation	Reason for exclusion
32113. *A Phase IIIB, Double Blind, Placebo-Controlled, Multcenter, Parallel Group, Extension Trial to Evaluate the Safety and Tolerability of Oral Cladribine in Subjects with Relapsing-Remitting Multiple Sclerosis Who Have Completed Trial 25643 (Clarity)*.2008. URL: https://onderzoekmetmensen.nl/en/trial/32113 (Accessed 8 May 2024).	Extension/expansion study
2010-024017-31. *A 6-month, Randomized, Active Comparator, Open-label, Multi-Center Study to Evaluate Patient OutComes, Safety and Tolerability of Fingolimod (FTY720) 0.5 mg/day in Patients with Relapsing Remitting Multiple Sclerosis who are candidates for MS therapy change from Previous Disease Modifying Therapy - GOLDEN*.2011. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-024017-31 (Accessed 8 May 2024).	Comparator not informative to the network
2014-001012-19. *Effects of fingolimod on advanced brain measures and clinical measures in multiple sclerosis*.2014. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-001012-19 (Accessed 8 May 2024).	Not a RCT
Zarbin M, Jampol L, Jager R, et al. Ophthalmic evaluations in clinical studies of fingolimod (FTY720) in multiple sclerosis. Ophthalmology. 2013;120(7):1432-9. doi:10.1016/j.ophtha.2012.12.040.	Extension/expansion study
Zavalishin I, Gusev E, Iakhno N, et al. [Results of a multicenter study of Rebif-22 mcg administration in Russia]. Rezul'taty multitsentrovogo issledovaniia effektivnosti preparata Rebif-22 mkg v Rossii. 2003;(Spec No 2):73-8.	Not a RCT
Zecca C, Riccitelli G, Calabrese P, et al. Treatment satisfaction, adherence and behavioral assessment in patients de-escalating from natalizumab to interferon beta. BMC neurology. 2014;14:38. doi:10.1186/1471-2377-14-38.	Did not evaluate intervention of interest
Ziemssen T, Bass A, Berkovich R, et al. Efficacy and Safety of Alemtuzumab Through 9 Years of Follow-up in Patients with Highly Active Disease: Post Hoc Analysis of CARE-MS I and II Patients in the TOPAZ Extension Study. CNS drugs. 2020;34(9):973-988. doi:10.1007/s40263-020-00749-x.	Extension/expansion study
Zimmermann C, Walther E, Goebels N, et al. [Interferon beta-1b for treatment of secondary chronic progressive multiple sclerosis]. Interferon beta-1b zur Behandlung der sekundar chronisch progredienten multiplen Sklerose. 1999;70(8):759-63. doi:10.1007/s001150050508.	MS but not >90% RRMS

Studies excluded at full-text screening (Review of Cost-effectiveness)

Table 42 Studies excluded at full-text screening (Review of Cost-effectiveness)

Citation	Reason for exclusion
Ahmad H, Campbell JA, van der Mei I, Taylor BV, Xia Q, Zhao T, et al. Estimating the disutility of relapse in relapsing-remitting and secondary progressive multiple sclerosis using the EQ-5D-5L, AQoL-8D, EQ-5D-5L-psychosocial, and SF-6D: implications for health economic evaluation models. Quality of Life Research 2023;32(12):	Exclude not an economic evaluation
Ahmad H, van der Mei I, Taylor B, Zhao T, Xia Q, Palmer AJ. Does health-related quality of life differ between people with relapse onset and progressive onset Multiple Sclerosis? Multiple Sclerosis and Related Disorders 2021;54	Exclude QoL
Alasdair Millar J. The cost of teriflunomide in the treatment of relapsing remitting multiple sclerosis. New Zealand Medical Journal 2019;132	Exclude RRMS New Zealand
Alharbi MA, Aldosari F, Althobaiti AH, Abdullah FM, Aljarallah S, Alkhawajah NM, et al. Clinical and economic evaluations of natalizumab, rituximab, and ocrelizumab for the management of relapsing-remitting multiple sclerosis in Saudi Arabia. BMC Health Services Research 2023;23(1):	Exclude RRMS Saudia Arabia
Allen F, Montgomery S, Maruszczak M, Kusel J, Adlard N. Convergence yet Continued Complexity: A Systematic Review and Critique of Health Economic Models of Relapsing-Remitting Multiple Sclerosis in the United Kingdom. Value in Health 2015;18(6):	Exclude not an economic evaluation
Allignol A, Boutmy E, Sabido Espin M, Marhardt K, Vermersch P. Effectiveness, Healthcare Resource Utilization and Adherence to Subcutaneous Interferon Beta-1a According to Age in Patients With Multiple Sclerosis: A Cohort Study Using a US Claims Database. Frontiers in neurology [electronic resource] 2021;12	Exclude not an economic evaluation
Alping P, Neovius M, Piehl F, Frisell T. Real-World Healthcare Cost Savings and Reduced Relapse Rate with Off-Label Rituximab versus Disease-Modifying Treatments Approved for Relapsing-Remitting Multiple Sclerosis: A Nationwide Cost-Effectiveness Study. Annals of Neurology 2024;26	Exclude RRMS Sweden
Alsaqa'aby MF, Vaidya V, Khreis N, Al Khairallah T, Al-Jedai AH. Cost-effectiveness of oral agents in relapsing-remitting multiple sclerosis compared to interferon-based therapy in Saudi Arabia. Annals of Saudi Medicine 2017;37	Exclude RRMS Saudi Arabia
Alvarez Ayuso L, Rodriguez Marrodan B, Blasco Quilez MR, Garcia-Merino JA, Sanchez Guerrero A. Economic impact of the new oral treatments for multiple sclerosis. Neurologia 2021;36(2):	Exclude RRMS Spain
Araujo L, Kyatham S, Bzdek KG, Higuchi K, Greene N. Assessing the Health Economic Outcomes from Commercially Insured Relapsing Multiple Sclerosis Patients Who Switched from Other Disease-Modifying Therapies to Teriflunomide, in the United States. Clinicoeconomics & Outcomes Research 2023;15	Exclude not an economic evaluation
Armoiry X, Spath HM, Henaine AM, Dussart C, Counsell C, Connock M. Ocrelizumab not recommended in France for patients with primary progressive multiple sclerosis while recommended in England: a review comparing the assessment by HAS and NICE. Expert Opinion on Biological Therapy 2021;21(6):	Exclude not an economic evaluation
Asadollahi M, Darvishi A, Azimi A, Annabi M, Jafariazar Z, Heshmat R. Economic Burden of Multiple Sclerosis Drugs in Iran during 2011-2019. Iranian Journal of Public Health 2023;52(2):	Exclude MS Iran
Auguste P, Colquitt J, Connock M, Loveman E, Court R, Ciccarelli O, et al. Ocrelizumab for Treating Patients with Primary Progressive Multiple Sclerosis: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. PharmacoEconomics 2020;38(6):	Exclude not an economic evaluation

Citation	Reason for exclusion
Aungsumart S, Apiwattanakul M. Clinical and fringe benefits of rituximab in multiple sclerosis treatment in a poor resource setting: Case series and cost analysis. *Multiple Sclerosis and Related Disorders* 2023;**73**	Exclude MS Thailand
Aungsumart S, Turongkaravee S, Youngkong S, Apiwattanakul M, Thakkinstian A, Chaikledkaew U. Rituximab for the treatment of relapsing-remitting multiple sclerosis in Thailand: an economic evaluation and budget impact analysis. *BMC Health Services Research* 2023;**23**(1):	Exclude MS Thailand
Avxentyev NA, Davydovskaya MV, Makarova YV, Frolov MY, Klabukova DL. [Pharmacoeconomic aspects of using cladribine (in tablets) for treatment of adult patients with remitting multiple sclerosis]. *Farmakoekonomicheskie aspekty primeneniya kladribina dlya lecheniya vzroslykh patsientov s vysokoaktivnym remittiruyushchim rasseyannym sklerozom* 2021;**121**(8): 30-36	Exclude RRMS Russia
Ayati N, Fleifel L, Sharifi S, Sahraian MA, Nikfar S. Cladribine tablets are a cost-effective strategy in high-disease activity relapsing multiple sclerosis patients in Iran. Current Journal of Neurology 2021;20(3):	Exclude RRMS Iran
Baharnoori M, Bhan V, Clift F, Thomas K, Mouallif S, Adlard N, et al. Cost-Effectiveness Analysis of Ofatumumab for the Treatment of Relapsing-Remitting Multiple Sclerosis in Canada. PharmacoEconomics Open 2022;6(6):	Exclude RRMS Canada
Bargiela D, Bianchi MT, Westover MB, Chibnik LB, Healy BC, De Jager PL, et al. Selection of first-line therapy in multiple sclerosis using risk-benefit decision analysis. Neurology 2017;88(7):	Exclude RRMS US
Bayen E, Papeix C, Pradat-Diehl P, Lubetzki C, Joel ME. Patterns of Objective and Subjective Burden of Informal Caregivers in Multiple Sclerosis. *Behavioural Neurology* 2015;**2015**	Exclude not an economic evaluation
Ben-Amor AF, Trochanov A, Fischer TZ. Cumulative Review of Thrombotic Microangiopathy, Thrombotic Thrombocytopenic Purpura, and Hemolytic Uremic Syndrome Reports with Subcutaneous Interferon beta-1a. *Advances in Therapy* 2015;**32**(5):	Exclude not an economic evaluation
Bergamaschi R, Agnello M, Colombo E, Della Giovanna M, Montomoli C, Nava A*, et al.* Detection of clinical relapses in multiple sclerosis cohorts: construction and validation of a model based on administrative data. *Neurological Sciences* 2014;**35**(2):	Exclude RRMS Italy
Bergvall N, Lahoz R, Reynolds T, Korn JR. Healthcare resource use and relapses with fingolimod versus natalizumab for treating multiple sclerosis: a retrospective US claims database analysis. *Current Medical Research & Opinion* 2014;**30**(8):	Exclude MS US
Bhan V, Clift F, Baharnoori M, Thomas K, Patel BP, Blanchette F*, et al.* Cost-consequence analysis of ofatumumab for the treatment of relapsing-remitting multiple sclerosis in Canada. *Journal of Comparative Effectiveness Research* 2023;**12**(9):	Exclude RRMS Canada
Blackney M, Kelly M, Zeidman R, Andreykiv M, Plich A. The Cost Burden of Switching Patients with Relapsing-Remitting Multiple Sclerosis from Glatiramer Acetate To Newly-Approved Disease Modifying Therapies. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2014;**17**(7): A393	Exclude abstract only
Bogosian A, Chadwick P, Windgassen S, Norton S, McCrone P, Mosweu I*, et al.* Distress improves after mindfulness training for progressive MS: A pilot randomised trial. *Multiple Sclerosis* 2015;**21**(9):	Exclude not an economic evaluation
Bohlega S, Elboghdady A, Al-Johani A, Mahajan K, Mughari MK, Al-Saqa'aby M*, et al.* Economic Evaluation of Cladribine Tablets in Patients With High Disease Activity-Relapsing-Remitting Multiple Sclerosis in the Kingdom of Saudi Arabia. *Value in Health Regional Issues* 2021;**25**	Exclude RRMS Saudi Arabia
Bowen JD, Kozma CM, Grosso MM, Phillips AL. A real-world comparison of relapse rates, healthcare costs and resource use among patients with multiple sclerosis newly initiating subcutaneous interferon beta-1a versus oral disease-modifying drugs. *Multiple Sclerosis Journal Experimental Translational & Clinical* 2018;**4**(4):	Exclude MS US
Bozkaya D, Livingston T, Migliaccio-Walle K, Odom T. The cost-effectiveness of disease-modifying therapies for the treatment of relapsing-remitting multiple sclerosis. *Journal of Medical Economics* 2017;**20**(3):	Exclude RRMS US

Citation	Reason for exclusion
Brown LJ, Li J, Brunner M, Snoke M, La HA. Societal costs of primary progressive multiple sclerosis in Australia and the economic impact of a hypothetical disease-modifying treatment that could delay disease progression. *Journal of Medical Economics* 2021;**24**(1):	Exclude PPMS Australia
Bruno D, Marc D, Ouarda P, Dominique S, Marc S, Laurene C*, et al.* Economic burden of multiple sclerosis in France estimated from a regional medical registry and national sick fund claims. *Multiple Sclerosis and Related Disorders* 2019;**36**	Exclude MS France
Burks J, Marshall TS, Ye X. Adherence to disease-modifying therapies and its impact on relapse, health resource utilization, and costs among patients with multiple sclerosis. *Clinicoeconomics & Outcomes Research* 2017;**9**	Exclude MS US
Burt RK, Tappenden P, Han X, Quigley K, Arnautovic I, Sharrack B*, et al.* Health economics and patient outcomes of hematopoietic stem cell transplantation versus disease-modifying therapies for relapsing remitting multiple sclerosis in the United States of America. *Multiple Sclerosis and Related Disorders* 2020;**45**	Exclude RRMS US
Cabreira V, Abreu P, Maia C, Costa A, Sa MJ. Trends in hospital readmissions in Multiple Sclerosis patients between 2009 and 2015. *Multiple Sclerosis and Related Disorders* 2020;**45**	Exclude not an economic evaluation
CADTH drug review of Ofatumumab (Kesimpta) submitted by Novartis	Exclude RRMS Canada
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Michel M, Le Page E, Laplaud DA, Wardi R, Lebrun C, Zagnoli F*, et al.* Cost-utility of oral methylprednisolone in the treatment of multiple sclerosis relapses: Results from the COPOUSEP trial. *Revue Neurologique* 2022;**178**(3):	Exclude RRMS France
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Michels RE, de Fransesco M, Mahajan K, Hengstman GJD, Schiffers KMH, Budhia S. Cost Effectiveness of Cladribine Tablets for the Treatment of Relapsing-Remitting Multiple Sclerosis in the Netherlands. *Applied Health Economics and Health Policy* 2019;**17**(6):	Exclude RRMS Netherlands
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Moccia M, Palladino R, Lanzillo R, Carotenuto A, Russo CV, Triassi M*, et al.* Healthcare Costs for Treating Relapsing Multiple Sclerosis and the Risk of Progression: A Retrospective Italian Cohort Study from 2001 to 2015. *PLoS ONE [Electronic Resource]* 2017;**12**(1):	Exclude RRMS Italy
Moccia M, Palladino R, Lanzillo R, Triassi M, Brescia Morra V. Predictors of the 10-year direct costs for treating multiple sclerosis. *Acta Neurologica Scandinavica* 2017;**135**(5):	Exclude RRMS Italy
Montgomery S, Woodhouse F, Vudumula U, Gudala K, Duddy M, Kroes M. Stick or twist? Cost-effectiveness of siponimod compared with continuing existing disease-modifying therapies in the treatment of active secondary progressive multiple sclerosis in the UK. *Journal of medical economics* 2022;**25**(1): 669-678	Exclude Intervention
Moccia M, Santoni L, Vaccari I, Affinito G, Caliendo D, Rubba F*, et al.* Utilization of peginterferon-beta-1a in the real-world practice for relapsing-remitting multiple sclerosis. *European Review for Medical & Pharmacological Sciences* 2024;**28**(1):	Exclude RRMS Italy
Montgomery S, Woodhouse F, Vudumula U, Gudala K, Duddy M, Kroes M. Stick or twist? Cost-effectiveness of siponimod compared with continuing existing disease-modifying therapies in the treatment of active secondary progressive multiple sclerosis in the UK. *Journal of Medical Economics* 2022;**25**(1):	Exclude SPMS UK

Citation	Reason for exclusion
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Nagpal A, Milte R, Kim SW, Hillier S, Hamilton-Bruce MA, Ratcliffe J*, et al.* Economic Evaluation of Stem Cell Therapies in Neurological Diseases: A Systematic Review. *Value in Health* 2019;**22**(2):	Exclude SPMS
Najafi B, Ghaderi H, Jafari M, Najafi S, Ahmad Kiadaliri A. Cost effectiveness analysis of Avonex and CinnoVex in Relapsing Remitting MS. *Global Journal of Health Science* 2014;**7**(2):	Exclude RRMS Iran
Nakhaipour HR, Vudumula U, Khurana V, Sebire G, Mah JK, Pohl D*, et al.* Cost-effectiveness of fingolimod versus interferon-beta1a for the treatment of pediatric-onset multiple sclerosis in Canada. *Journal of Medical Economics* 2020;**23**(12):	Exclude MS Canada
Navarro CE, Betancur JE. Cost-Utility Analysis Comparing Ocrelizumab Versus Rituximab in the Treatment of Relapsing-Remitting Multiple Sclerosis: The Colombian Perspective. *Value in Health Regional Issues* 2023;**36**	Exclude RRMS Colombia
Navarro CE, Ordonez-Callamand E, Alzate JP. Disease modifying therapies in multiple sclerosis: cost-effectiveness systematic review. *Farmacia Hospitalaria* 2020;**44**(2):	Exclude RRMS Colombia
Nazareth T, Datar M, Yu TC. Treatment Effectiveness for Resolution of Multiple Sclerosis Relapse in a US Health Plan Population. *Neurology & Therapy* 2019;**8**(2):	Exclude MS US
Ness NH, Schriefer D, Haase R, Ettle B, Cornelissen C, Ziemssen T. Differentiating societal costs of disability worsening in multiple sclerosis. *Journal of Neurology* 2020;**267**(4):	Exclude not an economic evaluation
Ness NH, Schriefer D, Haase R, Ettle B, Cornelissen C, Ziemssen T. Differentiating societal costs of disability worsening in multiple sclerosis. *Journal of Neurology* 2020;**267**(4):	Exclude RRMS Germany
Neuberger EE, Abbass IM, Jones E, Engmann NJ. Work Productivity Outcomes Associated with Ocrelizumab Compared with Other Disease-Modifying Therapies for Multiple Sclerosis. *Neurology & Therapy* 2021;**10**(1):	Exclude not an economic evaluation
Nicholas J, Zhou H, Deshpande C. Annual Cost Burden by Level of Relapse Severity in Patients with Multiple Sclerosis. *Advances in Therapy* 2021;**38**(1):	Exclude not an economic evaluation
Nicholas JA, Electricwala B, Lee LK, Johnson KM. Burden of relapsing-remitting multiple sclerosis on workers in the US: a cross-sectional analysis of survey data. *BMC Neurology* 2019;**19**(1):	Exclude RRMS US
O'Connell K, Kelly SB, Fogarty E, Duggan M, Buckley L, Hutchinson M*, et al.* Economic costs associated with an MS relapse. *Multiple Sclerosis and Related Disorders* 2014;**3**(6):	Exclude RRMS Republic of Ireland
O'Day K, Meyer K, Stafkey-Mailey D, Watson C. Cost-effectiveness of natalizumab vs fingolimod for the treatment of relapsing-remitting multiple sclerosis: analyses in Sweden. *Journal of Medical Economics* 2015;**18**(4):	Exclude RRMS Sweden
Owens GM. Economic burden of multiple sclerosis and the role of managed sare organizations in multiple sclerosis management. *American Journal of Managed Care* 2016;**22**(6):	Exclude not an economic evaluation
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Palmer AJ, Zhao T, Taylor BV, van der Mei I, Campbell JA. Exploring the cost-effectiveness of EBV vaccination to prevent multiple sclerosis in an Australian setting. *Journal of Neurology, Neurosurgery & Psychiatry* 2024;**95**(5):	Exclude MS Australia

Citation	Reason for exclusion
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Pastor-Quiros LJ, Correa-Diaz EP. The budgetary impact of alemtuzumab in multiple sclerosis in Quito, Ecuador. Payer's perspective. *Global & Regional Health Technology Assessment* 2021;**8**	Exclude RRMS Ecuador
Perrone V, Veronesi C, Giacomini E, Citraro R, Dell'Orco S, Lena F*, et al.* The Epidemiology, Treatment Patterns and Economic Burden of Different Phenotypes of Multiple Sclerosis in Italy: Relapsing-Remitting Multiple Sclerosis and Secondary Progressive Multiple Sclerosis. *Clinical Epidemiology* 2022;**14**	Exclude not an economic evaluation
Petruzzo M, Palladino R, Nardone A, Nozzolillo A, Servillo G, Orlando V*, et al.* The impact of diagnostic criteria and treatments on the 20-year costs for treating relapsing-remitting multiple sclerosis. *Multiple Sclerosis and Related Disorders* 2020;**38**	Exclude not an economic evaluation
Pharmacoeconomic Review Report: Daclizumab (Zinbryta) [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017 Jul. APPENDIX 4, Reviewer Worksheets. Available from: https://www.ncbi.nlm.nih.gov/books/NBK535202/	Exclude RRMS Canada
Philbin M, Niewoehner J, Wan GJ. Clinical and Economic Evaluation of Repository Corticotropin Injection: A Narrative Literature Review of Treatment Efficacy and Healthcare Resource Utilization for Seven Key Indications. *Advances in Therapy* 2017;**34**(8):	Exclude not an economic evaluation
Piccinni C, Ronconi G, Calabria S, Dondi L, Forcesi E, Rossi E*, et al.* Healthcare resources utilisation in primary progressive multiple sclerosis. *Neurological Sciences* 2018;**39**(7):	Exclude not an economic evaluation
Piena MA, Schoeman O, Harty GT, Wong SL. Desirability and acceptability of a treatment-sequencing model in relapsing-remitting multiple sclerosis: A health technology assessment perspective. *International Journal of Technology Assessment in Health Care* 2020;**36**(2):	Exclude RRMS Netherlands
Pinheiro B, Guerreiro R, Costa J, Miguel LS. Cost-effectiveness of cladribine tablets versus fingolimod in patients with highly active relapsing multiple sclerosis in Portugal. *Journal of Medical Economics* 2020;**23**(5):	Exclude RRMS Portugal
Pinol C. [Cost-effectiveness analysis of interferon beta-1b as treatment for patients with clinically isolated syndrome suggestive of multiple sclerosis in Spain]. *Neurologia* 2016;**31**(4):	Exclude MS Spain
Pipek LZ, Mahler JV, Nascimento RFV, Apostolos-Pereira SL, Silva GD, Callegaro D. Cost, efficacy, and safety comparison between early intensive and escalating strategies for multiple sclerosis: A systematic review and meta-analysis. *Multiple Sclerosis and Related Disorders* 2023;**71**	Exclude not an economic evaluation
Pipek LZ, Mahler JV, Nascimento RFV, Becker J, Apostolos-Pereira SL, Adoni T*, et al.* The myths that drive therapeutic inertia in multiple sclerosis: a cost-effectiveness analysis of high-efficacy drugs in Brazil. *Arquivos de Neuro-Psiquiatria* 2024;**82**(1):	Exclude not an economic evaluation
Polistena B, Spandonaro F, Capra R, Fantaccini S, Santoni L, Zimatore GB*, et al.* The societal impact of treatment with natalizumab of relapsing-remitting multiple sclerosis in Italian clinical practice: The Tysabri PharmacoEconomics (TyPE) Study. *Global and Regional Health Technology Assessment* 2019	Exclude RRMS Italy
Ponzio M, Gerzeli S, Brichetto G, Bezzini D, Mancardi GL, Zaratin P*, et al.* Economic impact of multiple sclerosis in Italy: focus on rehabilitation costs. *Neurological Sciences* 2015;**36**(2):	Exclude not an economic evaluation
Poudel N, Banjara B, Kamau S, Frost N, Ngorsuraches S. Factors influencing patients' willingness-to-pay for disease-modifying therapies for multiple sclerosis. *Multiple Sclerosis and Related Disorders* 2021;**48**	Exclude not an economic evaluation
Poveda JL, Trillo JL, Rubio-Terres C, Rubio-Rodriguez D, Polanco A, Torres C. Cost-effectiveness of Cladribine Tablets and fingolimod in the treatment of relapsing multiple sclerosis with high disease activity in Spain. *Expert Review of Pharmacoeconomics & Outcomes Research* 2020;**20**(3):	Exclude MS Spain

Citation	Reason for exclusion
Prathapan V, Eipert P, Wigger N, Kipp M, Appali R, Schmitt O. Modeling and simulation for prediction of multiple sclerosis progression. *Computers in Biology & Medicine* 2024;**175**	Exclude not an economic evaluation
Purmonen T, Hakkarainen T, Tervomaa M, Ruutiainen J. Impact of multiple sclerosis phenotypes on burden of disease in Finland. *Journal of Medical Economics* 2020;**23**(2):	Exclude not an economic evaluation
Quiros LP, Ugalde R. A budget impact analysis of alemtuzumab as second-line treatment, compared with natalizumab and fingolimod, in patients previously treated with interferon beta 1b, diagnosed with active relapsing remitting multiple sclerosis, treated under the Costa Rican Social Security. [Spanish]. *Global and Regional Health Technology Assessment* 2019	Exclude RRMS Costa Rica
Rahimi F, Rasekh HR, Abbasian E, Peiravian F, Etemadifar M, Ashtari F*, et al.* Patient preferences for interferon-beta in Iran: A discrete choice experiment. *PLoS ONE* 2018;**13**	Exclude not an economic evaluation
Rahn AC, Kopke S, Kasper J, Vettorazzi E, Muhlhauser I, Heesen C. Evaluator-blinded trial evaluating nurse-led immunotherapy DEcision Coaching In persons with relapsing-remitting Multiple Sclerosis (DECIMS) and accompanying process evaluation: study protocol for a cluster randomised controlled trial. *Trials* 2015;**16**	Exclude not an economic evaluation
Ravangard R, Rezaee M, Keshavarz K, Borhanihaghighi A, Izadi S. Cost-effectiveness and cost-utility of cinnovex versus recigen in patients with relapsing-remitting multiple sclerosis in Iran. *Shiraz E Medical Journal* 2018;**19**	Exclude RRMS Iran
Reen GK, Silber E, Langdon DW. Multiple sclerosis patients' understanding and preferences for risks and benefits of disease-modifying drugs: A systematic review. *Journal of the Neurological Sciences* 2017;**375**	Exclude not an economic evaluation
Rezaee M, Izadi S, Keshavarz K, Borhanihaghighi A, Ravangard R. Fingolimod versus natalizumab in patients with relapsing remitting multiple sclerosis: a cost-effectiveness and cost-utility study in Iran. *Journal of Medical Economics* 2019;**22**(4):	Exclude RRMS Iran
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Rodriguez-Regal A, Ramos-Rua L, Anibarro-Garcia L, Lopez Real AM, Amigo-Jorrin MDC. Effectiveness of Dimethyl Fumarate in Real-World Clinical Practice and Strategy to Minimize Adverse Effects and Use of Healthcare Resources. *Patient preference & adherence* 2021;**15**	Exclude not an economic evaluation
Rojas JI, Carnero Contentti E, Alonso R, Tavolini D, Burgos M, Federico B*, et al.* Burden of treatment and quality of life in relapsing remitting multiple sclerosis patients under early high efficacy therapy in Argentina: Data from the Argentinean registry. *Multiple Sclerosis and Related Disorders* 2024;**85**	Exclude RRMS Argentina
Romero-Pinel L, Bau L, Matas E, Leon I, Juvany R, Jodar R*, et al.* Cost associated with a relapse-free patient in multiple sclerosis: A real-world health indicator. *PLoS ONE [Electronic Resource]* 2022;**17**(4):	Exclude RRMS Spain
Rot U, Horvat-Ledinek A, Sega-Jazbec S. The economic burden of multiple sclerosis. [Slovene]. *Zdravniski Vestnik* 2014;**83**	Exclude MS Slovenia
Ruggeri M, D'Ausilio A, Lo Muto R, Cottone S, Ghezzi A, Mecozzi A*, et al.* Budget Impact Analysis of Fingolimod in Relapsing Remitting Multiple Sclerosis. *Value in Health* 2014;**17**(7):	Exclude not an economic evaluation
Ruutiainen J, Viita AM, Hahl J, Sundell J, Nissinen H. Burden of illness in multiple sclerosis (DEFENSE) study: the costs and quality-of-life of Finnish patients with multiple sclerosis. *Journal of Medical Economics* 2016;**19**(1):	Exclude MS Finland
Rzepinski L, Zawadka-Kunikowska M, Kucharczuk J, Newton J, Zalewski P. New insights into the socio-economic aspects of multiple sclerosis in a cohort of Polish patients. *Annals of Agricultural & Environmental Medicine* 2021;**28**(1):	Exclude not an economic evaluation

Citation	Reason for exclusion
Sabanov AV, Luneva AV, Matveev NV. [Pharmacoeconomic analysis of the efficacy of natalizumab in relapsing-remitting multiple sclerosis]. *Zhurnal Nevrologii i Psikhiatrii Imeni SS Korsakova* 2014;**114**(5):	Exclude RRMS Russia
Sanchez de la Rosa R, Garcia BL, Meca Lallana J. Cost Analysis of the Use of Glatiramer Acetate Compared to Interferon-A in Patients with Relapsing-Remitting Multiple Sclerosis and Spasticity in Spain. *Value in Health* 2014;**17**(7):	Exclude RRMS Spain
Sanchez-de la Rosa R, Garcia-Bujalance L, Meca-Lallana J. Cost analysis of glatiramer acetate versus interferon-beta for relapsing-remitting multiple sclerosis in patients with spasticity: the Escala study. *Health Economics Review* 2015;**5**(1):	Exclude RRMS Spain
Sanchirico M, Caldwell-Tarr A, Mudumby P, Hashemi L, Dufour R. Treatment Patterns, Healthcare Resource Utilization, and Costs Among Medicare Patients with Multiple Sclerosis in Relation to Disease-Modifying Therapy and Corticosteroid Treatment. *Neurology & Therapy* 2019;**8**(1):	Exclude not an economic evaluation
Sandroff BM, Benedict RH, Motl RW. Nonsignificant associations between measures of inhibitory control and walking while thinking in persons with multiple sclerosis. *Archives of Physical Medicine & Rehabilitation* 2015;**96**(8):	Exclude not an economic evaluation
Sanghera S, Coast J. Measuring Quality-Adjusted Life-Years When Health Fluctuates. *Value in Health* 2020;**23**(3):	Exclude not an economic evaluation
Sawad AB, Seoane-Vazquez E, Rodriguez-Monguio R, Turkistani F. Cost-effectiveness of different strategies for treatment relapsing-remitting multiple sclerosis. *Journal of Comparative Effectiveness Research* 2017;**6**(2):	Exclude RRMS US
Schauf M, Chinthapatla H, Dimri S, Li E, Hartung DM. Economic burden of multiple sclerosis in the United States: A systematic literature review. *Journal of Managed Care & Specialty Pharmacy* 2023;**29**(12):	Exclude not an economic evaluation
Schultz TJ, Thomas A, Georgiou P, Juaton MS, Cusack L, Simon L*, et al.* Home infusions of natalizumab for people with multiple sclerosis: a pilot randomised crossover trial. *Annals of Clinical & Translational Neurology* 2021;**8**(8):	Exclude not an economic evaluation
Sicras-Mainar A, Ruiz-Beato E, Navarro-Artieda R, Maurino J. Impact on healthcare resource utilization of multiple sclerosis in Spain. *BMC Health Services Research* 2017;**17**(1):	Exclude RRMS Spain
Silverio N, Sequeira L, Meletiche D. Cost-Effectiveness of Subcutaneous Verse Intramuscular Interferon Beta-1A In Portugal Based on the Findings of Cochrane Collaboration Review of First-Line Treatments for Relapsing-Remitting Multiple Sclerosis. *Value in Health* 2014;**17**(7):	Exclude RRMS Portugal
Sima DM, Esposito G, Van Hecke W, Ribbens A, Nagels G, Smeets D. Health Economic Impact of Software-Assisted Brain MRI on Therapeutic Decision-Making and Outcomes of Relapsing-Remitting Multiple Sclerosis Patients-A Microsimulation Study. *Brain Sciences* 2021;**11**(12):	Exclude RRMS US
Simoens S. Societal economic burden of multiple sclerosis and cost-effectiveness of disease-modifying therapies. *Frontiers in neurology* 2022;**13**	Exclude not an economic evaluation
Smets I, Versteegh M, Huygens S, Corsten C, Wokke B, Smolders J. Health-economic benefits of anti-CD20 treatments in relapsing multiple sclerosis estimated using a treatment-sequence model. *Multiple Sclerosis Journal Experimental Translational & Clinical* 2023;**9**(3):	Exclude RRMS Netherlands
Soini E, Asseburg C, Sumelahti ML. Cost-Utility Analysis (cua) Of First-Line Disease-Modifying Treatments (DMT) Versus Best Supportive Care (Bsc) In Finnish Relapsing-Remitting Multiple Sclerosis (RRMS) Patients. *Value in Health* 2014;**17**(7):	Exclude RRMS Finland
Soini E, Joutseno J, Sumelahti ML. Cost-utility of First-line Disease-modifying Treatments for Relapsing-Remitting Multiple Sclerosis. *Clinical Therapeutics* 2017;**39**(3):	Exclude RRMS Finland
Stanisic S, Bertolotto A, Berto P, Di Procolo P, Morawski J. The cost-effectiveness of alemtuzumab in the management of relapse-remitting multiple sclerosis in Italy. *Global and Regional Health Technology Assessment* 2019	Exclude RRMS Italy

Citation	Reason for exclusion
Su W, Kansal A, Vicente C, Deniz B, Sarda S. The cost-effectiveness of delayed-release dimethyl fumarate for the treatment of relapsing-remitting multiple sclerosis in Canada. *Journal of Medical Economics* 2016;**19**(7):	Exclude RRMS Canada
Svensson M, Fajutrao L. Costs of formal and informal home care and quality of life for patients with multiple sclerosis in sweden. *Multiple Sclerosis International* 2014;**2014**	Exclude MS Sweden
Taheri S, Sahraian MA, Yousefi N. Cost-effectiveness of alemtuzumab and natalizumab for relapsing-remitting multiple sclerosis treatment in Iran: decision analysis based on an indirect comparison. *Journal of Medical Economics* 2019;**22**(1):	Exclude RRMS Iran
Tappenden P, Saccardi R, Confavreux C, Sharrack B, Muraro PA, Mancardi GL*, et al.* Autologous haematopoietic stem cell transplantation for secondary progressive multiple sclerosis: an exploratory cost-effectiveness analysis. *Bone marrow transplantation* 2010;**45**(6): 1014-1021	Exclude SPMS UK
Torabipour A, Asl ZA, Majdinasab N, Ghasemzadeh R, Tabesh H, Arab M. A study on the direct and indirect costs of multiple sclerosis based on expanded disability status scale score in khuzestan, iran. *International Journal of Preventive Medicine* 2014;**5**(9):	Exclude MS Iran
Tosh J, Dixon S, Carter A, Daley A, Petty J, Roalfe A*, et al.* Cost effectiveness of a pragmatic exercise intervention (EXIMS) for people with multiple sclerosis: economic evaluation of a randomised controlled trial. *Multiple Sclerosis* 2014;**20**(8):	Exclude intervention
Touchette DR, Durgin TL, Wanke LA, Goodkin DE. A cost-utility analysis of mitoxantrone hydrochloride and interferon beta-1b in the treatment of patients with secondary progressive or progressive relapsing multiple sclerosis. *Clinical Therapeutics* 2003;**25**(2): 611-634	Exclude SPMS US
van Eijndhoven E, Brauer M, Kee R, MacEwan J, Mucha L, Wong SL*, et al.* Modeling the impact of patient treatment preference on health outcomes in relapsing-remitting multiple sclerosis. *Journal of medical economics* 2020;**23**(5): 474-483	Exclude Intervention
van Mastrigt GA, Evers SM, Heerings M, Visser LH, Ruimschotel RP, Hussaarts A*, et al.* An economic evaluation attached to a single-centre, parallel group, unmasked, randomized controlled trial of a 3-day intensive social cognitive treatment (can do treatment) in patients with relapsing remitting multiple sclerosis and low disability. *Journal of Medical Economics* 2019;**22**(10):	Exclude RRMS Netherlands
Vandhuick O, Payet M, Preaud E, Lortet-Tieulent J, Raguideau F, Chevreuil O*, et al.* Economic burden of highly active relapsing-remitting multiple sclerosis patients in the French national health insurance database. *Expert Review of Pharmacoeconomics & Outcomes Research* 2021;**21**(5):	Exclude RRMS France
Veauthier C, Hasselmann H, Gold SM, Paul F. The Berlin Treatment Algorithm: recommendations for tailored innovative therapeutic strategies for multiple sclerosis-related fatigue. *The EPMA Journal* 2016;**7**	Exclude not an economic evaluation
Versteegh MM, Huygens SA, Wokke BWH, Smolders J. Effectiveness and Cost-Effectiveness of 360 Disease-Modifying Treatment Escalation Sequences in Multiple Sclerosis. *Value in Health* 2022;**25**(6): 984-991	Exclude RRMS Netherlands
Viktor Chirikov, Ingrid Ma, Namita Joshi, Dipen Patel, Alden Smith, Cindy Giambrone, et al. Cost-Effectiveness of Alemtuzumab in the Treatment of Relapsing Forms of Multiple Sclerosis in the United States. Value in Health 2019;22(6):	Exclude RRMS US
Visser LA, Folcher M, Delgado Simao C, Gutierrez Arechederra B, Escudero E, Uyl-de Groot CA*, et al.* The Potential Cost-Effectiveness of a Cell-Based Bioelectronic Implantable Device Delivering Interferon-beta1a Therapy Versus Injectable Interferon-beta1a Treatment in Relapsing-Remitting Multiple Sclerosis. *PharmacoEconomics* 2022;**40**(1):	Exclude RRMS Netherlands
Walker A, Watson C, Alexopoulos ST, Deniz B, Arnold R, Bates D. A benefit-risk analysis of natalizumab in the treatment of patients with multiple sclerosis when considering the risk of progressive multifocal leukoencephalopathy. *Current Medical Research & Opinion* 2014;**30**(4):	Exclude RRMS Austria
Walter E, Berger T, Bajer-Kornek B, Deisenhammer F. Cost-utility analysis of alemtuzumab in comparison with interferon beta, fingolimod, and natalizumab treatment for relapsing-remitting multiple sclerosis in Austria. *Journal of Medical Economics* 2019;**22**(3):	Exclude RRMS Austria

Citation	Reason for exclusion
Walter E, Deisenhammer F. Socio-economic aspects of the testing for antibodies in MS-patients under interferon therapy in Austria: a cost of illness study. *Multiple Sclerosis and Related Disorders* 2014;**3**(6):	Exclude MS Austria
Wan GJ, Chopra I, Niewoehner J, Hunter SF. Cost per response analysis of repository corticotropin injection versus other alternative treatments for acute exacerbations of multiple sclerosis. *Drugs in Context* 2020;**9**	Exclude MS US
Watson C, Prosser C, Braun S, Landsman-Blumberg PB, Gleissner E, Naoshy S. Health care resource utilization before and after natalizumab initiation among patients with multiple sclerosis in Germany. *Clinicoeconomics & Outcomes Research* 2017;**9**	Exclude RRMS Germany
Watson C, Prosser C, Braun S, Landsman-Blumberg PB, Gleissner E, Naoshy S. Health care resource utilization before and after natalizumab initiation among patients with multiple sclerosis in Germany. *Clinicoeconomics & Outcomes Research* 2017;**9**	Exclude not an economic evaluation
Wilkinson SN, Dougall C, Kinsey-Henderson AE, Searle RD, Ellis RJ, Bartley R. Development of a time-stepping sediment budget model for assessing land use impacts in large river basins. *Science of the Total Environment* 2014;**468**	Exclude not an economic evaluation
Wilson S, Calocer F, Rollot F, Fauvernier M, Remontet L, Tron L*, et al.* Effects of socioeconomic status on excess mortality in patients with multiple sclerosis in France: A retrospective observational cohort study. *The Lancet Regional Health Europe* 2023;**24**	Exclude RRMS France
Wiyani A, Badgujar L, Khurana V, Adlard N. How have Economic Evaluations in Relapsing Multiple Sclerosis Evolved Over Time? A Systematic Literature Review. *Neurology and Therapy* 2021;**10**(2): 557-583	Exclude not an economic evaluation
Wiyani A, Badgujar L, Khurana V, Adlard N. How have Economic Evaluations in Relapsing Multiple Sclerosis Evolved Over Time? A Systematic Literature Review. *Neurology & Therapy* 2021;**10**(2):	Exclude not an economic evaluation
Xu Y, Mao N, Chirikov V, Du F, Yeh YC, Liu L*, et al.* Cost-effectiveness of Teriflunomide Compared to Interferon Beta-1b for Relapsing Multiple Sclerosis Patients in China. *Clinical Drug Investigation* 2019;**39**(3):	Exclude RRMS China
Yadlowsky S, Pellegrini F, Lionetto F, Braune S, Tian L. Estimation and Validation of Ratio-Based Conditional Average Treatment Effects Using Observational Data. *Journal of the American Statistical Association* 2021;**116**(533):	Exclude not an economic evaluation
Yang H, Duchesneau E, Foster R, Guerin A, Ma E, Thomas NP. Cost-effectiveness analysis of ocrelizumab versus subcutaneous interferon beta-1a for the treatment of relapsing multiple sclerosis. *Journal of Medical Economics* 2017;**20**(10):	Exclude RMS US
Zarco LA, Millan SP, Londono D, Parada L, Taborda A, Borda MG. [The cost-effectiveness of interferon beta treatment in patients with a clinically isolated syndrome in Colombia]. *Biomedica* 2014;**34**(1):	Exclude MS Colombia
Zarghami A, Fuh-Ngwa V, Claflin SB, Simpson-Yap S, Lucas R, Dear K*, et al.* Changes in employment status over time in multiple sclerosis following a first episode of central nervous system demyelination, a Markov multistate model study. *European Journal of Neurology* 2024;**31**	Exclude wrong population
Zhang X, Hay JW, Niu X. Cost effectiveness of fingolimod, teriflunomide, dimethyl fumarate and intramuscular interferon-beta1a in relapsing-remitting multiple sclerosis. *CNS Drugs* 2015;**29**(1):	Exclude RRMS China
Ziemssen T, Kurzeja A, Muresan B, Haas JS, Alexander J, Driessen MT. Real-world patient characteristics, treatment patterns and costs in relapsing multiple sclerosis patients treated with glatiramer acetate, dimethyl fumarate or teriflunomide in Germany. *Neurodegenerative Disease Management* 2022;**12**(2):	Exclude RRMS Germany
Zimmermann M, Brouwer E, Tice JA, Seidner M, Loos AM, Liu S*, et al.* Disease-Modifying Therapies for Relapsing-Remitting and Primary Progressive Multiple Sclerosis: A Cost-Utility Analysis. *CNS Drugs* 2018;**32**(12):	Exclude RRMS Germany

Appendix 3
Included study details

Study characteristics

Table 43 Overview of studies included in the review

Study Name	Population	Number enrolled	Duration (median follow-up)	Study Phase	Funding Sources	Study Location	MS Criteria	Previous treatment	Interventions evaluated
ADVANCE[80]	RRMS	1512	48 weeks (NR)	Phase III	Industry	183 sites in 26 countries	McDonald	Yes	Peginterferon beta 1a SC125
									Placebo
AFFIRM[77]	RRMS	943	2 years (NR)	Phase III	Industry	99 sites in Europe, North America, and New Zealand	McDonald	Yes	Natalizumab IV300
									Placebo
ANTELOPE[76]	RRMS	265	48 weeks (NR)	Phase III	Industry	48 sites in 7 countries	McDonald	Yes	Natalizumab IV300
									Natalizumab biosimilar
APOLITOS[69]	RRMS	64	24 weeks (NR)	Phase II	Industry	Japan and Russia	McDonald	Yes	Ofatumumab SC20
									Placebo
ASCLEPIOS I[68]	RRMS (94%)	927	30 months (1.5 years)	Phase III	Industry	385 sites in 37 countries	McDonald	Yes	Ofatumumab SC20
									Teriflunomide O14
ASCLEPIOS II[68]	RRMS (94%)	955	30 months (1.6 years)	Phase III	Industry		McDonald	Yes	Ofatumumab SC20
									Teriflunomide O14
ASSESS[81]	RRMS	1064	12 months (NR)	Phase III	Industry	127 sites in 6 countries	McDonald	Yes	Fingolimod O0.5
									Glatiramer acetate SC20
BEYOND[82]	RRMS	1345	2 years (NR)	Phase III	Industry	98 centres in 26 countries worldwide	McDonald	No	Interferon beta 1b SC250
									Glatiramer acetate SC20
Calabrese 2012[83]	RRMS	165	2 years (NR)	Phase IV	Industry	Italy	McDonald	No	Interferon beta 1a SC44
									Interferon beta 1a IM30
									Glatiramer acetate SC20
CAMMS223[84]	RRMS	334	36 months (NR)	Phase II	Industry	49 sites in Europe and the United States.	McDonald	No	Interferon beta 1a SC44
									Alemtuzumab IV12

Study Name	Population	Number enrolled	Duration (median follow-up)	Study Phase	Funding Sources	Study Location	MS Criteria	Previous treatment	Interventions evaluated
CARE-MS I[85]	RRMS	581	2 years (NR)	Phase III	Industry	101 sites in 16 countries	McDonald	No	Alemtuzumab IV12
									Interferon beta 1a SC44
CARE-MS II[71]	HARRMS	840	2 years (NR)	Phase III	Industry	194 sites in 23 countries	McDonald	Yes	Interferon beta 1a SC44
									Alemtuzumab IV12
CLARITY[86]	RRMS + HARRMS	1326	96 weeks (NR)	Phase III	Industry	155 sites in 32 countries	McDonald	Yes	Cladribine O3.5
									Placebo
CombiRx[87]	RRMS	1008	36 months (NR)	Phase III	Mixed	68 sites in USA and Canada	Poser or McDonald	Yes	Glatiramer acetate SC20
									Interferon beta 1a IM30
CONFIDENCE[88]	RRMS	861	6 months (NR)	Phase IV	Industry	14 countries	McDonald	Yes	Glatiramer acetate SC40
									Glatiramer acetate SC20
CONFIRM[89]	RRMS + HARRMS	1430	2 years (NR)	Phase III	Industry	200 sites in 28 countries	McDonald	Yes	Glatiramer acetate SC20
									Placebo
Copolymer 1 Multiple Sclerosis Study Group[90]	RRMS	251	2 years (NR)	Phase III	Mixed	USA	Poser	No	Glatiramer acetate SC20
									Placebo
Etemedifar 2006[91]	RRMS	90	2 years (NR)	NR	Not reported	Iran	Poser	No	Interferon beta 1b SC250
									Interferon beta 1a IM30
									Interferon beta 1a SC44
European/Canadian glatiramer acetate study group[92]	RRMS	239	9 months (NR)	NR	Industry	29 sites in 6 European countries and Canada	Poser	No	Glatiramer acetate SC20
									Placebo
EVIDENCE[93]	RRMS	677	48 weeks (NR)	NR	Industry	56 sites (15 in Europe, 5 in Canada, and 36in the United States)	Poser	No	Interferon beta 1a SC44
									Interferon beta 1a IM30
FREEDOMS[74]	RRMS + HARRMS	1272	2 years (NR)	Phase III	Industry	138 sites in 22 countries.	McDonald	Yes	Fingolimod O0.5
									Placebo
FREEDOMS II[73]	RRMS + HARRMS	1083		Phase III	Industry	117 sites in eight countries	McDonald	Yes	Fingolimod O0.5

Study Name	Population	Number enrolled	Duration (median follow-up)	Study Phase	Funding Sources	Study Location	MS Criteria	Previous treatment	Interventions evaluated
			24 months (NR)						Placebo
GALA[94]	RRMS	1404	1 year (NR)	Phase III	Industry	142 sites in 17 countries	McDonald	Yes	Glatiramer acetate SC40
									Placebo
GATE[95]	RRMS	796	9 months (NR)	Phase III	Industry	18 sites in 17 countries	McDonald	Yes	Glatiramer acetate SC20
									Placebo
GOLDEN[96]	RRMS	157	18 months (NR)	NR	Industry	36 sites 28 in Italy and 8 in Germany	McDonald	Yes	Fingolimod O0.5
									Interferon beta 1b SC250
IMPROVE[98]	RRMS	180	16 weeks double-blind then 24 week rater-blind (NR)	Phase III	Industry	International	McDonald	No	Interferon beta 1a SC44
									Placebo
INCOMIN[99]	RRMS	188	2 years (NR)	NR	Non-industry	15 sites in Italy	Poser	No	Interferon beta 1a IM30
									Interferon beta 1b SC250
IFNB Multiple Sclerosis Study Group[97]	RRMS	372	Unclear (NR)	NR	Industry	United States and Canada	Poser	No	Interferon beta 1b SC250
									Placebo
Kappos 2011[100]	RRMS	220	48 weeks (NR)	Phase II	Industry	International	McDonald	Yes	Ocrelizumab IV600
									Interferon beta 1a IM30
									Placebo
MIST[72]	HARRMS	110	Enrolment between 2005-2016, with final follow-up	NR	Non-industry	International	McDonald	Yes	AHSCT
									iDMT

Study Name	Population	Number enrolled	Duration (median follow-up)	Study Phase	Funding Sources	Study Location	MS Criteria	Previous treatment	Interventions evaluated
			in 2018 (2 years)						
Multiple Sclerosis Collaborative Research Group[105]	RRMS	301	2 years (NR)	Phase III	Mixed	USA	Poser	Yes	Interferon beta 1a IM30
									Placebo
OPERA I[67]	RRMS + HARRMS	821	96 weeks (NR)	Phase III	Industry	141 trial sites across 32 countries	McDonald	Yes	Ocrelizumab IV600
									Interferon beta 1a SC44
OPERA II[67]	RRMS + HARRMS	835	96 weeks (NR)	Phase III	Industry	166 trial sites across 24 countries	McDonald	Yes	Ocrelizumab IV600
									Interferon beta 1a SC44
OPTIMUM[70]	RRMS (97%)	1133	108 weeks (NR)	Phase III	Industry	162 sites across 28 countries	McDonald	Yes	Ponesimod O20
									Teriflunomide O14
PEGINTEGRITY[65]	RRMS	168	96 weeks (NR)	Phase III	Industry	9 sites in Iran	McDonald	No	Peginterferon beta 1a SC125
									Interferon beta 1a IM30
Ponesimod Phase II study Group[101]	RRMS	387	24 weeks (NR)	Phase II	Industry	94 sites in 23 countries	McDonald	Yes	Ponesimod O20
									Placebo
PRISMS[102]	RRMS	560	2 years (NR)	NR	Industry	22 sites in 9 countries	Poser	No	Interferon beta 1a SC22
									Interferon beta 1a SC44
									Placebo
REGARD[103]	RRMS	764	96 weeks (NR)	Phase IV	Industry	81 sites in 14 countries	McDonald	Yes	Interferon beta 1a SC44
									Glatiramer acetate SC20
REVEAL[78]	RRMS	111	52 weeks (Natalizumab 40.1 weeks; Fingolimod 36.7 weeks)	Phase IV	Industry	43 sites in nine countries.	McDonald	Yes	Natalizumab IV300
									Fingolimod O0.5

Study Name	Population	Number enrolled	Duration (median follow-up)	Study Phase	Funding Sources	Study Location	MS Criteria	Previous treatment	Interventions evaluated
Saida 2012[104]	RRMS (98%)	171	6 months (NR)	Phase II	Industry	43 centres in Japan	McDonald	No	Fingolimod O0.5
									Placebo
Saida 2017[79]	RRMS and close to HARRMS	94	24 weeks (NR)	Phase II	Industry	25 sites in Japan	McDonald	Yes	Natalizumab IV300
									Placebo
TRANSFORMS[75]	RRMS + HARRMS	1291	12 months (NR)	Phase III	Industry	172 sites in 18 countries.	McDonald	Yes	Fingolimod O0.5
									Interferon beta 1a IM30

Included studies and reports

Table 44 Studies included in the review showing primary and related reports and whether additional data were extracted from related reports

Study Name	Report	Additional Data report
ADVANCE	Primary report[80]	NA
	Related report - data extracted[198]	Quality of life data
	Related report - no relevant data[199]	no evidence of disease - NEDA data
	Related report - no relevant data[200]	Post hoc analysis of evolution of MRI lesions
	Related report - no relevant data[201]	Pharmacokinetics and pharmacodynamics data
	TA624[32]	Additional data on disease progression
AFFIRM	Primary report[77]	NA
	Related report - data extracted[202]	Reports on AFFIRM and SENTINEL EDSS
	Related report - no relevant data[203]	Visual outcomes
	Related report - no relevant data[204]	Free from disease activity
	Related report - no relevant data[205]	Data in patients who have relapsed
	Related report - no relevant data[206]	MRI outcomes
	Related report - no relevant data[207]	MRI outcomes
	Trial Registry Entry[208]	NA
AFFIRM/SENTINEL	Synthesis across related studies[209]	Visual outcomes
	Synthesis across related studies[210]	Participants of African descent
	Synthesis across related studies[211]	Subgroup analyses
	TA127[34]	Additional data on disease progression; additional potentially relevant data on disease progression redacted
AFFIRM/TIMER	Synthesis across related studies[212]	Ambulation outcomes
ANTELOPE	Primary report[76]	NA
	Trial Registry Entry[213]	NA
APOLITOS	Primary report[69]	NA
ASCLEPIOS I/II	Primary report[68]	NA
	Related report - no relevant data[214]	Sub analysis on treatment naïve patients

Study Name	Report	Additional Data report
	Trial registry[215]	NA
	TA699[41]	No additional data – data for highly active population redacted
ASSESS	Primary report[81]	NA
	Trial Registry Entry[216]	NA
BEYOND	Primary report[82]	NA
	Related report - no relevant data[217]	Additional MRI outcomes (black hole development)
Calabrese 2012	Primary report[83]	NA
CAMMS223	Primary report[84]	NA
	Related report - no relevant data[218]	Subgroup analyses, freedom from disease activity, sustained disability reduction
	Related report - no relevant data[219]	Follow-up of 6 patients with thrombocytopenia
	Related report - no relevant data[220]	Thyroid dysfunction outcome data
	Related report - no relevant data[221]	individual functional scores of EDSS outcomes
	Related report - no relevant data[222]	Visual outcomes
	Trial Registry Entry[223]	NA
	TA312[39]	No additional data; data on QoL redacted
CARE-MS I	Primary report[85]	NA
	Trial Registry Entry[224]	NA
	Trial Registry Entry[225]	NA
	TA312[39]	No additional data
CARE-MS II	Primary report[71]	NA
	Related report - no relevant data[226]	QoL Data
	Related report - no relevant data[227]	Additional EDSS data
	Trial Registry Entry[228]	NA
	Trial Registry Entry[229]	NA
	Trial Registry Entry[230]	NA
	TA312[39]	No additional data
CARE-MS I/II	Synthesis across related studies[231]	Additional MRI outcomes
	Synthesis across related studies[232]	QoL data
	Synthesis across related studies[233]	Neutropenia

Study Name	Report	Additional Data report
	Synthesis across related studies[234]	Post-hoc analysis looking at age
	Synthesis across related studies[235]	QoL - FAMS only
	Synthesis across related studies[236]	Safety data in Russian patients
CLARITY	Primary report[86]	NA
	Related report - data extracted[237]	QoL data
	Related report - data extracted[238]	Additional data on freedom from disease activity
	Related report - highly active population[239]	Data extracted for this population
	Related report - no relevant data[240]	Additional MRI outcomes
	Related report - no relevant data[241]	Additional safety data
	Related report - no relevant data[242]	Additional MRI outcomes
	Related report - no relevant data[243]	Brain volume changes
	Related report - no relevant data[244]	Relapses in main and extension trial
	Related report - no relevant data[245]	Additional data on highly active subgroup
	Related report - no relevant data[246]	Cardiac outcomes
	Related report - no relevant data[247]	Subgroup data including rapidly evolving severe MS
	Trial Registry Entry[248]	NA
	Trial Registry Entry[249]	NA
	TA616[38]	No additional data
CLARITY/CARE-MS-I	Synthesis across related studies[250]	lymphocyte data
CombiRx	Primary report[87]	NA
	Related report - no relevant data[251]	Risk factors for early treatment failure
	Related report - no relevant data[252]	Designs and baseline characteristics
	Related report - no relevant data[253]	Imaging biomarker data
CONFIDENCE	Primary report[88]	NA
CONFIRM	Primary report[89]	NA
	Related report - data extracted[254]	quality of life data
	Related report - highly active population[255]	subgroup analyses

Study Name	Report	Additional Data report
	Related report - no relevant data[256]	Effect of DF on MRI measures
	Synthesis across related studies[257]	Effect of DF on prior interferon users
	Synthesis across related studies[258]	Effect of DF on no evidence of disease
	Trial Registry Entry[259]	NA
Copolymer 1 Multiple Sclerosis Study Group	Primary report[90]	NA
	Related report - no relevant data[260]	Area under disability time curves
	Related report - no relevant data[261]	Neuropsychological outcomes
	Trial Registry Entry[262]	NA
Etemedifar 2006	Primary report[91]	NA
European/Canadian glatiramer acetate study group	Primary report[92]	NA
	Related report - no relevant data[263]	Additional MRI Outcomes
EVIDENCE	Primary report[93]	
	Related report - data extracted[264]	outcomes at 16 months
	Related report - data extracted[265]	Data for comparative phase and crossover phase
	Related report - no relevant data[266]	data on NEDA
	Related report - no relevant data[267]	specific safety and tolerability data
	Related report - no relevant data[268]	data after crossover
	Related report - no relevant data[269]	MRI T2 burden of disease data
FREEDOMS	Primary report[74]	NA
	Related report - data extracted[270]	Highly active subgroup data
	Related report - no relevant data[271]	Post hoc analysis of subgroups based on previous treatments
	Related report - no relevant data[272]	Additional MRI data
	Trial Registry Entry[273]	NA
	Trial Registry Entry[274]	NA
	TA254[40]	Baseline data for HA population; redacted data on: baseline relapse rate, HR for disability progression in highly active population and EQ-5D data
FREEDOMS II	Primary report[73]	NA
	Related report - no relevant data[275]	Corrections to paper
	Trial Registry Entry[276]	NA

Study Name	Report	Additional Data report
	Trial Registry Entry[277]	NA
FREEDOMS/ FREEDOMS II	Synthesis across related studies[278]	MRI brain volume
	Synthesis across related studies[108]	Highly active subgroup
	Synthesis across related studies[279]	MRI outcomes
	Synthesis across related studies[280]	Early (3 and 6 months) outcomes
FREEDOMS/ FREEDOMS II/ TRANSFORMS	Synthesis across related studies[281]	Hispanic patients
	Synthesis across related studies[282]	Relapse rates in different patient subgroups
FREEDOMS/ TRANSFORMS	Synthesis across related studies[283]	Hungarian poster with clinical and MRI outcomes
GALA	Primary report[94]	NA
	Related report - data extracted[284]	post-hoc analysis of the study but think it is just focusing on a russian patient subset?
	Related report - no relevant data[285]	Timing of efficacy onset
	Related report - no relevant data[286]	looks at total t1 lesions vs t1 non enhanced lesions
	Trial Registry Entry[287]	NA
GATE	Primary report[95]	NA
	Trial Registry Entry[288]	NA
GOLDEN	Primary report[96]	NA
	Trial Registry Entry[289]	NA
	Trial Registry Entry[290]	NA
IFNB Multiple Sclerosis Study Group	Primary report[97]	NA
	Related report - data extracted[291]	Additional MRI data
	Related report - data extracted[292]	Additional MRI data
	Related report - no relevant data[293]	Additional MRI data
	Related report - no relevant data[294]	Additional MRI data
IMPROVE	Primary report[98]	NA
	Related report - data extracted[295]	baseline data
	Related report - no relevant data[296]	Other MRI outcomes
	Trial Registry Entry[297]	NA
	Trial Registry Entry[298]	NA

Study Name	Report	Additional Data report
INCOMIN	Primary report[99]	NA
	Related report - no relevant data[299]	Additional MRI outcomes
Kappos2011	Primary report[100]	NA
	Trial Registry Entry[300]	NA
	Trial Registry Entry[301]	NA
MIST	Primary report[72]	NA
	Trial Registry Entry[302]	NA
Multiple Sclerosis Collaborative Research Group	Primary report[105]	NA
	Related report - no relevant data[303]	Baseline details
	Related report - no relevant data[304]	Additional data on disability
OPERA I/II	Primary report[67]	NA
	Synthesis across related studies[305]	Brain volume
	Synthesis across related studies[306]	MRI outcomes
	Synthesis across related studies[307]	Data for participants of African descent
	Synthesis across related studies[308]	Risk of requiring walking aid after 6.5 years - open label extension
	Synthesis across related studies[309]	Infusion related reactions
	Synthesis across related studies[310]	Data for highly active disease
	Synthesis across related studies[311]	Subgroup of patients with increased disability at baseline
	NICE TA533[33]	Additional data on highly active disease (combined across both trials); redacted data on EQ-5D
OPTIMUM	Primary report[70]	NA
	Related report - no relevant data [312]	Subgroup analysis in women
	Trial registry entry[313]	NA
	TA767[42]	No additional data – data for highly active population redacted
PEGINTEGRITY	Primary report[65]	NA
	Trial Registry Entry[314]	NA
Ponesimod Phase II study Group	Primary report[101]	NA
	Related report - no relevant data[315]	Erratum relating to Figure
	Synthesis across related studies[316]	Core and extension studies
	Trial Registry Entry[317]	NA

Study Name	Report	Additional Data report
PRISMS	Primary report[102]	NA
	Related report - data extracted[318]	MRI outcomes
	Related report - data extracted[319]	NEDA data
	Related report - no relevant data[320]	Erratum relating to author COI
	Related report - no relevant data[321]	Additional EDSS outcomes
	Related report - no relevant data[322]	Additional EDSS outcomes
	Related report - no relevant data[323]	Depression outcomes
PRISMS/SPECTRIMS	Synthesis across related studies[324]	Posthoc analysis of combined data
	Synthesis across related studies[325]	MRI outcomes
REGARD	Primary report[103]	NA
	Trial Registry Entry[326]	NA
REVEAL	Primary report[78]	NA
	Trial Registry Entry[327]	NA
	Trial Registry Entry[328]	NA
Saida 2012	Primary report[104]	NA
Saida 2017	Primary report[79]	NA
	Trial Registry Entry[329]	NA
	Related report - no relevant data[330]	subanalysis of patients who achieved no evidence of disease
TRANSFORMS	Primary report[75]	NA
	Related report - no relevant data[331]	MRI brain volume outcomes
	Related report - no relevant data[332]	Highly active and other subgroup data but not in format for inclusion
	Related report - no relevant data[333]	subgroup analysis
	Trial Registry Entry[334]	NA
	Trial Registry Entry[335]	NA

Baseline characteristics

Table 45 Baseline participant details (RRMS population)

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	% White	% Black	% Asian	% Other	Annual Relapse rate (SD)	% treated	Previous treatments
ADVANCE[80]	Placebo	500	36.3 (9.7)	72	3.5(4.6)	2.4 (1.2)	82	0.6	11	6	1.6(0.7)	7	DMT
	Peginterferon beta 1a SC125	512	36.9 (9.8)	71	4(5.1)	2.5 (1.3)	81	0.58	12	7	1.6(0.7)	8	
AFFIRM[77]	Natalizumab IV300	627	35.6 (8.5)	72	NR(NR)	2.3 (1.2)	96	NR	NR	4	1.5(0.9)	9	interferon beta-1a interferon beta-1b or glatiramer acetate
	Placebo	315	36.7 (7.8)	67	NR(NR)	2.3 (1.2)	94	NR	NR	6	1.5(0.8)	8	
ANTELOPE[76]	Natalizumab biosimilar	131	36.8 (9.1)	64.1	5.3(4.7)	3.4 (1.1)	100	0	0	0	1.4(0.7)	NR	NR
	Natalizumab IV300	133	36.6 (9.7)	58.6	5.3(4.8)	3.2 (1.2)	100	0	0	0	1.4(0.6)	NR	
APOLITOS[69]	Ofatumumab SC20	43	35 (9.5)	83.7	5.1(6.3)	2.2 (1)	51.2	NR	48.8	NR	1.6(0.9)	67	interferon beta; glatiramer; dimethyl fumarate; fingolimod; natalizumab; other DMTS
	Placebo	21	35.5 (8.9)	90.5	6(6.4)	2.2 (1.3)	47.6	NR	52.4	NR	1.2(0.7)	71	
ASCLEPIOS I[68]	Ofatumumab SC20	465	38.9 (8.8)	68	5.8 (6.1)	3.0 (1.4)	88	3	3	5	1.2(0.6)	59	interferon beta, glatiramer acetate, dimethyl fumarate,
	Teriflunomide O14	462	37.8 (9.0)	69	5.6 (6.2)	3.0 (1.4)	89	4	4	3	1.3(0.7)	61	
ASCLEPIOS II[68]	Ofatumumab SC20	481	38.0 (9.3)	66	5.6 (6.4)	2.9 (1.3)	87	3	4	4	1.3(0.7)	60	

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	% White	% Black	% Asian	% Other	Annual Relapse rate (SD)	% treated	Previous treatments
	Teriflunomide O14	474	38.2 (9.5)	67	5.5 (6.0)	2.9 (1.4)	88	4	4	3	1.3(0.7)	62	natalizumab, B-cell therapy, lanquinimod, other DMT
ASSESS[81]	Fingolimod O0.5	352	40.3 (11.1)	75	4.3(5.9)	2.7 (1.5)	76.1	9.7	0	11.9	1.4(0.8)	52	NR
	Glatiramer acetate SC20	342	39.6 (10.8)	73.7	4.7(6.2)	2.7 (1.4)	71.1	12	0	14.3	1.4(0.8)	55	
BEYOND[82]	Interferon beta 1b SC250	897	35.8 (IQR 28-43)	70	5.3(NR)	2.4 (IQR 1.5-3.0)	93	NR	NR	NR	1.6(NR)	0	None
	Glatiramer acetate SC20	448	35.2 (IQR 27-43)	68	5.1(NR)	2.3 (IQR 1.5-3.1)	91	NR	NR	NR	1.6(NR)	0	
Calabrese 2012[83]	Interferon beta 1a SC44	46	35.9 (9.1)	69.5	5.7(4.9)	1.9 (1)	NR	NR	NR	NR	1.2(0.6)	NR	NR
	Interferon beta 1a IM30	47	34.8 (9.6)	68	5.3(5.1)	1.9 (0.8)	NR	NR	NR	NR	1.2(0.7)	NR	
	Glatiramer acetate SC20	48	38.9 (10.2)	72.9	5.5(6.1)	2.1 (1.1)	NR	NR	NR	NR	1.3(0.7)	NR	
CAMMS223[84]	Interferon beta 1a SC44	111	32.8 (8.8)	64	NR(NR)	1.9 (0.8)	90.1	NR	NR	NR	NR	0	None
	Alemtuzumab IV12	112	31.9 (8.0)	64.3	NR(NR)	1.9 (0.7)	91.1	NR	NR	NR	NR	0	
CARE-MS I[85]	Interferon beta 1a SC44	187	33.2 (8.5)	65	2(1.3)	2 (0.8)	96	NR	NR	NR	1.8(0.8)	0	None
	Alemtuzumab IV12	376	33 (8.0)	65	2.1(1.4)	2 (0.8)	94	NR	NR	NR	1.8(0.8)	0	
CLARITY[86]	Placebo	437	38.7 (9.9)	65.9	8.9(7.4)	2.9 (1.3)	98.2	0.2	NR	1.6	NR	33	interferon beta 1a, interferon beta 1b, glatiramer acetate
	Cladribine O3.5	433	37.9 (10.3)	68.8	7.9(7.2)	2.8 (1.2)	98.2	0.5	NR	1.4	NR	32	

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	% White	% Black	% Asian	% Other	Annual Relapse rate (SD)	% treated	Previous treatments
CombiRx[87]	Glatiramer acetate SC20	259	39 (9.5)	71.4	1(2.9)	1.9 (1.2)	90.3	NR	NR	NR	1.6(0.7)	NR	NR
	Interferon beta 1a IM30	250	37.6 (10.2)	69.2	1.4(4)	2 (1.2)	84.8	NR	NR	NR	1.7(0.9)	NR	
CONFIDENCE[88]	Glatiramer acetate SC40	431	41 (11.2)	66.8	5.7(6.5)	2.2 (1.3)	83.3			16.7	0.8(0.9)	60	Any DMT
	Glatiramer acetate SC20	430	40.1 (10.7)	71.4	5.6(6.3)	2.1 (1.3)	84.4			15.6	0.7(0.7)	59	
CONFIRM[89]	Placebo	363	36.9 (9.2)	69	4.8(5)	2.6 (1.2)	84	2	8	6	1.4(0.8)	31	interferon beta 1a, interferon beta 1b, glatiramer, natalizumab
	Glatiramer acetate SC20	350	36.7 (9.1)	71	4.4(4.7)	2.6 (1.2)	83	3	7	7	1.4(0.6)	29	
Copolymer 1 Multiple Sclerosis Study Group[90]	Glatiramer acetate SC20	125	34.6 (6)	70.4	7.3(4.9)	2.8 (1.2)	94.4	NR	NR	5.6	1.5(0.7)	NR	NR
	Placebo	126	34.3 (6.5)	76.2	6.6(5.1)	2.4 (1.3)	93.6	NR	NR	6.3	1.5(0.6)	NR	
Etemedifar 2006[91]	Interferon beta 1b SC250	30	NR (NR)	30.9	3.7(2.3)	NR (NR)	NR	NR	NR	NR	2.2(0.7)	NR	NR
	Interferon beta 1a IM30	30	NR (NR)	35.3	2.9(2.3)	NR (NR)	NR	NR	NR	NR	2.0(0.8)	NR	
	Interferon beta 1a SC44	30	NR (NR)	33.8	3.0(2.2)	NR (NR)	NR	NR	NR	NR	2.4(1.0)	NR	
European/ Canadian glatiramer acetate study group[92]	Glatiramer acetate SC20	119	34.1 (7.4)	NR	7.9(5.5)	2.3 (1.1)	NR	NR	NR	NR	1.4(0.9)	NR	NR
	Placebo	120	34 (7.5)	NR	8.3(5.5)	2.4 (1.2)	NR	NR	NR	NR	1.2(0.7)	NR	
EVIDENCE[93]	Interferon beta 1a SC44	339	38.3 (NR)	74.9	4.0(6.5)	2.0 (2.3)	92.3	NR	NR	NR	2.0(2.6)	0	None

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	% White	% Black	% Asian	% Other	Annual Relapse rate (SD)	% treated	Previous treatments
	Interferon beta 1a IM30	338	37.4 (NR)	74.6	4.1(6.7)	2.0 (2.3)	89.6	NR	NR	NR	2.0(2.6)	0	
FREEDOMS[74]	Fingolimod O0.5	425	36.6 (8.8)	69.6	8.0(6.6)	2.3 (1.3)	NR	NR	NR	NR	1.5(0.8)	43	Interferon beta 1a, interferon beta 1b, glatiramer acetate,
	Placebo	418	37.2 (8.6)	71.3	8.1(6.4)	2.5 (1.3)	NR	NR	NR	NR	1.4(0.7)	40	
FREEDOMS II[73]	Fingolimod O0.5	358	40.6 (8.4)	77	10.4(8.0)	2.4 (1.3)	NR	NR	NR	NR	1.4(0.9)	74	Interferon beta 1a, interferon beta 1b, glatiramer acetate, natalizumab
	Placebo	355	40.1 (8.4)	81	10.6(7.9)	2.4 (1.3)	NR	NR	NR	NR	1.5(0.9)	73	
GALA[94]	Glatiramer acetate SC40	943	37.4 (9.4)	68	NR	2.8 (1.2)	97.1	1.3	0.2	1.4	1.3(0.6)	14	Prior DMT treatment
	Placebo	461	38.1 (9.2)	67.9	NR(NR)	2.7 (1.2)	98.7	0.7	0	0.6	1.3(0.6)	14	
GATE[95]	Glatiramer acetate SC20	357	33.8 (9)	66.7	6.4(6)	2.7 (1.2)	NR	NR	NR	NR	0.9(0.5)	83	NR
	Placebo	84	32.6 (8.7)	67.9	5.7(6)	2.7 (1.2)	NR	NR	NR	NR	0.9(0.5)	88	
GOLDEN[96]	Fingolimod O0.5	104	39.5 (9.3)	65.4	NR(NR)	NR (NR)	NR	NR	NR	NR	NR	NR	NR
	Interferon beta 1b SC250	47	37.5 (9.3)	63.8	NR(NR)	NR (NR)	NR	NR	NR	NR	NR	NR	
IFNB Multiple Sclerosis Study Group[336]	Placebo	123	36.0 (6.7)	NR	3.9(3.3)	2.8 (1.1)	94.3	NR	NR	5.7	1.8(0.6)	0	No
	Interferon beta 1b SC250	124	35.2 (6.7)	NR	4.7(4.5)	3.0 (1.1)	93.6	NR	NR	6.4	1.7(1.1)	0	No
IMPROVE[98]	Placebo	60	35.2 (10.5)	70	NR(NR)	2.3 (NR)	NR	NR	NR	NR	NR	NR	NR
	Interferon beta 1a SC44	120	34 (7.8)	73.3	NR(NR)	2.5 (NR)	NR	NR	NR	NR	NR	NR	

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	% White	% Black	% Asian	% Other	Annual Relapse rate (SD)	% treated	Previous treatments
INCOMIN[99]	Interferon beta 1a IM30	92	34.9 (7.9)	62	6.7(5.4)	2 (0.7)	NR	NR	NR	NR	1.4(0.5)	0	None
	Interferon beta 1b SC250	96	38.8 (7.1)	69	5.9(4.2)	2 (0.7)	NR	NR	NR	NR	1.5(0.7)	0	
Kappos 2011[100]	Placebo	54	38 (8.8)	67	2.7(0.1-19.2)	3.2 (1.4)	96	NR	NR	NR	NR	30	β interferons, glatiramer acetate, intravenous immuno-globulin, plasmaphere sis, and immune-suppresive treatment
	Ocrelizumab IV600	55	35.6 (8.5)	64	3.6(0.1-16.5)	3.5 (1.5)	93	NR	NR	NR	NR	53	
	Interferon beta 1a IM30	54	38.1 (9.3)	59	3.3(0.1-20.2)	3.1 (1.5)	98	NR	NR	NR	NR	31	
Multiple Sclerosis Collaborative Research Group[105]	Interferon beta 1a IM30	158	36.7 (8.0)	75	6.6(6.2)	2.4 (0.9)	93	7	NR	0	1.2(0.6)	NR	NR
	Placebo	143	36.9 (6.8)	72	6.4(5.5)	2.3 (0.7)	92	6	NR	2	1.2(0.6)	NR	NR
OPERA I[67]	Ocrelizumab IV600	410	37.1 (9.3)	65.9	3.8(4.8)	2.9 (1.2)	NR	NR	NR	NR	1.3(0.7)	26	Interferon, Glatiramer acetate, Fingolimod, Dimethyl fumarate, Other (NR)
	Interferon beta 1a SC44	411	36.9 (9.3)	66.2	3.7(4.6)	2.8 (1.3)	NR	NR	NR	NR	1.3(0.6)	29	Interferon, Glatiramer acetate, Natalizumab, Other (NR)

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	% White	% Black	% Asian	% Other	Annual Relapse rate (SD)	% treated	Previous treatments
OPERA II[67]	Ocrelizumab IV600	417	37.2 (9.1)	65	4.2(5)	2.8 (1.3)	NR	NR	NR	NR	1.3(0.7)	27	Interferon, Glatiramer acetate, Natalizumab, Fingolimod, Other (NR)
	Interferon beta 1a SC44	418	37.4 (9.0)	67	4.1(5.1)	2.8 (1.4)	NR	NR	NR	NR	1.3(0.7)	25	Interferon, Glatiramer acetate, Other (NR)
OPTIMUM[70]	Ofatumumab SC20	567	36.7 (8.7)	64	7.6 (6.8)	2.6 (1.2)	97	0.5	NR	2.3	1.2 (0.6)	38	Interferon beta 1a, interferon beta 1b, or glatiramer acetate
	Teriflunomide O14	566	36.8 (8.7)	66	7.7 (6.8)	2.6 (1.2)	98	0.4	NR	2.0	1.3 (0.7)	37	
PEGINTEGRITY[65]	Peginterferon beta 1a SC125	84	30 (6.5)	84.52	NR(NR)	1.1 (0.9)	NR	NR	NR	NR	NR	0	None
	Interferon beta 1a IM30	84	30.8 (7.4)	83.33	NR(NR)	1 (0.8)	NR	NR	NR	NR	NR	0	
Ponesimod Phase II study Group[101]	Ponesimod O20	116	35.5 (8.5)	67.5	NR(NR)	2.2 (1.3)	98.2	NR	NR	NR	NR	NR	NR
	Placebo	121	36.6 (8.6)	70.2	NR(NR)	2.2 (1.2)	94.2	NR	NR	NR	NR	NR	
PRISMS[102]	Placebo	187	34.6 (NR)	75	NR(NR)	2.4 (1.2)	NR	NR	NR	NR	1.5(0.7)	0	None
	Interferon beta 1a SC22	189	34.8 (NR)	67	NR(NR)	2.5 (1.2)	NR	NR	NR	NR	1.5(0.6)	0	
	Interferon beta 1a SC44	184	35.6 (NR)	66	NR(NR)	2.5 (1.3)	NR	NR	NR	NR	1.5(0.6)	0	
REGARD[103]	Interferon beta 1a SC44	386	36.7 (9.8)	69	NR(NR)	2.4 (1.3)	93%	4%	<1%	2%	NR	NR	NR
	Glatiramer acetate SC20	378	36.8 (9.5)	72	NR(NR)	2.3 (1.3)	94%	4%	<1%	2%	NR	NR	

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	% White	% Black	% Asian	% Other	Annual Relapse rate (SD)	% treated	Previous treatments
REVEAL[78]	Natalizumab IV300	54	38.2 (8.8)	68.5	5(5.8)	NR (NR)	NR	NR	NR	NR	1.9(0.7)	48	Less than 6 months of glatiramer acetate or interferon beta
	Fingolimod O0.5	54	34.9 (8.7)	70.4	4.5(5.8)	NR (NR)	NR	NR	NR	NR	1.9(0.6)	52	
Saida 2012[104]	Placebo	57	35 (8.9)	68.4	8.2(7.3)	NR (NR)	0	0	100	0	1.7(1.6)	NR	NR
	Fingolimod O0.5	57	35 (9)	70.2	8.2(6.8)	NR (NR)	0	0	100	0	1.4(1.0)	NR	
Saida 2017[79]	Natalizumab IV300	47	37.7 (8.6)	72	5.9(5)	2.5 (1.6)	0	0	100	0	2.0(1.2)	91	IFN beta 1a, IFN beta 1b, azathioprine, fingolimod
	Placebo	47	35.1 (8.2)	68	5.1(4.9)	2.1 (1.5)	0	0	100	0	1.9(1.0)	85	
TRANSFORMS[75]	Fingolimod O0.5	431	36.7 (8.8)	65.4	7.5(6.2)	2.2 (1.3)	94.8	NR	NR	NR	1.5(1.2)	55	Interferon beta, glatiramer acetate, natalizumab
	Interferon beta 1a IM30	435	36 (8.3)	67.8	7.4(6.3)	2.2 (1.3)	93.8	NR	NR	NR	1.5(0.8)	56	

Table 46 Baseline participant details (HARRMS population)

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	Annual Relapse rate (SD)	% treated	Previous treatments	Highly active definition
CLARITY[86]	Placebo	56	37.5 (9.3)	71.4	NR	NR	NR	100	Interferon beta 1a, interferon beta 1b, glatiramer acetate	≥ 2 relapses in previous year or ≥1 relapse and ≥1 T1 Gd+ or ≥9 T2 lesions
	Cladribine O3.5	46	36.6 (8.6)	71.7	NR	NR	NR	100		
CARE-MS II[71]	Interferon beta 1a SC44	202	35.8 (8.8)	65	4.7(2.9)	2.7 (1.2)	1.5(0.8)	100	interferon beta, glatiramer, natalizumab, immunoglobulin, azathioprine	≥ 2 relapses in previous 2 years with at ≥1 in previous year; at least one relapse while on interferon beta or glatiramer after at least 6 months of treatment
	Alemtuzumab IV12	426	34.8 (8.4)	66	4.5(2.7)	2.7 (1.3)	1.7(0.9)	100		
FREEDOMS I & II[73]	Fingolimod O0.5	249	39.3 (8.8)	76.3	6.3(5.6)	2.5 (1.3)	1.5(0.8)	100	Interferon beta 1a SC, interferon beta 1a IM, interferon beta 1b SC, glatiramer acetate, natalizumab	(1) ≥1 relapse in the previous year and either ≥1 gadolinium (Gd) enhancing T1 lesion or ≥9 T2 lesions at baseline and/or (2) as many or more relapses in the year before baseline as in the previous year
	Placebo	257	39.2 (8.4)	74.7	6.2(5.5)	2.7 (1.4)	1.6(0.9)	100		
MIST[72]	AHSCT	55	35.6 (8.4)	62	5.3 (3.7)	3.4 (1.2)	NR	100	glatiramer acetate, interferon beta 1a, interferon beta 1b, dimethyl fumarate, natalizumab, intravenous immunoglobulin, fingolimod, teriflunomide, azathioprine, methotrexate	2 or more clinical relapses or 1 relapse and MRI gadolinium-enhancing lesion(s) at a separate time within the previous 12 months despite receiving treatment with DMT
	iDMT	55	35.6 (8.2)	66	7.1 (5.1)	3.3 (1)	NR	100		
OPERA I & II combined[67]	Ocrelizumab IV600	143	NR	NR	NR	NR	NR	NR	NR	

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	Annual Relapse rate (SD)	% treated	Previous treatments	Highly active definition
	Interferon beta 1a SC44	140	NR	NR	NR	NR	NR	NR		Treated with interferons or glatiramer acetate for at least 1 year, and • ≥1 relapse in previous year • ≥1 least one T1 Gd-enhancing lesion on brain MRI at baseline • ≥1 9 T2 hyperintense lesions on brain MRI at baseline
Saida 2017[79]	Natalizumab IV300	47	37.7 (8.6)	72	5.9(5)	2.5 (1.6)	2.0(1.2)	91	IFN beta 1a, IFN beta 1b, azathioprine, fingolimod	Not fully HARRMS; one relapse in previous year but only 88% received previous DMT
	Placebo	47	35.1 (8.2)	68	5.1(4.9)	2.1 (1.5)	1.9(1.0)	85		
TRANSFORMS[75]	Fingolimod O0.5	189	37.1 (8.8)	70.9	6.4(4.7)	2.5 (1.4)	NR	100	Beta interferon, glatiramer acetate, natilizumab	Patients who received DMT in the previous year with unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year
	Interferon beta 1a IM30	191	37.1 (8.4)	67.5	6.8(6)	2.4 (1.2)	NR	100		

Appendix 4
Included study results and outcome definitions

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Table 47 Definitions of relapse, broken down into definition components, used in each of the included trials

Study Name	Symptoms	Symptom duration	Absence of	EDSS/neurological examination	Preceding stability period	Verification
ADVANCE[80]	New or recurrent neurologic symptoms	≥ 24 hours	Fever or infection	New objective neurologic findings	NR	Independent neurological evaluation committee
AFFIRM[77]	New or recurrent neurologic symptoms	≥ 24 hours	Fever or infection	New objective neurologic findings	NR	Examining neurologist
ANTELOPE[76]	New or worsening neurologic symptom	≥ 24 hours	Fever or infection	NR	≥30 days	NR
APOLITOS[69]	Symptoms (not defined)	NR	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	NR	NR
ASCLEPIOS I[68]	New or worsening neurologic symptom	≥ 24 hours	Fever or infection	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	Investigator
ASSESS[81]	Symptoms (not defined)	NR	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	NR	Examiner ≤ 7 days of notification
BEYOND[82]	New or recurrent neurologic symptoms	≥ 24 hours	Fever or infection	Increase in EDSS or functional system scores	≥30 days	Evaluating physician
Calabrese 2012[83]	Definition not reported	NR	NR	NR	NR	NR
CAMMS223[84]	New or worsening symptoms	≥ 48 hours	Fever	New objective neurologic findings attributable to MS that	≥30 days	NR
CARE-MS I[85]	New or worsening neurologic symptom	≥ 48 hours	NR	New objective neurologic findings	≥30 days	Masked examiner

Study Name	Symptoms	Symptom duration	Absence of	EDSS/neurological examination	Preceding stability period	Verification
CARE-MS II[71]	New or worsening neurologic symptom attributable to MS	≥ 48 hours	Fever	Objective change on neurological examination.	≥30 days	NR
CLARITY[86]	Symptoms (not defined)	≥ 24 hours	Fever	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	NR
CombiRx[87]	New or worsening neurologic symptom attributable to MS	≥ 24 hours	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	NR
CONFIDENCE[88]	*Did not report on relapse rate*					
CONFIRM[89]	New or recurrent neurologic symptoms	≥ 24hours	Fever or infection	New objective neurologic findings	≥30 days	NR
Copolymer 1 Multiple Sclerosis Study Group[90]	New or recurrent neurologic symptoms	≥ 48 hours	Fever	EDSS increase ⩾0.5 points, or an increase or ⩾2 on one functional score	≥30 days	NR
Etemedifar 2006[91]	New or severely worsening neurologic symptom	≥ 24 hours	NR	EDSS increase ⩾1 point	NR	NR
European/Canadian glatiramer acetate study group[92]	New or recurrent neurologic symptoms	≥ 48 hours	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	Visit ≤ 7 days of notification.
EVIDENCE[93]	New or worsening neurologic symptom	≥ 24 hours	Fever	Objective change on neurological examination.	≥30 days	NR
FREEDOMS[74]	Symptoms (not defined)	NR	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	NR	Examining neurologist ≤ 7 days of notification
FREEDOMS II[73]	Symptoms (not defined)	NR	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	NR	NR
GALA[94]	New or recurrent neurologic symptoms	≥ 48 hours	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	NR

Study Name	Symptoms	Symptom duration	Absence of	EDSS/neurological examination	Preceding stability period	Verification
GATE[95]	New or recurrent neurologic symptoms	≥ 24 hours	Fever or infection	New objective neurologic findings	NR	NR
GOLDEN[96]	*No definition provided*					
IFNB Multiple Sclerosis Study Group[97]	New or worsening neurologic symptom attributable to MS	≥ 24 hours	Fever	New objective neurologic findings	≥30 days	NR
IMPROVE[98]	*No definition provided*					
INCOMIN[99]	New or worsening neurologic symptom	≥ 24 hours	NR	⩾1 point increase in Kurtzke's functional system scale score	≥30 days	Investigating doctor ≤ 7 days of notification
Kappos 2011[100]	New or worsening neurologic symptom attributable to MS	≥ 24 hours	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	NR
MIST[72]	Neurologic symptoms requiring corticosteroids	≥ 24 hours	Fever, infection, or heat intolerance	NR	NR	Investigator not masked to treatment.
Multiple Sclerosis Collaborative Research Group[105]	New or worsening neurologic symptom	≥ 48 hours	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	Study physician
OPERA I[67]	New or worsening neurologic symptom attributable to MS	≥ 24 hours	Fever, infection, injury, or adverse reactions to medications	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	NR
OPTIMUM[70]	New, worsening or recurrent neurologic symptom	≥ 24 hours	Fever or infection	Documented increase of EDSS score or its functional system scores	≥30 days	NR
PEGINTEGRITY[65]	*No definition provided*					

Study Name	Symptoms	Symptom duration	Absence of	EDSS/neurological examination	Preceding stability period	Verification
Ponesimod Phase II study Group[101]	New or worsening symptoms of MS	≥ 24 hours	Fever or infection	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	Independent neurologist ≤ 7 days of notification
PRISMS[102]	New or worsening neurologic symptom attributable to MS	≥ 24 hours	NR	NR	≥30 days	NR
REGARD[103]	New or worsening neurologic symptom	≥ 48 hours	Fever	Change in KFS score.	NR	NR
REVEAL[78]	New or recurrent neurologic symptoms	≥ 24 hours	Fever	NR	≥30 days	NR
Saida 2012[104]	New, worsening or recurrent neurologic symptom	≥ 24 hours	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	NR
Saida 2017[79]	New or recurrent neurologic symptoms	≥ 24 hours	Fever or infection	NR	NR	NR
TRANSFORMS[75]	New, worsening or recurrent neurologic symptom	≥ 24 hours	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	Neurologist

Table 48 Annualised relapse rate analysis details

Study Name	Analysis details	Baseline characteristics adjusted for	Other factors adjusted for
ADVANCE[80]	Negative binomial regression model	EDSS score (<4 vs ≥4); relapse rate (number of relapses in 3 years before study entry divided by 3); age (<40 vs ≥40 years)	NR
AFFIRM[77]	Poisson regression	NR	NR
ANTELOPE[76]	Analysed descriptively – summarised as A: no. relapses per patient and overall, B: duration of follow-up time per patient and overall, A/B: the ratio of relapses per patient year	NR	NR
APOLITOS[69]	Negative binomial regression models	Treatment; region; number of Gd + T1 lesions (0 or ⩾1)	Offset to adjust for time in study
ASCLEPIOS I[68]	Negative binomial-regression model	NR	Offset to adjust for time spent in trial in years
ASCLEPIOS II[68]	Negative binomial-regression model	NR	Offset to adjust for variable study duration in years
ASSESS[81]	Negative binomial-regression model	EDSS score; no. gadolinium-enhancing T1 lesions; no. relapses in previous year before enrolment	Time in study (offset variable); number of confirmed relapses for each participant (response variable)
BEYOND[82]	Hazard ratios derived from generalised linear Poisson regression	NR	NR
Calabrese 2012[83]	Only statistical analysis information provided: Between-group differences were assessed using analysis of variance, followed by the Tukey test to account for multiple comparisons. Pearson chi-square was applied to test the effect of disease-modifying on the percentage of patients that developed new cortical inflammatory lesions compared with untreated patients.	NR	NR
CAMMS223[84]	Poisson regression	NR	NR
CARE-MS I[85]	Negative binomial regression	Geographic region	Robust variance estimation used as covariate

Study Name	Analysis details	Baseline characteristics adjusted for	Other factors adjusted for
CARE-MS II[71]	NA	NA	NA
CLARITY[86]	Proportion of relapse-free patients analysed with logistic-regression model that included study-group and region effects. Odds ratio and 95% confidence intervals estimated for each study group. Groups compared with approximate chi-square test on the basis of Wald statistics.	Region; study group	NR
CombiRx[87]	Cox proportional hazards model with Anderson Gill modification to handle repeated occurrences of relapses within a participant.	Baseline covariates that differed across treatment arms	NR
CONFIDENCE[88]	NA	NA	NA
CONFIRM[89]	Negative binomial regression model	age; region; no. relapses in the 12 months before study entry	
Copolymer 1 Multiple Sclerosis Study Group[90]	ANCOVA	EDSS score; sex; duration of disease (years); prior 2-year relapse rate	
Etemedifar 2006[91]	Comparison between groups made using one-way ANOVA and repeated-measures ANOVA over time; comparisons between, before, and after 24 months of treatment within each group made using paired Student's t-test. Comparisons between proportions made by using chi-square or Fisher's exact test. Results expressed as mean (SD) and P<0.05 considered statistically significant. All statistical tests were two-sided.	NR	NR
European/Canadian glatiramer acetate study group[92]	Continuous variables analysed with two-sample two-sided t test or Mann–Whitney test	NR	NR
EVIDENCE[93]	Poisson regression model	Treatment; centre	Offset variable for time on study
FREEDOMS[74]	Negative binomial regression model	EDSS score; study group; country; no. relapses within 2 years;	NR
FREEDOMS II[73]	Negative binomial regression model		NR

Study Name	Analysis details	Baseline characteristics adjusted for	Other factors adjusted for
		EDSS score; treatment; region; no. relapses within 2 years	
GALA[94]	Negative binomial regression model	EDSS score; treatment group; no. relapses in the previous 2 years; volume of T2 lesions; status of Gd-enhancing T1 activity; country or geographical region	Offset variable for patient's exposure to treatment
GATE[95]	Not formally tested but summarized per treatment group with point estimates and 95% CIs using an appropriate covariance model	Stratification variables included as covariates	NR
GOLDEN[96]	Continuous data were summarised by mean, standard deviation (SD), median, interquartile range, minimum and maximum, and 95% confidence limits (CLs), where applicable.	NR	NR
IMPROVE[98]	Poisson regression model	Treatment	Offset variable for time on study
INCOMIN[99]	Parametric or non-parametric tests, according to distribution of variables	NR	NR
IFNB Multiple Sclerosis Study Group[97]	Treatment-group differences were analysed using ANOVA based on ranked data. In display of group exacerbation rates, 95% CI were calculated using Poisson distribution based on no. observed exacerbations in each group. Survival curves were calculated with life-table methods for length of time before onset of first and second exacerbations. Data on patients were censored at time of withdrawal. Log-rank statistic was used to test comparability of the survival curves for each group.	ANOVA accounted for treatment group; study site; treatment group by study site	NR
Kappos 2011[100]	Poisson regression	Geographical region	Offset variable for exposure time in years
MIST[72]	NA	NA	NA
Multiple Sclerosis Collaborative Research Group[105]	Divided the total number of exacerbations during the first 104 weeks by the total person-years of exposure	NR	NR

Study Name	Analysis details	Baseline characteristics adjusted for	Other factors adjusted for
OPERA I[67]	Negative binomial model	EDSS score; geographic region	NR
OPERA II[67]	Negative binomial model	EDSS score; geographic region	NR
OPTIMUM[70]	Negative binomial regression model	NR	Offset variable for log time in study in years
PEGINTEGRITY[65]	Poisson regression model with robust error variance	EDSS score; age	NR
Ponesimod Phase II study Group[101]	Rate ratio provided; time to first confirmed relapse was analysed using the Kaplan–Meier method	NR	NR
PRISMS[102]	Generalised linear model (GLM) with a log link and variance proportional to the mean	NR	NR
REGARD[103]	Poisson regression model	Treatment; centre	Offset variable for time on study
REVEAL[78]	Negative binomial regression models	NR	NR
Saida 2012[104]	Logistic regression model	EDSS score; treatment; no. relapses in two years prior to study	NR
Saida 2017[79]	Poisson regression model	NR	NR
TRANSFORMS[75]	Logistic regression model	EDSS score; country; no. relapses in previous two years	

Table 49 Estimates of ARR for each study arm in the included studies (RRMS population)

Study Name	Intervention	Follow-up (months)	N	ARR (95% CI or SD)	RR (95% CI)	ROB
ADVANCE[80]	Peginterferon beta 1a SC125	12	512	0.26 (0.21, 0.32)	0.64 (0.50, 0.83)	Low
	Placebo		500	0.4 (0.33, 0.48)	1.0	
AFFIRM[77]	Natalizumab IV300	12	627	0.27 (0.21, 0.33)	0.35 (0.26, 0.47)	Low
	Placebo		315	0.78 (0.64, 0.94)	1.0	
	Natalizumab IV300	24	627	0.23 (0.19, 0.28)	0.32 (0.24, 0.41)	
	Placebo		315	0.73 (0.62, 0.87)	1.0	
ANTELOPE[76]	Natalizumab biosimilar	6	131	0.17 (NR)	1.55 (NR)	Low
	Natalizumab IV300		133	0.11 (NR)	1.0	
APOLITOS[69]	Ofatumumab SC20	6	43	0.26 (0.11, 0.63)	0.42 (0.14, 1.25)	Some concerns
	Placebo		21	0.63 (0.28, 1.43)	1.0	
ASCLEPIOS I[68]	Ofatumumab SC20	30	454	0.11 (0.09, 0.14)	0.49 (0.37, 0.65)	Low
	Teriflunomide O14		452	0.22 (0.18, 0.26)	1.0	
ASCLEPIOS II[68]	Ofatumumab SC20	30	469	0.1 (0.08, 0.13)	0.42 (0.31, 0.56)	Low
	Teriflunomide O14		469	0.25 (0.21, 0.3)	1.0	
ASSESS[81]	Fingolimod O0.5	12	345	0.15 (0.11, 0.21)	0.59 (0.37, 0.95)	High
	Glatiramer acetate SC20		324	0.26 (0.2, 0.34)	1.0	
BEYOND[82]	Glatiramer acetate SC20	24	448	0.34 (NR)	0.94 (NR)	Some concerns
	Interferon beta 1b IM 250		897	0.36 (NR)	1.0	
Calabrese 2012[83]	Glatiramer acetate SC40	24	48	0.5 (0.39, 0.61)	1.25 (0.75, 2.07)	Some concerns
	Interferon beta 1a IM30		47	0.5 (0.33, 0.67)	1.25 (0.70, 2.22)	
	Interferon beta 1a SC44		46	0.4 (0.23, 0.57)	1.0	
CAMMS223[84]	Alemtuzumab IV12	36	112	0.11 (0.08, 0.16)	0.33 (0.2, 0.55)	High
	Interferon beta 1a SC44		111	0.36 (0.29, 0.44)	1.0	
CARE-MS I[85]	Alemtuzumab IV12	24	376	0.18 (0.13, 0.23)	0.45 (0.32, 0.63)	High
	Interferon beta 1a SC44		187	0.39 (0.29, 0.53)	1.0	
CLARITY[86]	Cladribine O3.5	24	433	0.14 (0.12, 0.17)	0.42 (0.34, 0.53)	Some concerns
	Placebo		437	0.33 (0.29, 0.38)	1.0	
CombiRx[87]	Glatiramer acetate SC20	36	259	0.23 (NR)	0.72 (NR)	Low
	Interferon beta 1a IM30		250	0.32 (NR)	1.0	
CONFIRM[89]	Glatiramer acetate SC20	24	350	0.29 (0.23, 0.35)	0.73 (0.54, 0.97)	Some concerns
	Placebo		363	0.4 (0.33, 0.49)	1.0	
Copolymer 1 Multiple Sclerosis Study Group[90]	Glatiramer acetate SC20	24	125	0.59 (NR)	0.7 (NR)	Some concerns
	Placebo		126	0.84 (NR)	1.0	
Etemedifar 2006[91]	Interferon beta 1a IM30	24	30	0.6 (NR)	2.0 (NR)	Some concerns
	Interferon beta 1b IM 250		30	0.35 (NR)	1.17 (NR)	
	Interferon beta 1a SC44		30	0.3 (NR)	1.0	
European/Canadian glatiramer acetate study group[92]	Glatiramer acetate SC20	9	119	0.81 (NR)	0.67 (NR)	Some concerns
	Placebo		120	1.21 (NR)	1.0	
EVIDENCE[93]	Interferon beta 1a IM30	16	338	0.65 (NR)	1.2(NR)	Some concerns
	Interferon beta 1a SC44		339	0.54 (NR)	1.0	
FREEDOMS[74]	Fingolimod O0.5	24	425	0.18 (0.15, 0.22)	0.45 (0.35, 0.58)	Low
	Placebo		418	0.4 (0.34, 0.47)	1.0	
FREEDOMS II[73]	Fingolimod O0.5	24	358	0.21 (0.17, 0.25)	0.52 (0.4, 0.66)	High
	Placebo		355	0.4 (0.34, 0.48)	1.0	

Study Name	Intervention	Follow-up (months)	N	ARR (95% CI or SD)	RR (95% CI)	ROB
GALA[94]	Glatiramer acetate SC40	12	943	0.33 (0.28, 0.39)	0.66 (0.54, 0.8)	Low
	Placebo		461	0.51 (0.42, 0.61)	1.0	
GATE[95]	Glatiramer acetate SC20	9	357	0.4 (0.26, 0.62)	1.05 (0.52, 2.12)	Low
	Placebo		84	0.38 (0.22, 0.66)	1.0	
GOLDEN[96]	Fingolimod O0.5	18	104	0.12 (NR)	0.31(NR)	High
	Interferon beta 1b IM 250		47	0.39 (NR)	1.0	
IFNB Multiple Sclerosis Study Group[97]	Interferon beta 1b IM 250	21.6	115	0.84 (0.72, 0.97)	0.66 (0.55, 0.80)	Some concerns
	Placebo	22.4	112	1.27 (1.12, 1.43)	1	
	Interferon beta 1b IM 250	36	124	0.84 (NR)	0.69 (NR)	
	Placebo		123	1.21 (NR)	1.0	
IMPROVE[98]	Interferon beta 1a SC44	4	120	0.14 (0.09, 0.23)	0.43 (0.23, 0.82)	Some concerns
	Placebo		60	0.33 (0.22, 0.52)	1.0	
INCOMIN[99]	Interferon beta 1b IM 250	24	96	0.5 (0.7)	0.71(NR)	High
	Interferon beta 1a IM30		92	0.7 (0.9)	1.0	
Kappos 2011[100]	Interferon beta 1a IM30	6	54	0.36 (0.22, 0.6)	0.56 (0.30, 1.06)	Low
	Ocrelizumab IV600		55	0.13 (0.03, 0.29)	0.20 (0.06, 0.67)	
	Placebo		54	0.64 (0.43, 0.94)	1.0	
Multiple Sclerosis Collaborative Research Group[105]	Interferon beta 1a IM30	24	158	0.67 (NR)	0.82(NR)	Some concerns
	Placebo	24	143	0.82 (NR)	1.0	
OPERA I[67]	Ocrelizumab IV600	24	410	0.16 (0.12, 0.2)	0.54 (0.4, 0.72)	Low
	Interferon beta 1a SC44		411	0.29 (0.24, 0.36)	1.0	
OPERA II[67]	Ocrelizumab IV600	24	417	0.16 (0.12, 0.2)	0.53 (0.4, 0.71)	Low
	Interferon beta 1a SC44		418	0.29 (0.23, 0.36)	1.0	
OPTIMUM[70]	Ponesimod O20	27	567	0.2 (0.17, 0.23)	0.69 (0.54, 0.9)	Low
	Teriflunomide O14		566	0.29 (0.25, 0.33)	1.0	
PEGINTEGRITY[65]	Interferon beta 1a IM30	24	83	0.12 (0.05, 0.27)	0.54 (0.23, 1.29)	High
	Peginterferon beta 1a SC125		84	0.06 (0.03, 0.14)	1.0	
Ponesimod Phase II study Group[101]	Ponesimod O20	6	114	0.42 (0.27, 0.65)	0.79 (0.44, 1.43)	Low
	Placebo		121	0.53 (0.36, 0.77)	1.0	
PRISMS[102]	Interferon beta 1a SC22	12	189	1.01 (0.86, 1.19)	0.68 (0.55, 0.84)	Some concerns
	Interferon beta 1a SC44		184	0.92 (0.78, 1.09)	0.62 (0.50, 0.77)	
	Placebo		187	1.49 (1.29, 1.72)	1.0	
	Interferon beta 1a SC22	24	189	0.91 (NR)	0.71 (NR)	
	Interferon beta 1a SC44		184	0.87 (NR)	0.68 (NR)	
	Placebo		187	1.28 (NR)	1.0	
REGARD[103]	Glatiramer acetate SC20	24	378	0.29 (NR)	0.97(NR)	Some concerns
	Interferon beta 1a SC44		386	0.3 (NR)	1.0	
REVEAL[78]	Natalizumab IV300	9	54	0.02 (0.01, 0.13)	0.09 (0.01, 0.72)	Some concerns
	Fingolimod O0.5		54	0.2 (0.11, 0.37)	1.0	
Saida 2012[104]	Fingolimod O0.5	6	57	0.5 (0.29, 0.87)	0.51 (0.26, 0.99)	Low
	Placebo		57	0.99 (0.67, 1.45)	1.0	
Saida 2017[79]	Natalizumab IV300	6	47	0.53 (0.29, 0.99)	0.31 (0.15, 0.62)	Low
	Placebo		47	1.73 (1.22, 2.45)	1.0	
TRANSFORMS[75]	Fingolimod O0.5	12	429	0.16 (0.12, 0.21)	0.48 (0.34, 0.70)	Low
	Interferon beta 1a IM30		431	0.33 (0.26, 0.42)	1.0	

For RR: light grey shading indicates RR estimates reported by the included studies; darker grey shading indicates studies that where RR and 95% CI were calculated from reported ARR and 95% CI for studies arms; unshaded indicates studies that did not report CIs.

Table 50 Estimates of ARR for each study arm in the included studies (HARRMS population)

Study Name	Intervention	Follow-up (months)	N	ARR (95% CI or SD)	ROB
CARE-MS II[71]	Interferon beta 1a SC44	24	202	0.52 (0.41, 0.66)	High
	Alemtuzumab IV12	24	426	0.26 (0.21, 0.33)	
CLARITY[86]	Placebo	24	56	0.44 (0.33, 0.6)	Some concerns
	Cladribine O3.5	24	46	0.25 (0.16, 0.39)	
FREEDOMS 1/II[108]	Placebo	24	257	0.46 (0.39, 0.55)	High
	Fingolimod O0.5	24	249	0.24 (0.19, 0.3)	
OPERA I/II[67]	Ocrelizumab IV600	24	143	0.099 (NR, NR)	Low
	Interferon beta 1a SC44	24	140	0.313 (NR, NR)	
Saida 2017[79]	Natalizumab IV300	6	47	0.53 (0.29, 0.99)	Low
	Placebo		47	1.73 (1.22, 2.45)	
TRANSFORMS[75]	Fingolimod O0.5	12	189	0.252 (NR, NR)	Low
	Interferon beta 1a IM30	12	191	0.506 (NR, NR)	

Disease progression

Table 51 CDP definitions and estimates of proportion of patients with CDP3 and CDP6 for each study arm in the included trials and Hazard Ratios (HR) comparing time to CDP3 and CDP6 between arms (RRMS population)

Study Name	CDP definition based on baseline EDSS scores			Intervention	Follow-up (mths)	CDP3		CDP6		ROB
	EDSS increase 0.5 point	EDSS increase 1 point	EDSS increase 1.5 pts			n/N (%)	HR (95% CI)	n/N (%)	HR (95% CI)	
ADVANCE[80]	NA	≥1	0	Peginterferon beta 1a SC125	12	31/512(6)	0.62 (0.4, 0.97)	NR/512 (NR)	0.46 (0.26, 0.81)	Low
				Placebo	12	50/500(10)	1.0	NR/500 (NR)	1.0	
AFFIRM[77]	NA	≥1	0	Natalizumab IV300	24	107/627(17)	0.58 (0.43, 0.77)	69/627 (11)	0.46 (0.33, 0.64)	Some concerns
				Placebo	24	91/315(29)	1.0	72/315 (23)	1.0	
ASCLEPIOS I[68]	>5.0	1-5	0	Ofatumumab SC20	24	45/465(10)	0.65 (0.45, 0.96)	35/465 (8)	0.61 (0.4, 0.93)	Low
				Teriflunomide O14	24	63/459(14)	1.0	53/459 (12)	1.0	
ASCLEPIOS II[68]	>5.0	1-5	0	Ofatumumab SC20	24	43/479(9)	0.66 (0.45, 0.97)	36/479 (8)	0.76 (0.49, 1.17)	Low
				Teriflunomide O14	24	62/472(13)	1.0	46/472 (10)	1.0	
BEYOND[82]	NA	All	NA	Interferon beta 1b IM 250	24	244/897(27)	NR	NR		Some concerns
				Glatiramer acetate SC20	24	92/448(21)				
CAMMS223[84]	NA	≥1	0	Alemtuzumab IV12	36	12/112(11)	0.42 (0.23, 0.77)	8/112 (7)	0.25 (0.11, 0.57)	High
				Interferon beta 1a SC44	36	16/111(14)	1.0	24/111 (22)	1.0	
CARE-MS I[85]	NA	≥1	0	Alemtuzumab IV12	24	NR		30/376 (8)	0.7 (0.4, 1.23)	High
				Interferon beta 1a SC44	24			20/187 (11)	1.0	
CLARITY[86]	NA	≥1	0	Cladribine O3.5	24	62/433(14)	0.67 (0.48, 0.93)	168/392 (43)	NR	Some concerns
				Placebo	24	90/437(21)	1.0	164/374 (44)		
CombiRx[87]	>5.0	0 to 5	NA	Interferon beta 1a IM30	36	NR		52/241 (22)	NR	Low
				Glatiramer acetate SC20	36			61/246 (25)		
CONFIRM[89]	NA	≥1	0	Glatiramer acetate SC20	24	16/350(5)	0.93 (0.63, 1.37)	NR		Some concerns
				Placebo	24	17/363(5)	1.0			
	NA	All	NA	Glatiramer acetate SC20	24	27/125(22)	NR	NR		

Study Name	CDP definition based on baseline EDSS scores			Intervention	Follow-up (mths)	CDP3		CDP6		ROB
	EDSS increase 0.5 point	EDSS increase 1 point	EDSS increase 1.5 pts			n/N (%)	HR (95% CI)	n/N (%)	HR (95% CI)	
Copolymer 1 Multiple Sclerosis Study Group[90]				Placebo	24	31/126(25)				Some concerns
EVIDENCE[93]	NA	≥1	0	Interferon beta 1a SC44	6	43/339(13)	0.87 (0.58, 1.31)	20/339 (6)	0.7 (0.39, 1.25)	Some concerns
				Interferon beta 1a IM30	6	49/338(14)	NR	30/338 (9)	1.0	
FREEDOMS[74]	>5.0	≤5	NA	Fingolimod O0.5	24	NR/425 (NR)	0.70 (0.52, 0.96)	NR/425 (NR)	0.63 (0.44, 0.90)	Low
				Placebo	24	NR/418 (NR)	1.0	NR/418 (NR)	1.0	
FREEDOMS II[73]	>5.0	≤5	NA	Fingolimod O0.5	24	91/358(25)	0.83 (0.61, 1.12)	49/358 (14)	0.72 (0.48, 1.07)	High
				Placebo	24	103/355(29)	1.0	63/355 (18)	1.0	
INCOMIN[99]	NA	All	NA	Interferon beta 1b IM 250	24	NR		13/96 (14)	0.44 (0.25, 0.8)	High
				Interferon beta 1a IM30	24			28/92 (30)	1.0	
Multiple Sclerosis Collaborative Research Group[105]	NA	All	NA	Interferon beta 1a IM30		NR		18/85 (21)	NR	Some concerns
				Placebo				29/87 (33)		
OPERA I[67]	> 5.5	≤5.5	NA	Ocrelizumab IV600	24	31/410(8)	0.57 (0.37, 0.9)	24/410 (6)	0.57 (0.34, 0.95)	Low
				Interferon beta 1a SC44	24	50/411(12)	1.0	39/411 (9)	1.0	
OPERA II[67]	> 5.5	≤5.5	NA	Ocrelizumab IV600	24	44/417(11)	0.63 (0.42, 0.92)	33/417 (8)	0.63 (0.4, 0.98)	Low
				Interferon beta 1a SC44	24	63/418(15)	1.0	48/418(11)	1.0	
OPTIMUM[70]	> 5.5	1 to 5.5	0	Ponesimod O20	27	57/567(10)	0.83 (0.58, 1.18)	46/567(8)	0.84 (0.57, 1.24)	Low
				Teriflunomide O14	27	70/566(12)	1.0	56/566(10)	1.0	
PEGINTEGRITY[65]	> 5.5	1 to 5.5	0	Peginterferon beta 1a SC125	24	1/78(1)	0.58 (0.05, 6.47)	NR		High
				Interferon beta 1a IM30	24	2/81(2)	1.0			
PRISMS[102]	> 5.5	≤5.5	NA	Interferon beta 1a SC22	12	NR/189	0.55 (0.35, 0.85)	NR		Some concerns
				Interferon beta 1a SC44	12	NR/184	0.62 (0.41, 0.95)			
				Placebo	12	NR/187	1.0			
REGARD[103]	≥5	0.5-4.5	0	Glatiramer acetate SC20	24	NR		33/378(9)	NR	Some concerns
				Interferon beta 1a SC44	24			45/386(12)		

Study Name	CDP definition based on baseline EDSS scores			Intervention	Follow-up (mths)	CDP3		CDP6		ROB
	EDSS increase 0.5 point	EDSS increase 1 point	EDSS increase 1.5 pts			n/N (%)	HR (95% CI)	n/N (%)	HR (95% CI)	
TRANSFORMS[75]	>5.0	≤5	NA	Interferon beta 1a IM30	12	34/431(8)	NR	NR		Low
				Fingolimod O0.5	12	36/429(8%)				

Table 52 CDP definitions and estimates of proportion of patients with CDP3 and CDP6 for each study arm in the included trials and Hazard Ratios (HR) comparing time to CDP3 and CDP6 between arms (HARRMS population)

Study Name	CDP definition based on baseline EDSS scores			Intervention	Follow-up (mths)	CDP3		CDP6		ROB
	EDSS increase 0.5 point	EDSS increase 1 point	EDSS increase 1.5 pts			n/N (%)	HR (95% CI)	n/N (%)	HR (95% CI)	
CARE-MS II[71]	NA	≥2	NA	Alemtuzumab IV12	24	NR		54/426(13)	0.58 (0.38, 0.87)	High
				Interferon beta 1a SC44				40/202(20)		
CLARITY[86]	NA	≥1	0	Cladribine O3.5	24	NR/46	0.25 (0.07, 0.89)	NR/46	0.20 (0.04, 0.91)	Some concerns
				Placebo		NR/56	1.0	NR/56	1.0	
FREEDOMS 1/II[108]	>5.0	≤5	NA	Fingolimod O0.5	24	NR		26/248 (10)	0.50 (0.34, 0.90)	High
				Placebo				43/257 (17)	1.0	
MIST[72]	NA	All	NA	AHSCT	34	NR		3/52 (6)	0.07 (0.02, 0.24)	High
				iDMT				34/51 (67)	1.0	
OPERA I/II[67]	> 5.5	≤5.5	NA	Ocrelizumab IV600	24	12/143 (8)	0.47 (0.23, 0.95)	10/143 (7)	0.50 (0.23, 1.09)	Low
				Interferon beta 1a SC44		22/140 (16)	1.0	17/140 (12)	1.0	

MRI outcomes

Table 53 Definitions and estimates of proportion of patients with lesions on MRI for each study arm in the included trials (RRMS population)

Study Name	Gd+ lesion definition	T2 lesions definition	Follow-up (months)	Intervention	% Gd+ lesions	% T2 lesions	ROB
AFFIRM[77]	Any Gd+ lesions	New or enlarging T2 hyperintense lesions	24	Natalizumab IV300	19/627 (3%)	267/627 (43%)	Low
				Placebo	88/315 (28%)	269/315 (85%)	
			12	Natalizumab IV300	22/627 (4%)	245/627 (39%)	
				Placebo	102/315 (32%)	243/315 (77%)	
ANTELOPE[76]	New Gd+ lesions	New or enlarging T2 lesion	6	Natalizumab biosimilar	17/126 (13%)	51/126 (40%)	Low
				Natalizumab IV300	22/127 (17%)	55/127 (43%)	
ASSESS[81]	Any Gd+ lesions	New or enlarging T2 lesions	12	Fingolimod O0.5	41/302 (14%)	147/303 (49%)	High
				Glatiramer acetate SC20	70/272 (26%)	176/272 (65%)	
CARE-MS I[85]	Any Gd+ lesions	New or enlarging T2 hyperintense lesions	24	Alemtuzumab IV12	26/366 (7%)	176/363 (48%)	High
				Interferon beta 1a SC44	34/178 (19%)	99/172 (58%)	
CLARITY[86]	Any Gd+ lesion	Active T2 lesions	24	Cladribine O3.5	54/422 (13%)	148/422 (35%)	High
				Placebo	223/424 (53%)	284/424 (67%)	
CombiRx[87]	And Gd+ lesions	NR	36	Interferon beta 1a IM30	25/187 (13%)	NR	Some concerns
				Glatiramer acetate SC20	33/215 (15%)	NR	
EVIDENCE[93]	Any Gd+ lesions	New or enlarging T2 hyperintense lesions	6	Interferon beta 1a SC44	270/325 (83%)	265/325 (82%)	Some concerns
				Interferon beta 1a IM30	287/325 (88%)	282/325 (87%)	
FREEDOMS[74]	Any Gd+ lesions	New or enlarging T2 lesion	24	Fingolimod O0.5	38/369 (10%)	183/370 (49%)	Some concerns
				Placebo	116/332 (35%)	267/339 (79%)	
FREEDOMS II[73]	Any Gd+ lesions	New hyperintense T2 lesions	24	Fingolimod O0.5	35/269 (13%)	131/264 (50%)	High
				Placebo	89/256 (35%)	186/251 (74%)	
GATE[95]	Any Gd+ lesions	New hyperintense T2 lesions	9	Glatiramer acetate SC20	193/335 (58%)	NR	Low
				Placebo	59/82 (72%)	NR	
IMPROVE[98]	New Gd+ lesions	New T2 lesions	4	Interferon beta 1a SC44	47/120 (39%)	27/120 (23%)	Some concerns
				Placebo	48/60 (80%)	30/60 (50%)	

Study Name	Gd+ lesion definition	T2 lesions definition	Follow-up (months)	Intervention	% Gd+ lesions	% T2 lesions	ROB
INCOMIN[99]	Any Gd+ lesions	New T2 lesions	12	Interferon beta 1b IM 250	7/76 (9%)	53/76 (70%)	High
				Interferon beta 1a IM30	16/73 (22%)	33/73 (45%)	
			24	Interferon beta 1b IM 250	18/76 (24%)	34/76 (45%)	
				Interferon beta 1a IM30	37/73 (51%)	54/73 (74%)	
Multiple Sclerosis Collaborative Research Group[105]	Any Gd+ lesions	NR	12	Interferon beta 1a IM30	40/134 (30%)	NR	Some concerns
				Placebo	52/123 (42%)	NR	
OPERA I[67]	Any Gd+ lesions	New or enlarging T2 lesions	24	Ocrelizumab IV600	21/410 (5%)	155/410 (38%)	Low
				Interferon beta 1a SC44	112/411 (27%)	249/411 (61%)	
OPERA II[67]	Any Gd+ lesions	New or enlarging T2 lesions	24	Ocrelizumab IV600	20/417 (5%)	153/417 (37%)	Low
				Interferon beta 1a SC44	139/418 (33%)	255/418 (61%)	
PRISMS[102]	NR	Active T2 lesions	12	Interferon beta 1a SC44	NR	66/182 (36%)	Some concerns
				Interferon beta 1a SC22	NR	94/185 (51%)	
				Placebo	NR	136/184 (74%)	
			24	Interferon beta 1a SC44	NR	126/182 (69%)	
				Interferon beta 1a SC22	NR	150/185 (81%)	
				Placebo	NR	169/184 (92%)	
REGARD[103]	Any Gd+ lesions	Active T2 lesions	24	Interferon beta 1a SC44	44/230 (19%)	137/230 (60%)	Some concerns
				Glatiramer acetate SC20	76/230 (33%)	144/230 (63%)	
REVEAL[78]	New Gd+ lesions	New/newly enlarging T2 lesions	6	Natalizumab IV300	16/47 (34%)	6/15 (40%)	Some concerns
				Fingolimod O0.5	24/45 (53%)	10/16 (63%)	
Saida 2012[104]	Any Gd+ lesions	New or enlarging T2 lesions	6	Fingolimod O0.5	11/45 (24%)	17/48 (35%)	Some concerns
				Placebo	23/50 (46%)	32/50 (64%)	
TRANSFORMS[75]	Any Gd+ lesions	New or enlarged T2-weighted hyperintense lesions	12	Fingolimod O0.5	37/374 (10%)	168/372 (45%)	Some concerns
				Interferon beta 1a IM30	68/354 (19%)	196/361 (54%)	

Table 54 Definitions and estimates of proportion of patients with lesions on MRI for each study arm in the included trials (HARRMS population)

Study Name	Gd+ lesion definition	T2 lesions definition	Follow-up (months)	Intervention	% Gd+ lesions	% T2 lesions	ROB
CARE-MS II[71]	Any Gd+ lesions	New or enlarging T2-hyperintense lesions	24	Alemtuzumab IV12	38/410 (9%)	186/403 (46%)	High
				Interferon beta 1a SC44	44/190 (23%)	127/187 (68%)	

Adverse events

Table 55 Proportion of participants reporting each of the safety outcomes of interest (RRMS population)

Study Name	Follow-up (Months)	Intervention	Number of patients experiencing each type of AE/total number of patients (% of patients)				ROB
			Any AEs	SAEs	AEs leading to treatment discontinuation	TRAE	
ADVANCE[80]	12	Placebo	417/500 (83%)	76/500 (15%)	7/500 (1%)	266/500 (53%)	Low
		Peginterferon beta 1a SC125	481/512 (94%)	5/512 (1%)	25/512 (5%)	459/512 (90%)	
AFFIRM[77]	24	Placebo	300/312 (96%)	75/312 (24%)	12/312 (4%)	NR	Low
		Natalizumab IV300	596/627 (95%)	119/627 (19%)	38/627 (6%)	NR	
ANTELOPE[76]	12	Natalizumab biosimilar	85/131 (65%)	NR	8/131 (6%)	31/131 (24%)	Low
		Natalizumab IV300	71/103 (69%)	NR	3/103 (3%)	22/103 (21%)	
APOLITOS[69]	6	Placebo	NR	0/21 (0%)	NR	17/21 (81%)	Some concerns
		Ofatumumab SC20	NR	1/43 (2%)	NR	30/43 (70%)	
ASCLEPIOS I[68]	30	Teriflunomide O14	380/462 (82%)	38/462 (8%)	24/462 (5%)	NR	Low
		Ofatumumab SC20	382/465 (82%)	48/465 (10%)	27/465 (6%)	NR	
ASCLEPIOS II[68]	30	Teriflunomide O14	408/474 (86%)	36/474 (8%)	25/474 (5%)	NR	Low
		Ofatumumab SC20	409/481 (85%)	38/481 (8%)	27/481 (6%)	NR	
ASSESS[81]	12	Fingolimod O0.5	312/345 (90%)	25/345 (7%)	32/345 (9%)	NR	High
		Glatiramer acetate SC20	283/324 (87%)	20/324 (6%)	45/324 (14%)	NR	
BEYOND[82]	Up to 42 months	Interferon beta 1b IM 250	NR	100/888 (11%)	13/888 (1%)	NR	Some concerns
		Glatiramer acetate SC20	NR	57/445 (13%)	8/445 (2%)	NR	
Calabrese 2012[83]	Did not report safety data						
CAMMS223[84]	36	Interferon beta 1a SC44	107/107 (100%)	24/107 (22%)	13/107 (12%)	NR	High
		Alemtuzumab IV12	108/108 (100%)	24/108 (22%)	2/108 (2%)	NR	
CARE-MS I[85]	24	Interferon beta 1a SC44	172/187 (92%)	27/187 (14%)	11/187 (6%)	NR	High
		Alemtuzumab IV12	361/376 (96%)	69/376 (18%)	5/376 (1%)	NR	
CLARITY[86]	24	Cladribine O3.5	347/430 (81%)	NR	15/430 (3%)	NR	Low

Study Name	Follow-up (Months)	Intervention	Number of patients experiencing each type of AE/total number of patients (% of patients)				ROB
			Any AEs	SAEs	AEs leading to treatment discontinuation	TRAE	
		Placebo	319/435 (73%)	NR	9/435 (2%)	NR	
CombiRx[87]	36	Glatiramer acetate SC20	NR	30/259 (12%)	NR	NR	Low
		Interferon beta 1a IM30	NR	38/250 (15%)	NR	NR	
CONFIDENCE[88]	6	Glatiramer acetate SC20	219/427 (51%)	8/427 (2%)	18/427 (4%)	142/427 (33%)	Some concerns
		Glatiramer acetate SC40	231/430 (54%)	13/430 (3%)	13/430 (3%)	143/430 (33%)	
CONFIRM[89]	24	Glatiramer acetate SC20	334/351 (95%)	60/351 (17%)	NR	NR	Low
		Placebo	333/363 (92%)	79/363 (22%)	NR	NR	
Copolymer 1 Multiple Sclerosis Study Group[90]	24	Placebo	NR	NR	1/126 (1%)	NR	Some concerns
		Glatiramer acetate SC20	NR	NR	5/125 (4%)	NR	
Etemedifar 2006[91]	Did not report safety data						
European/Canadian glatiramer acetate study group[92]	9	Placebo	NR	6/120 (5%)	2/120 (2%)	NR	Some concerns
		Glatiramer acetate SC20	NR	10/119 (8%)	3/119 (3%)	NR	
EVIDENCE[93]	6	Interferon beta 1a IM30	NR	18/338 (5%)	14/338 (4%)	NR	Some concerns
		Interferon beta 1a SC44	NR	21/339 (6%)	16/339 (5%)	NR	
	16	Interferon beta 1a IM30	NR	NR	18/338 (5%)	NR	
		Interferon beta 1a SC44	NR	NR	19/339 (6%)	NR	
FREEDOMS[74]	24	Placebo	387/418 (93%)	56/418 (13%)	32/418 (8%)	NR	Low
		Fingolimod O0.5	401/425 (94%)	43/425 (10%)	32/425 (8%)	NR	
FREEDOMS II[73]	24	Placebo	343/355 (97%)	45/355 (13%)	37/355 (10%)	NR	Low
		Fingolimod O0.5	350/358 (98%)	53/358 (15%)	66/358 (18%)	NR	
GALA[94]	12	Glatiramer acetate SC40	680/943 (72%)*	42/943 (4%)	29/943 (3%)	NR	Low
		Placebo	284/461 (62%)*	21/461 (5%)	6/461 (1%)	NR	
GATE[95]	9	Placebo	47/84 (56%)	2/84 (2%)	2/84 (2%)	NR	Low
		Glatiramer acetate SC20	194/357 (54%)	17/357 (5%)	4/357 (1%)	NR	
GOLDEN[96]	18	Interferon beta 1b IM 250	28/47 (60%)	1/47 (2%)	3/47 (6%)	NR	High

Study Name	Follow-up (Months)	Intervention	Number of patients experiencing each type of AE/total number of patients (% of patients)				ROB
			Any AEs	SAEs	AEs leading to treatment discontinuation	TRAE	
		Fingolimod O0.5	83/104 (80%)	9/104 (9%)	5/104 (5%)	NR	
IMPROVE[98]	4	Placebo	NR	3/60 (5%)	NR	NR	Some concerns
		Interferon beta 1a SC44	NR	4/120 (3%)	NR	NR	
INCOMIN[99]	Did not report any safety outcomes of interest; reported data for specific AEs only						
IFNB Multiple Sclerosis Study Group[97]	24	Placebo	NR	NR	1/123 (1%)	NR	Some concerns
		Interferon beta 1b IM 250	NR	NR	10/124 (8%)	NR	
Kappos 2011[100]	6	Ocrelizumab IV600	34/55 (62%)	1/55 (2%)	2/55 (4%)	17/55 (31%)	Low
		Interferon beta 1a IM30	30/54 (56%)	2/54 (4%)	1/54 (2%)	19/54 (35%)	
		Placebo	38/54 (70%)	2/54 (4%)	0/54 (0%)	25/54 (46%)	
Multiple Sclerosis Collaborative Research Group[105]	24	Placebo	NR	NR	2/143 (1%)	NR	Some concerns
		Interferon beta 1a IM30	NR	NR	7/158 (4%)	NR	
OPERA I[67]	24	Ocrelizumab IV600	327/408 (80%)	28/408 (7%)	NR	NR	Low
		Interferon beta 1a SC44	331/409 (81%)	32/409 (8%)	NR	NR	
OPERA II[67]	24	Ocrelizumab IV600	360/417 (86%)	29/417 (7%)	NR	NR	Low
		Interferon beta 1a SC44	357/417 (86%)	40/417 (10%)	NR	NR	
OPTIMUM[70]	27	Teriflunomide O14	499/566 (88%)	46/566 (8%)	34/566 (6%)	NR	Low
		Ponesimod O20	502/565 (89%)	49/565 (9%)	49/565 (9%)	NR	
PEGINTEGRITY[65]	24	Peginterferon beta 1a SC125	84/84 (100%)	2/84 (2%)	NR	63/84 (75%)	High
		Interferon beta 1a IM30	83/83 (100%)	2/83 (2%)	NR	66/83 (80%)	
Ponesimod Phase II study Group[101]	6	Placebo	90/121 (74%)	5/121 (4%)	NR	NR	Low
		Ponesimod O20	88/114 (77%)	7/114 (6%)	NR	NR	
PRISMS[102]	Did not report any safety outcomes of interest; reported data for specific AEs only						
REGARD[103]	24	Glatiramer acetate SC20	1917/375 (511%)*	27/375 (7%)	19/375 (5%)	618/375 (165%)*	Some concerns

Study Name	Follow-up (Months)	Intervention	Number of patients experiencing each type of AE/total number of patients (% of patients)				ROB
			Any AEs	SAEs	AEs leading to treatment discontinuation	TRAE	
		Interferon beta 1a SC44	1880/381 (493%)*	29/381 (8%)	23/381 (6%)	632/381 (166%)*	
REVEAL[78]	6	Natalizumab IV300	NR	0/54 (0%)	1/54 (2%)	23/54 (43%)	Some concerns
		Fingolimod O0.5	NR	2/54 (4%)	3/54 (6%)	32/54 (59%)	
Saida 2012[104]	6	Placebo	45/57 (79%)	3/57 (5%)	3/57 (5%)	NR	Low
		Fingolimod O0.5	52/57 (91%)	5/57 (9%)	6/57 (11%)	NR	
Saida 2017[79]	6	Natalizumab IV300	34/47 (72%)	7/47 (15%)	0/47 (0%)	NR	Low
		Placebo	41/47 (87%)	11/47 (23%)	1/47 (2%)	NR	
TRANSFORMS[75]	12	Interferon beta 1a IM30	395/431 (92%)	25/431 (6%)	16/431 (4%)	NR	Low
		Fingolimod O0.5	369/429 (86%)	30/429 (7%)	24/429 (6%)	NR	

*Studies reported total number of events rather than number of patients with events

Table 56 Proportion of participants reporting each of the safety outcomes of interest (HARRMS population)

Study Name	Follow-up (Months)	Intervention	Number of patients experiencing each type of AE/total number of patients (% of patients)				ROB
			Any AEs	SAEs	AEs leading to treatment discontinuation	TRAE	
CARE-MS II[71]	24	Alemtuzumab IV12	428/435 (98%)	138/435 (32%)	14/435 (3%)	NR	High
		Interferon beta 1a SC44	191/202 (95%)	77/202 (38%)	15/202 (7%)	NR	
Saida 2017[79]	6	Natalizumab IV300	34/47 (72%)	7/47 (15%)	0/47 (0%)	NR	Low
		Placebo	41/47 (87%)	11/47 (23%)	1/47 (2%)	NR	

HRQoL

Table 57 Quality of Life data (RRMS population)

Study Name	Intervention	Timepoint	EQ-5D			SF-36			Other measure reported	ROB
			N	Mean utility score (SD)	Mean VAS (SD)	Compo nent	N	mean (SD or 95% CI)		
CLARITY[86]	Cladribine O3.5	Baseline	353	0.72 (0.20)	70.22 (19.1)	NR			NR	High
	Placebo		349	0.72 (0.19)	68.9 (21.1)					
	Cladribine O3.5	12	338	0.72 (0.22)	70.7 (18.1)					
	Placebo		318	0.70 (0.22)	67.7 (20.6)					
	Cladribine O3.5	24	345	0.73 (0.22)	71.9 (19.4)					
	Placebo		338	0.66 (0.26)	66.3 (22.6)					
FREEDOMS II[73]	Fingolimod O0.5	24	358	Mean change from baseline = –0·016 (0·20)	Mean change from baseline 0·04 (15·0)	NR			NR	High
	Placebo		355	Mean change from baseline= –0·004 (0·23); p=0.328	–0·67 (15·21); p=0·143					
ADVANCE[80]	Peginterferon beta 1a SC125	11	512	No significant change from baseline (results not reported)		MCS & PCS	512	No significant change from baseline (results not reported)	MSIS-29	Low
	Placebo	11	500			MCS	500			
CARE-MS I[85]	Alemtuzumab IV12	24	376	No difference between groups (p>0.05)		MCS & PCS	376	No difference between groups (p>0.05)	FAMS	High
	Interferon beta 1a SC44		187				187			
CONFIRM[89]	Glatiramer acetate SC20	24	338	No difference between groups (p>0.05)	No difference between groups (p>0.05)	MCS	330	Greater improvement with GA than placebo (p<0.05)	NR	Low for VAS some concerns for other QoL data
	Placebo		349				344			

Study Name	Intervention	Timepoint	EQ-5D			SF-36			Other measure reported	ROB
			N	Mean utility score (SD)	Mean VAS (SD)	Component	N	mean (SD or 95% CI)		
	Glatiramer acetate SC20		NA			PCS	330	No difference between groups (p>0.05)		
	Placebo						344			
AFFIRM[77]	Natalizumab IV300	24M	NR			MCS	536	2.00 (10.91)	NR	High
	Placebo						264	-0.53 (10.52)		
	Natalizumab IV300					PCS	536	0.67 (8.05)		
	Placebo						264	-1.34 (8.47)		
OPERA I[67]	Ocrelizumab IV600	24M	NR			PCS	410	MD change from baseline=0.69 (95% CI -0.41, 1.80); p=0.22	NR	Low
	Interferon beta 1a SC44	24M					411			
OPERA II[67]	Ocrelizumab IV600	24M	NR			PCS	417	MD change from baseline=1.16 (95% CI 0.05, 2.27); p=0.04	NR	Low
	Interferon beta 1a SC44	24M					418			

Table 58 Quality of Life data (HARRMS population)

Study Name	Intervention	Timepoint	EQ-5D			SF-36			Other QoL measures reported	ROB
			N	Mean utility score (SD)	Mean VAS (SD)	Component	N	mean (SD or 95% CI)		
CARE-MS II[71]	Alemtuzumab IV12	24	412	No difference between groups (p>0.05)	Significantly greater improvement with Alemtuzumab	MCS	410	No difference between groups (p>0.05)	FAMS	High
	Interferon beta 1a SC44		173			PCS	172	Significantly greater improvement with Alemtuzumab (p<0.01)		
MIST[72]	AHCT	12	NR			Overall	49	70 (21.3)	NR	High
	iDMT						49	46.1 (22.5); p<0.001		

Appendix 5
Additional NMA Results

ARR (RRMS population)

Table 59 Comparison of results from fixed and random effects NMA for ARR (RRMS population)

	Fixed Effects	Random effects
Intervention	**RR (95% Credible interval)**	**RR (95% Credible interval)**
Alemtuzumab IV12	0.26 (0.19, 0.36)	0.26 (0.19, 0.36)
Cladribine O3.5	0.43 (0.34, 0.53)	0.42 (0.33, 0.54)
Fingolimod O0.5	0.45 (0.39, 0.52)	0.45 (0.39, 0.53)
Glatiramer acetate SC20	0.67 (0.60, 0.75)	0.67 (0.59, 0.77)
Glatiramer acetate SC40	0.69 (0.58, 0.83)	0.70 (0.57, 0.85)
Interferon beta 1a IM30	0.83 (0.73, 0.95)	0.84 (0.72, 0.97)
Interferon beta 1a SC22	0.69 (0.56, 0.84)	0.69 (0.55, 0.86)
Interferon beta 1a SC44	0.64 (0.56, 0.73)	0.64 (0.55, 0.74)
Interferon beta 1b IM 250	0.69 (0.60, 0.80)	0.70 (0.59, 0.82)
Natalizumab biosimilar	0.47 (0.23, 0.92)	0.47 (0.24, 0.99)
Natalizumab IV300	0.31 (0.24, 0.39)	0.31 (0.23, 0.40)
Ocrelizumab IV600	0.34 (0.27, 0.43)	0.34 (0.26, 0.44)
Ofatumumab SC20	0.49 (0.27, 0.86)	0.50 (0.28, 0.90)
Peginterferon beta 1a SC125	0.63 (0.49, 0.79)	0.62 (0.48, 0.81)
Ponesimod O20	0.76 (0.46, 1.28)	0.76 (0.45, 1.30)
Teriflunomide O14	1.08 (0.62, 1.89)	1.10 (0.63, 1.92)
Tau (95% CrI)	NA	0.05 (0.002, 0.14)
Mean log odds ratio	-0.59	-0.59
Residual deviance:	49.8 (on 55 data points)	49.9 (on 55 data points)
pD	27.9	30
DIC	77.7	79.9

Note: the random effects model had good convergence (all Rhat <1.01) and so informative priors were not needed.

Chosen model: Fixed effects model

Figure 28 Model fit for ARR assessed by individual study residual deviance (fixed effects analysis; RRMS population)

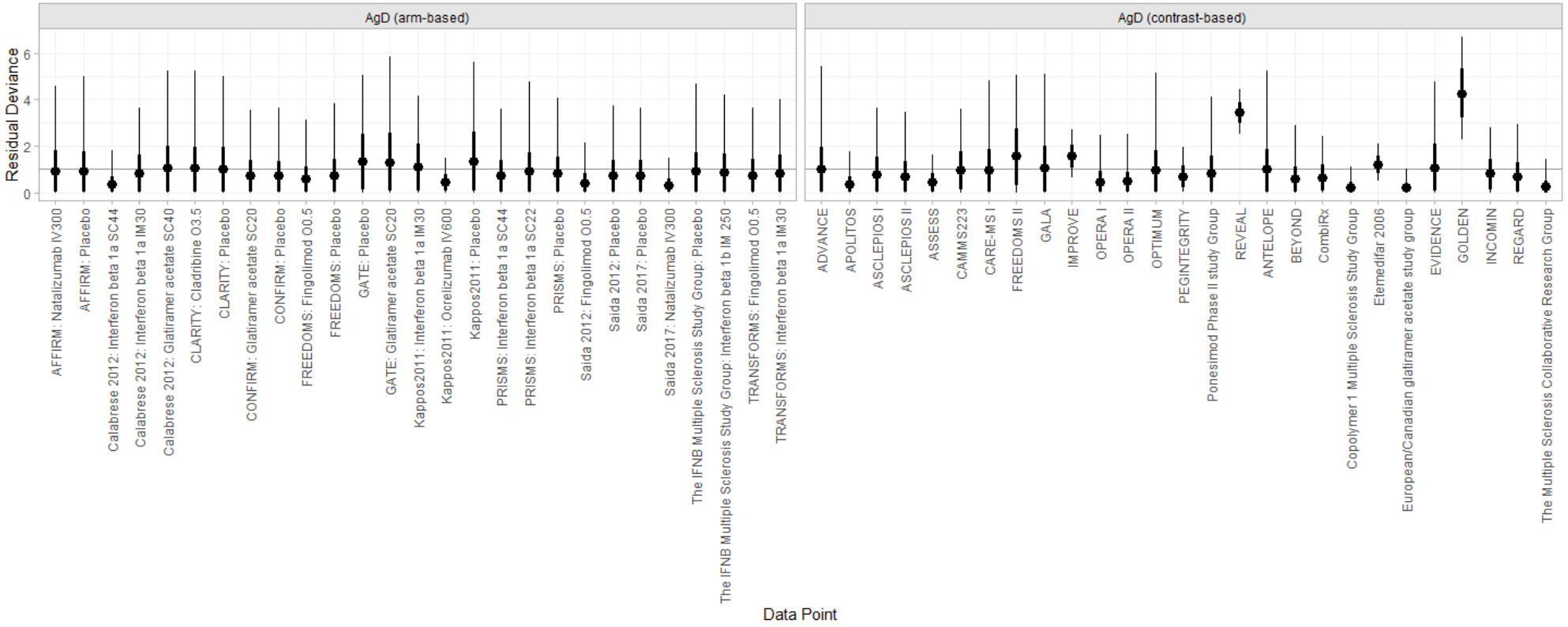

Table 60 Comparison (RR and 95% CrI) for each intervention pair for ARR (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Glatiramer acetate SC40	Interferon beta 1a IM30	Interferon beta 1a SC22	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab biosimilar	Natalizumab IV300	Ocrelizumab IV600	Ofatumumab SC20	Peginterferon beta 1a SC125	Ponesimod O20
Alemtuzumab IV12	0.26 (0.19, 0.36)															
Cladribine O3.5	0.43 (0.34, 0.53)	1.62 (1.10, 2.36)														
Fingolimod O0.5	0.45 (0.39, 0.52)	1.72 (1.22, 2.38)	1.06 (0.81, 1.39)													
Glatiramer acetate SC20	0.67 (0.60, 0.75)	2.56 (1.85, 3.51)	1.58 (1.22, 2.05)	1.49 (1.26, 1.77												
Glatiramer acetate SC40	0.69 (0.58, 0.83)	2.63 (1.84, 3.73)	1.63 (1.23, 2.17)	1.53 (1.22, 1.93	1.03 (0.83, 1.27)											
Interferon beta 1a IM30	0.83 (0.73, 0.95)	3.17 (2.30, 4.31)	1.96 (1.51, 2.54)	1.84 (1.55, 2.21	1.24 (1.07, 1.45)	1.20 (0.98, 1.48										
Interferon beta 1a SC22	0.69 (0.56, 0.84)	2.62 (1.84, 3.71)	1.62 (1.20, 2.20)	1.52 (1.20, 1.95	1.02 (0.83, 1.28)	0.99 (0.76, 1.31	0.83 (0.66, 1.03									
Interferon beta 1a SC44	0.64 (0.56, 0.73)	2.44 (1.84, 3.20)	1.51 (1.16, 1.97)	1.42 (1.18, 1.72	0.95 (0.82, 1.11)	0.93 (0.76, 1.14	0.77 (0.67, 0.89	0.93 (0.76, 1.14								
Interferon beta 1b IM 250	0.69 (0.60, 0.80)	2.63 (1.88, 3.65)	1.62 (1.24, 2.11)	1.53 (1.27, 1.87	1.03 (0.90, 1.19)	1.00 (0.80, 1.26	0.83 (0.70, 0.98	1.01 (0.79, 1.28	1.08 (0.91, 1.29							
Natalizumab biosimilar	0.47 (0.23, 0.92)	1.80 (0.82, 3.81)	1.11 (0.53, 2.29)	1.05 (0.50, 2.07	0.70 (0.34, 1.40)	0.68 (0.33, 1.38	0.57 (0.28, 1.13	0.69 (0.33, 1.40	0.74 (0.36, 1.46	0.68 (0.33, 1.36						
Natalizumab IV300	0.31 (0.24, 0.39)	1.16 (0.78, 1.70)	0.72 (0.51, 1.00)	0.68 (0.51, 0.90	0.46 (0.35, 0.60)	0.44 (0.33, 0.59	0.37 (0.27, 0.48	0.45 (0.32, 0.61	0.48 (0.36, 0.63	0.44 (0.33, 0.58	0.65 (0.34, 1.26					
Ocrelizumab IV600	0.34 (0.27, 0.43)	1.29 (0.91, 1.81)	0.79 (0.57, 1.10)	0.75 (0.57, 0.99	0.50 (0.39, 0.65)	0.49 (0.37, 0.65	0.41 (0.32, 0.52	0.49 (0.37, 0.66	0.53 (0.43, 0.64	0.49 (0.37, 0.64	0.71 (0.35, 1.50	1.10 (0.79, 1.53				
Ofatumumab SC20	0.49 (0.27, 0.86)	1.87 (0.99, 3.65)	1.16 (0.63, 2.15)	1.09 (0.60, 1.93	0.73 (0.40, 1.31)	0.71 (0.39, 1.30	0.59 (0.33, 1.06	0.72 (0.39, 1.31	0.77 (0.43, 1.38	0.71 (0.39, 1.28	1.04 (0.43, 2.61	1.61 (0.86, 3.01	1.46 (0.79, 2.71			
Peginterferon beta 1a SC125	0.63 (0.49, 0.79)	2.38 (1.63, 3.55)	1.47 (1.05, 2.05)	1.38 (1.05, 1.82	0.93 (0.72, 1.21)	0.90 (0.67, 1.22	0.75 (0.58, 0.98	0.91 (0.67, 1.23	0.98 (0.75, 1.29	0.90 (0.69, 1.18	1.32 (0.65, 2.82	2.04 (1.45, 2.87	1.85 (1.32, 2.59	1.27 (0.70, 2.39		
Ponesimod O20	0.76 (0.46, 1.28)	2.88 (1.60, 5.40)	1.78 (1.02, 3.18)	1.67 (0.98, 2.90	1.13 (0.67, 1.96)	1.09 (0.64, 1.92	0.91 (0.54, 1.57	1.10 (0.64, 1.96	1.18 (0.70, 2.03	1.09 (0.64, 1.91	1.60 (0.69, 3.85	2.47 (1.42, 4.42	2.24 (1.28, 4.02	1.54 (1.10, 2.13	1.21 (0.68, 2.15	
Teriflunomide O14	1.08 (0.62, 1.89)	4.13 (2.25, 7.88)	2.55 (1.41, 4.69)	2.40 (1.35, 4.28	1.61 (0.92, 2.83)	1.57 (0.89, 2.78	1.30 (0.74, 2.31	1.58 (0.88, 2.87	1.69 (0.96, 2.95	1.57 (0.87, 2.79	2.29 (0.97, 5.60	3.54 (1.94, 6.54	3.21 (1.78, 5.91	2.21 (1.79, 2.71	1.73 (0.94, 3.16	1.44 (1.11, 1.85)

Table 61 Probability that each intervention will rank in each position for ARR (fixed effects analysis; RRMS population)

Intervention	Probability of ranking position																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.16	0.61	1.00
Alemtuzumab IV12	0.72	0.91	0.98	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Cladribine O3.5	0.00	0.01	0.06	0.37	0.70	0.91	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Fingolimod O0.5	0.00	0.00	0.01	0.14	0.50	0.84	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Glatiramer acetate SC20	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.11	0.26	0.45	0.68	0.85	0.96	0.99	1.00	1.00	1.00
Glatiramer acetate SC40	0.00	0.00	0.00	0.00	0.00	0.00	0.04	0.12	0.22	0.36	0.49	0.65	0.84	0.96	0.99	1.00	1.00
Interferon beta 1a IM30	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.11	0.43	0.84	1.00	1.00
Interferon beta 1a SC22	0.00	0.00	0.00	0.00	0.00	0.01	0.05	0.13	0.25	0.38	0.52	0.67	0.83	0.95	0.99	1.00	1.00
Interferon beta 1a SC44	0.00	0.00	0.00	0.00	0.00	0.02	0.11	0.31	0.55	0.75	0.89	0.96	0.99	1.00	1.00	1.00	1.00
Interferon beta 1b IM 250	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.07	0.16	0.30	0.48	0.70	0.88	0.97	1.00	1.00	1.00
Natalizumab biosimilar	0.05	0.10	0.18	0.32	0.43	0.58	0.72	0.77	0.81	0.84	0.86	0.89	0.92	0.95	0.98	0.99	1.00
Natalizumab IV300	0.17	0.65	0.93	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ocrelizumab IV600	0.04	0.27	0.71	0.93	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ofatumumab SC20	0.02	0.06	0.12	0.24	0.36	0.55	0.75	0.80	0.84	0.87	0.89	0.92	0.97	0.99	1.00	1.00	1.00
Peginterferon beta 1a SC125	0.00	0.00	0.00	0.00	0.01	0.06	0.24	0.48	0.62	0.71	0.79	0.87	0.94	0.98	1.00	1.00	1.00
Ponesimod O20	0.00	0.00	0.00	0.00	0.01	0.03	0.09	0.21	0.27	0.32	0.36	0.42	0.50	0.65	0.85	1.00	1.00
Teriflunomide O14	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.02	0.03	0.04	0.05	0.07	0.11	0.19	0.40	1.00

ARR (RRMS population) – sensitivity analysis restricted to studies judged at low risk of bias

Figure 29 Network plot for NMA for ARR – studies at low risk of bias

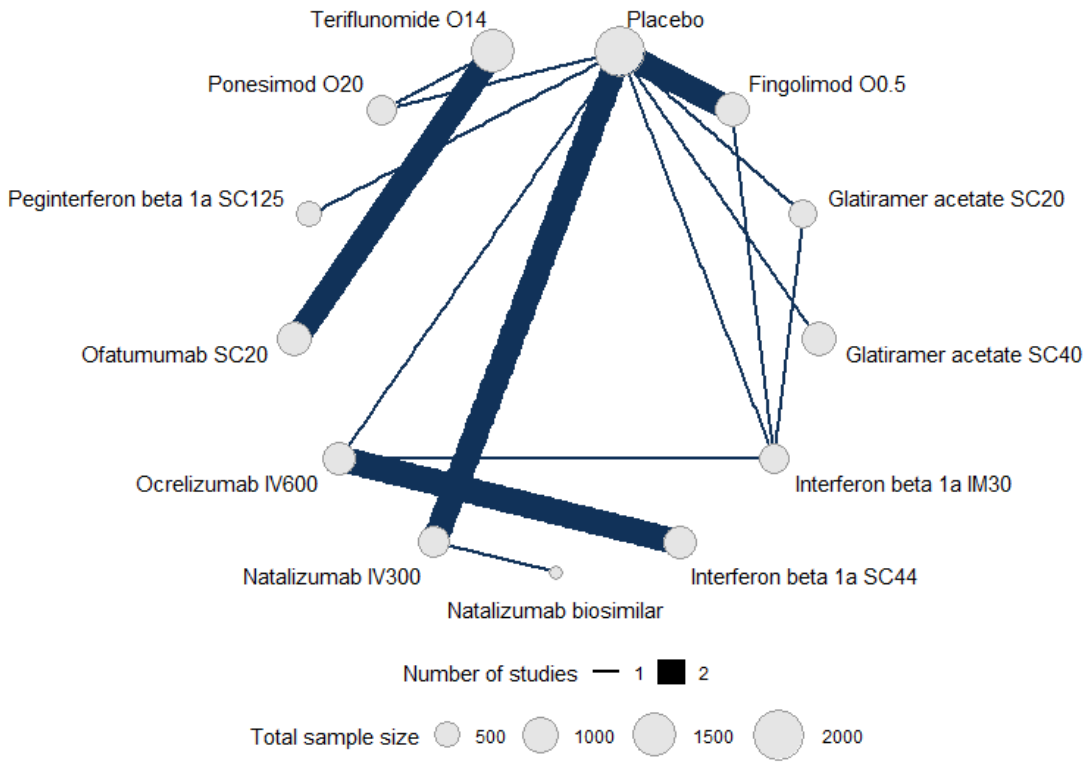

Table 62 Comparison of results from fixed and random effects NMA for ARR (RRMS population) – studies at low risk of bias

	Fixed Effects	Random effects
Intervention	**RR (95% Credible interval)**	**RR (95% Credible interval)**
Fingolimod O0.5	0.45 (0.36, 0.55)	0.45 (0.32, 0.60)
Glatiramer acetate SC20	0.70 (0.47, 1.05)	0.71 (0.45, 1.17)
Glatiramer acetate SC40	0.66 (0.54, 0.80)	0.65 (0.46, 0.95)
Interferon beta 1a IM30	0.89 (0.64, 1.23)	0.88 (0.57, 1.31)
Interferon beta 1a SC44	0.44 (0.13, 1.46)	0.45 (0.13, 1.61)
Natalizumab biosimilar	0.49 (0.25, 0.99)	0.48 (0.22, 1.09)
Natalizumab IV300	0.31 (0.25, 0.40)	0.31 (0.22, 0.45)
Ocrelizumab IV600	0.24 (0.07, 0.77)	0.24 (0.07, 0.81)
Ofatumumab SC20	0.52 (0.26, 1.01)	0.53 (0.23, 1.20)
Peginterferon beta 1a SC125	0.64 (0.50, 0.82)	0.64 (0.42, 0.92)
Ponesimod O20	0.79 (0.43, 1.41)	0.80 (0.41, 1.56)
Teriflunomide O14	1.14 (0.59, 2.15)	1.16 (0.55, 2.54)
Tau (95%CrI)	NA	0.12 (0.004, 0.40)
Mean log odds ratio	-0.58	-0.58
Residual deviance:	23.3 (on 25 data points)	23.4 (on 25 data points)
pD	19	20.4
DIC	42.2	43.9

Note: (all Rhat <1.01)

Parameters for the random effects model:

seed	437219664
prior_intercept	normal(0, scale = 5)
prior_trt	normal(0, scale = 10)
prior_het	half_normal(scale = 2)
adapt_delta	0.99

Table 63 Comparison of results from fixed and random effects NMA for ARR (RRMS population) – studies at low risk of bias

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]	p_rank[12]	p_rank[13]
Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.03	0.12	0.39	0.77	1.00
Fingolimod O0.5	0.00	0.06	0.27	0.61	0.89	0.98	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Glatiramer acetate SC20	0.00	0.00	0.01	0.03	0.10	0.22	0.37	0.54	0.75	0.89	0.97	0.99	1.00
Glatiramer acetate SC40	0.00	0.00	0.00	0.02	0.09	0.27	0.50	0.73	0.90	0.97	1.00	1.00	1.00
Interferon beta 1a IM30	0.00	0.00	0.00	0.00	0.00	0.01	0.02	0.07	0.21	0.45	0.71	0.91	1.00
Interferon beta 1a SC44	0.00	0.27	0.41	0.52	0.63	0.70	0.75	0.79	0.83	0.88	0.91	0.95	1.00
Natalizumab biosimilar	0.04	0.13	0.28	0.46	0.61	0.72	0.80	0.86	0.90	0.95	0.97	0.99	1.00
Natalizumab IV300	0.27	0.64	0.93	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ocrelizumab IV600	0.66	0.79	0.87	0.91	0.94	0.96	0.97	0.98	0.99	0.99	1.00	1.00	1.00
Ofatumumab SC20	0.03	0.10	0.23	0.39	0.55	0.69	0.78	0.86	0.93	0.98	1.00	1.00	1.00
Peginterferon beta 1a SC125	0.00	0.00	0.01	0.04	0.13	0.32	0.56	0.76	0.89	0.97	1.00	1.00	1.00
Ponesimod O20	0.00	0.00	0.01	0.02	0.06	0.14	0.25	0.35	0.49	0.66	0.81	1.00	1.00
Teriflunomide O14	0.00	0.00	0.00	0.00	0.00	0.01	0.02	0.05	0.08	0.15	0.26	0.40	1.00

Disease progression: CDP3 (RRMS population)

Table 64 Comparison of results from fixed and random effects NMA for CDP3 (RRMS population)

	Fixed Effects	Random Effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	0.26 (0.13, 0.53)	0.26 (0.11, 0.62)
Cladribine O3.5	0.67 (0.48, 0.95)	0.67 (0.42, 1.04)
Fingolimod O0.5	0.77 (0.63, 0.94)	0.77 (0.55, 1.05)
Glatiramer acetate SC20	0.91 (0.66, 1.24)	0.91 (0.60, 1.34)
Interferon beta 1a IM30	0.72 (0.49, 1.06)	0.73 (0.43, 1.21)
Interferon beta 1a SC22	0.55 (0.35, 0.85)	0.55 (0.31, 0.98)
Interferon beta 1a SC44	0.62 (0.43, 0.89)	0.63 (0.38, 1.02)
Interferon beta 1b IM 250	1.21 (0.82, 1.78)	1.20 (0.66, 2.16)
Natalizumab IV300	0.58 (0.43, 0.76)	0.58 (0.37, 0.93)
Ocrelizumab IV600	0.38 (0.24, 0.61)	0.38 (0.19, 0.70)
Peginterferon beta 1a SC125	0.61 (0.39, 0.95)	0.61 (0.33, 1.07)
Tau (95% CrI)	NA	0.14 (0.005, 0.5)
Mean log odds	-0.48	-0.48
Residual deviance	11.8 (on 16 data points)	12.8 (on 16 data points)
pD	11	12.3
DIC	22.8	25.1

Note: (all Rhat <1.01)

Parameters for the random effects model:

prior_intercept	normal(0, scale = 10)
prior_trt	normal(0, scale = 10)
prior_het	half_normal(scale = 2)
adapt_delta	0.999

Chosen model: Fixed effects model

Figure 30 Model fit for CDP3 assessed by individual study residual deviance (fixed effects analysis; RRMS population)

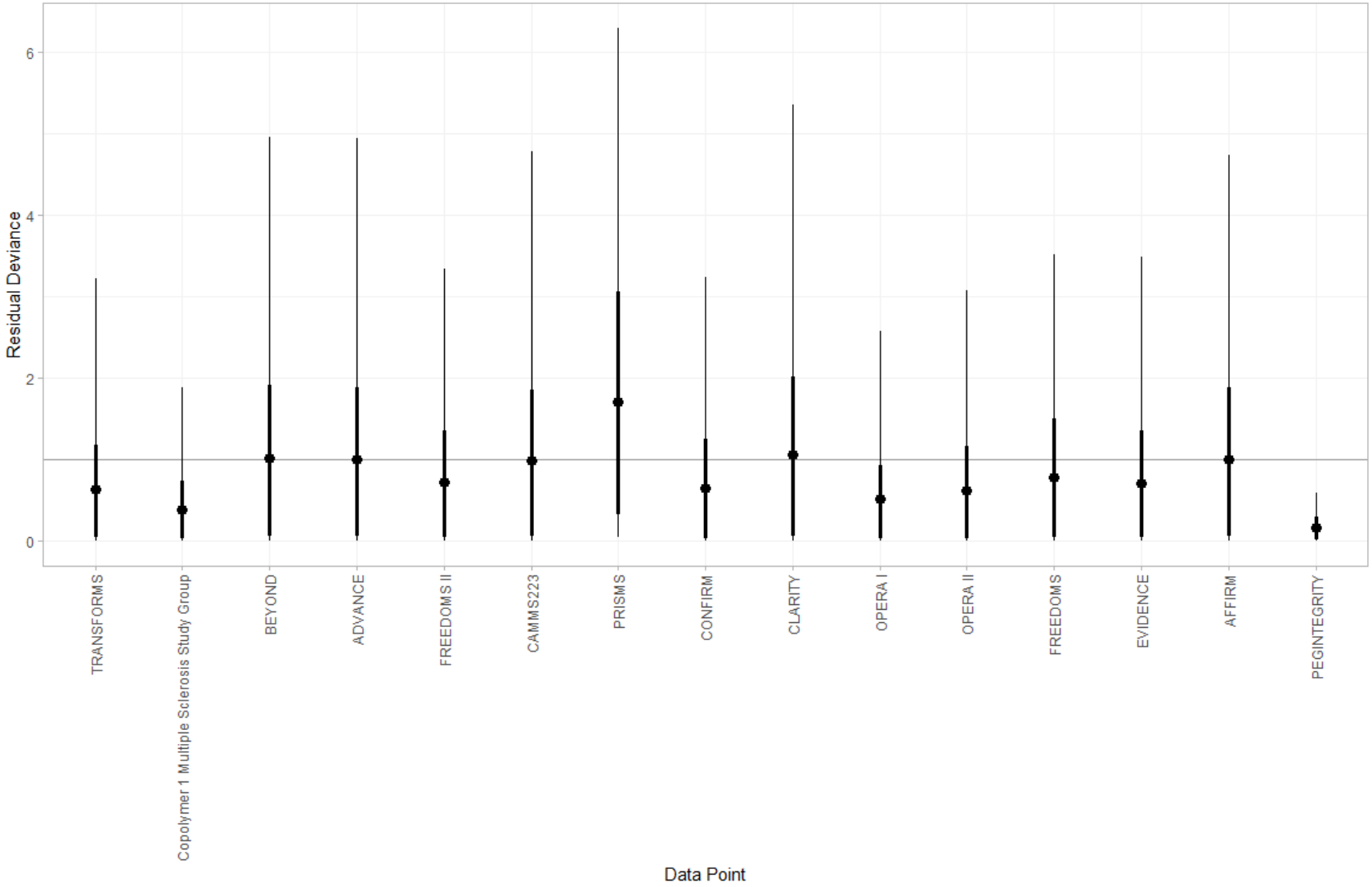

Table 65 Comparison (HR and 95% CrI) for each intervention pair for CDP3 (random effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Interferon beta 1a IM30	Interferon beta 1a SC22	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab IV300	Ocrelizumab IV600
Alemtuzumab IV12	0.26 (0.13, 0.53)										
Cladribine O3.5	0.67 (0.48, 0.95)	2.57 (1.19, 5.60)									
Fingolimod O0.5	0.77 (0.63, 0.94)	2.92 (1.43, 5.87)	1.14 (0.76, 1.70)								
Glatiramer acetate SC20	0.91 (0.66, 1.24)	3.48 (1.62, 7.35)	1.35 (0.85, 2.11)	1.19 (0.81, 1.72)							
Interferon beta 1a IM30	0.72 (0.49, 1.06)	2.75 (1.39, 5.44)	1.07 (0.63, 1.80)	0.94 (0.65, 1.38)	0.79 (0.49, 1.31)						
Interferon beta 1a SC22	0.55 (0.35, 0.85)	2.10 (0.92, 4.73)	0.82 (0.47, 1.42)	0.72 (0.44, 1.15)	0.60 (0.35, 1.02)	0.76 (0.42, 1.40)					
Interferon beta 1a SC44	0.62 (0.43, 0.89)	2.38 (1.31, 4.26)	0.93 (0.57, 1.53)	0.81 (0.56, 1.17)	0.68 (0.43, 1.09)	0.87 (0.62, 1.22)	1.14 (0.64, 2.02)				
Interferon beta 1b IM 250	1.21 (0.82, 1.78)	4.60 (2.05, 10.32)	1.79 (1.06, 2.99)	1.57 (1.01, 2.41)	1.32 (1.04, 1.68)	1.67 (0.95, 2.92)	2.20 (1.22, 4.00)	1.93 (1.13, 3.28)			
Natalizumab IV300	0.58 (0.43, 0.76)	2.21 (1.05, 4.76)	0.86 (0.55, 1.33)	0.76 (0.54, 1.08)	0.64 (0.42, 0.98)	0.80 (0.50, 1.31)	1.06 (0.62, 1.78)	0.93 (0.59, 1.48)	0.48 (0.30, 0.79)		
Ocrelizumab IV600	0.38 (0.24, 0.61)	1.44 (0.74, 2.81)	0.56 (0.32, 1.01)	0.49 (0.30, 0.80)	0.41 (0.24, 0.73)	0.52 (0.33, 0.81)	0.68 (0.36, 1.30)	0.60 (0.45, 0.81)	0.31 (0.17, 0.57)	0.65 (0.38, 1.13)	
Peginterferon beta 1a SC125	0.61 (0.39, 0.95)	2.34 (1.04, 5.26)	0.91 (0.53, 1.57)	0.80 (0.49, 1.30)	0.67 (0.40, 1.13)	0.85 (0.47, 1.50)	1.11 (0.60, 2.09)	0.98 (0.56, 1.69)	0.51 (0.28, 0.91)	1.06 (0.63, 1.77)	1.63 (0.84, 3.04)

Table 66 Probability that each intervention will rank in each position for CDP3 (random effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]	p_rank[12]
Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.32	0.84	1.00
Alemtuzumab IV12	0.83	0.96	0.98	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Cladribine O3.5	0.00	0.01	0.07	0.18	0.33	0.50	0.67	0.81	0.94	0.98	1.00	1.00
Fingolimod O0.5	0.00	0.00	0.00	0.01	0.04	0.11	0.28	0.58	0.90	0.99	1.00	1.00
Glatiramer acetate SC20	0.00	0.00	0.00	0.00	0.01	0.04	0.08	0.16	0.33	0.73	1.00	1.00
Interferon beta 1a IM30	0.00	0.00	0.03	0.09	0.19	0.33	0.50	0.70	0.86	0.95	0.98	1.00
Interferon beta 1a SC22	0.02	0.12	0.40	0.58	0.72	0.82	0.89	0.95	0.99	1.00	1.00	1.00
Interferon beta 1a SC44	0.00	0.00	0.12	0.30	0.50	0.69	0.85	0.94	0.98	1.00	1.00	1.00
Interferon beta 1b IM 250	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.02	0.06	0.19	1.00
Natalizumab IV300	0.00	0.04	0.24	0.48	0.69	0.84	0.93	0.97	1.00	1.00	1.00	1.00
Ocrelizumab IV600	0.14	0.82	0.94	0.98	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Peginterferon beta 1a SC125	0.01	0.05	0.21	0.38	0.53	0.67	0.79	0.88	0.95	0.99	1.00	1.00

Disease progression: CDP6 (RRMS population)

Table 67 Comparison of results from fixed and random effects NMA for CDP6 (RRMS population)

Note: the random effects model had good convergence and so informative priors were not needed.

	Fixed effects	Random Effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	0.34 (0.14, 0.80)	0.29 (0.05, 1.42)
Cladribine O3.5	0.98 (0.79, 1.20)	0.99 (0.33, 2.94)
Fingolimod O0.5	0.67 (0.51, 0.88)	0.67 (0.31, 1.44)
Glatiramer acetate SC20	0.63 (0.31, 1.25)	0.60 (0.16, 2.65)
Interferon beta 1a IM30	0.64 (0.35, 1.16)	0.65 (0.21, 2.05)
Interferon beta 1a SC44	0.67 (0.32, 1.39)	0.63 (0.15, 2.52)
Interferon beta 1b IM 250	0.28 (0.12, 0.66)	0.29 (0.06, 1.47)
Natalizumab IV300	0.46 (0.33, 0.63)	0.46 (0.17, 1.28)
Ocrelizumab IV600	0.40 (0.18, 0.91)	0.38 (0.07, 1.95)
Peginterferon beta 1a SC125	0.46 (0.26, 0.81)	0.47 (0.15, 1.50)
Tau (95% CrI)	NA	0.39 (0.02, 1.19)
Mean log odds	-0.65	-0.68
Residual deviance	17.9 (on 14 data points)	14.9 on 14 data points
pD	10	12.9
DIC	28	27.9

(all Rhat <1.01)

Parameters for the random effects model:

Seed	437219664
trt_effects	"random"
prior_intercept	normal(0, scale = 10)
prior_trt	normal(0, scale = 10)
prior_het	half_normal(scale = 2)
control	list(max_treedepth = 12),
adapt_delta	0.999

Chosen model: Fixed effects model

Figure 31 Model fit for CDP6 assessed by individual study residual deviance (random effects analysis; RRMS population)

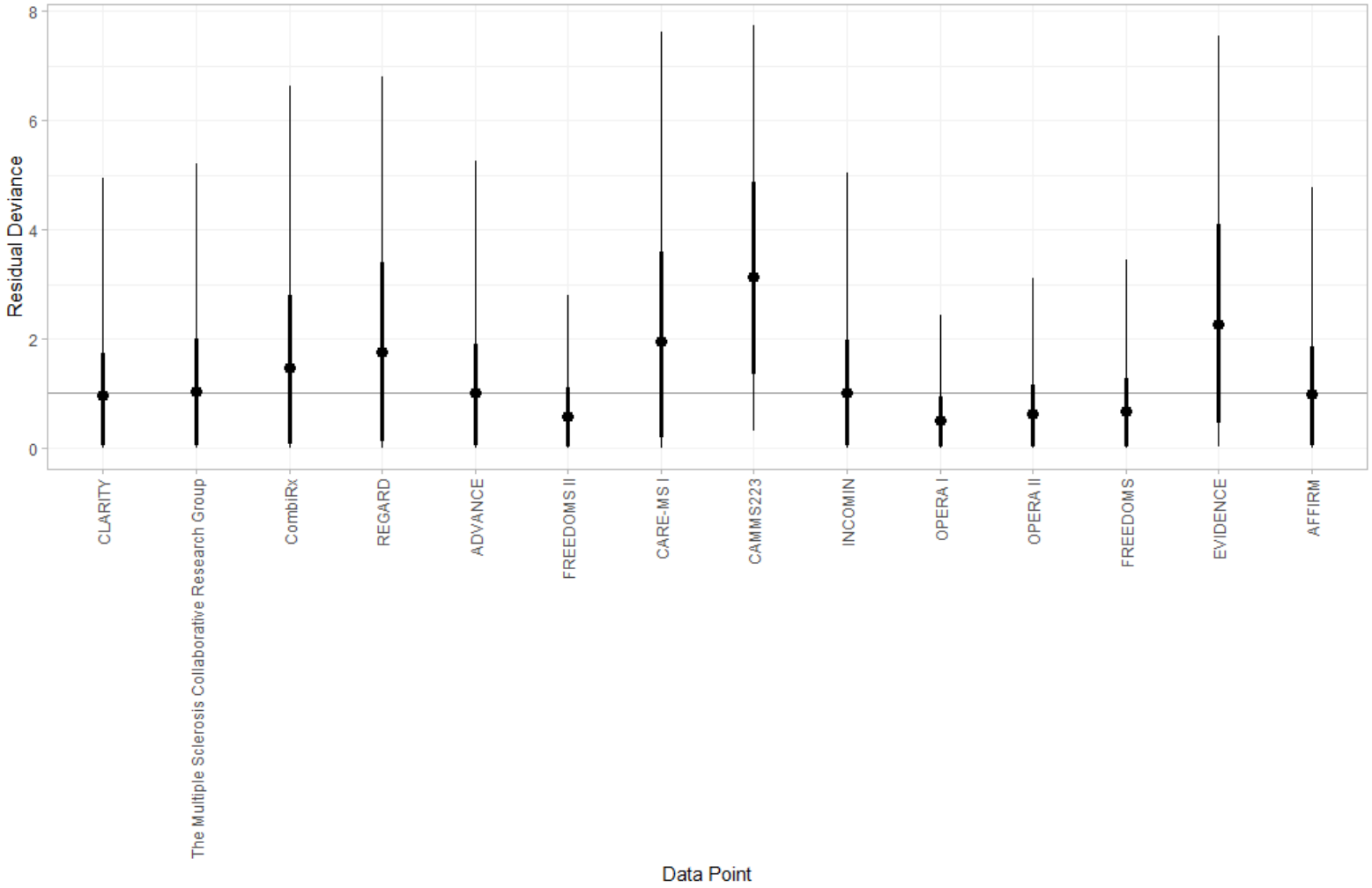

Table 68 Comparison (HR and 95% CrI) for each intervention pair for CDP6 (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab IV300	Ocrelizumab IV600
Alemtuzumab IV12	0.34 (0.14, 0.80)									
Cladribine O3.5	0.98 (0.79, 1.20)	2.88 (1.18, 7.20)								
Fingolimod O0.5	0.67 (0.51, 0.88)	1.98 (0.79, 4.90)	0.69 (0.49, 0.96)							
Glatiramer acetate SC20	0.63 (0.31, 1.25)	1.88 (1.05, 3.40)	0.65 (0.32, 1.34)	0.95 (0.45, 1.93)						
Interferon beta 1a IM30	0.64 (0.35, 1.16)	1.90 (1.02, 3.54)	0.66 (0.35, 1.23)	0.96 (0.50, 1.83)	1.01 (0.73, 1.41)					
Interferon beta 1a SC44	0.67 (0.32, 1.39)	1.98 (1.24, 3.15)	0.69 (0.31, 1.49)	1.00 (0.46, 2.16)	1.05 (0.73, 1.53)	1.04 (0.69, 1.58)				
Interferon beta 1b IM 250	0.28 (0.12, 0.66)	0.84 (0.36, 1.93)	0.29 (0.12, 0.70)	0.42 (0.18, 1.03)	0.45 (0.23, 0.87)	0.44 (0.25, 0.78)	0.42 (0.21, 0.85)			
Natalizumab IV300	0.46 (0.33, 0.63)	1.36 (0.54, 3.47)	0.47 (0.32, 0.70)	0.69 (0.46, 1.03)	0.73 (0.34, 1.59)	0.72 (0.38, 1.44)	0.69 (0.31, 1.55)	1.62 (0.67, 4.00)		
Ocrelizumab IV600	0.40 (0.18, 0.91)	1.20 (0.67, 2.15)	0.41 (0.17, 0.95)	0.60 (0.26, 1.44)	0.64 (0.38, 1.06)	0.63 (0.36, 1.08)	0.60 (0.43, 0.85)	1.42 (0.64, 3.16)	0.88 (0.36, 2.09)	
Peginterferon beta 1a SC125	0.46 (0.26, 0.81)	1.35 (0.48, 3.79)	0.47 (0.26, 0.87)	0.68 (0.37, 1.30)	0.72 (0.30, 1.77)	0.71 (0.32, 1.60)	0.68 (0.27, 1.74)	1.61 (0.59, 4.42)	0.99 (0.51, 1.89)	1.13 (0.43, 2.96)

Table 69 Probability that each intervention will rank in each position for CDP6 (fixed effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]
Placebo	0.00	0.00	0.01	0.02	0.04	0.07	0.11	0.19	0.31	0.68	1.00
Alemtuzumab IV12	0.30	0.57	0.73	0.83	0.90	0.93	0.96	0.97	0.99	1.00	1.00
Cladribine O3.5	0.01	0.02	0.04	0.07	0.10	0.15	0.20	0.27	0.39	0.63	1.00
Fingolimod O0.5	0.01	0.04	0.09	0.17	0.27	0.39	0.50	0.64	0.89	0.96	1.00
Glatiramer acetate SC20	0.01	0.03	0.08	0.19	0.33	0.48	0.64	0.76	0.87	0.93	1.00
Interferon beta 1a IM30	0.00	0.01	0.03	0.08	0.18	0.37	0.58	0.76	0.89	0.96	1.00
Interferon beta 1a SC44	0.00	0.01	0.04	0.14	0.27	0.42	0.57	0.71	0.83	0.91	1.00
Interferon beta 1b IM 250	0.38	0.58	0.73	0.82	0.88	0.92	0.95	0.97	0.98	0.99	1.00
Natalizumab IV300	0.09	0.22	0.36	0.50	0.63	0.72	0.81	0.90	0.95	0.98	1.00
Ocrelizumab IV600	0.10	0.30	0.53	0.69	0.80	0.87	0.91	0.95	0.97	0.99	1.00
Peginterferon beta 1a SC125	0.11	0.23	0.36	0.50	0.60	0.69	0.77	0.87	0.94	0.97	1.00

Disease progression: CDP3 and CDP6 combined (RRMS population)

Table 70 Comparison of results from fixed and random effects NMA for CDP3 and CDP6 combined (RRMS population)

	Fixed effects	Random Effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	0.36 (0.21, 0.63)	0.33 (0.14, 0.77)
Cladribine O3.5	0.98 (0.78, 1.22)	0.97 (0.44, 2.04)
Fingolimod O0.5	0.71 (0.55, 0.90)	0.73 (0.45, 1.19)
Glatiramer acetate SC20	0.72 (0.57, 0.92)	0.71 (0.44, 1.12)
Interferon beta 1a IM30	0.80 (0.61, 1.05)	0.81 (0.49, 1.30)
Interferon beta 1a SC22	0.55 (0.36, 0.87)	0.57 (0.26, 1.34)
Interferon beta 1a SC44	0.71 (0.52, 0.96)	0.71 (0.40, 1.23)
Interferon beta 1b IM 250	0.83 (0.60, 1.15)	0.66 (0.29, 1.29)
Natalizumab IV300	0.46 (0.33, 0.64)	0.46 (0.21, 1.02)
Ocrelizumab IV600	0.43 (0.27, 0.68)	0.43 (0.19, 0.98)
Peginterferon beta 1a SC125	0.46 (0.27, 0.80	0.46 (0.19, 1.08)
Tau (95% CrI)	NA	0.33 (0.07, 0.69)
Mean log odds	-0.50	-0.52
Residual deviance	33.2 (on 21 data points)	21.3 (on 21 data points)
pD	11.1	117.3
DIC	44.3	38.7

Note: the random effects model had good convergence (all Rhat <1.01) and so informative priors were not needed.

Chosen model: Fixed effects model

Figure 32 Model fit for CDP3 and CDP6 combined assessed by individual study residual deviance (random effects analysis; RRMS population)

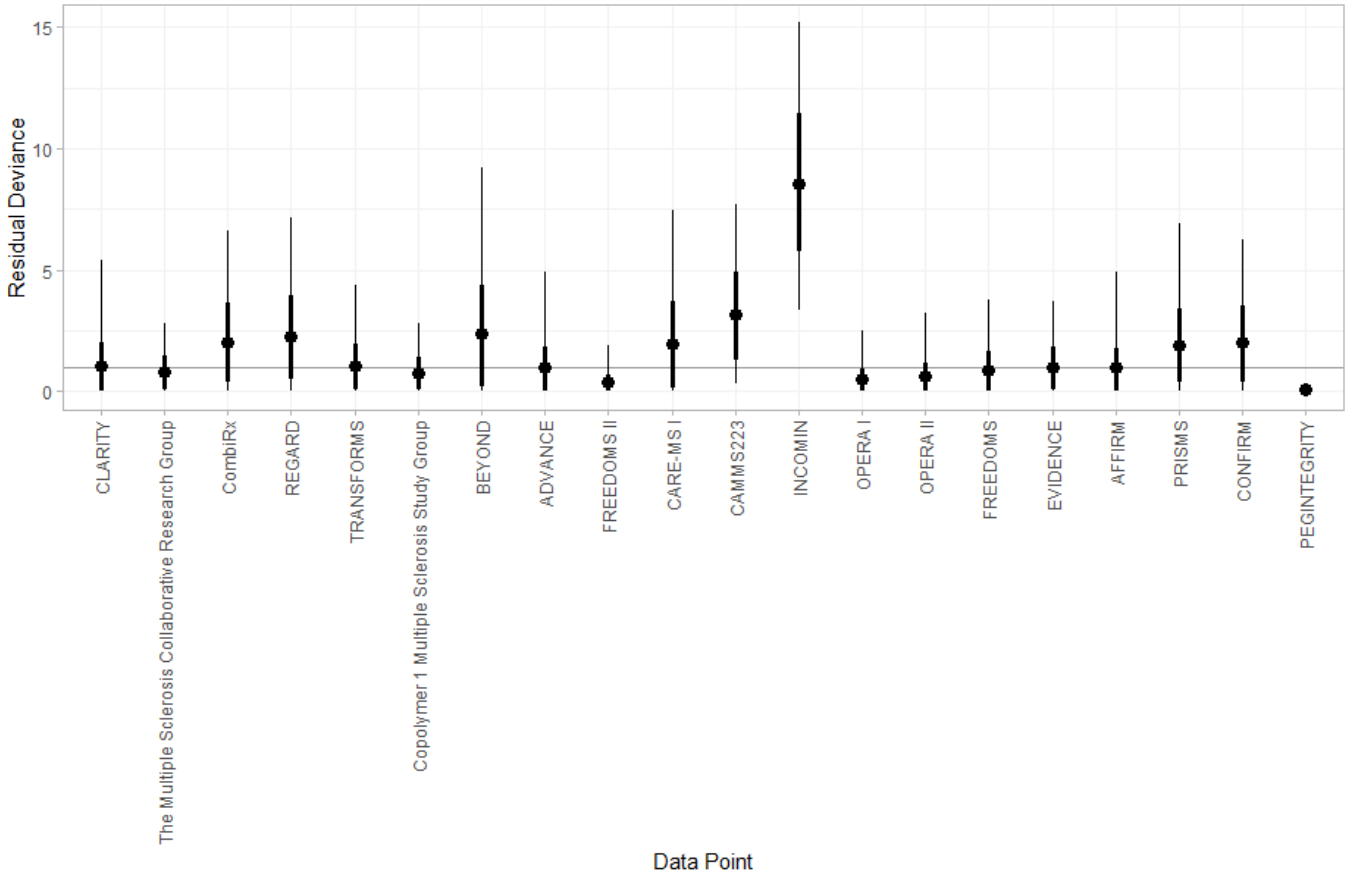

Table 71 Comparison (HR and 95% CrI) for each intervention pair for CDP3 and CDP6 combined (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Interferon beta 1a IM30	Interferon beta 1a SC22	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab IV300	Ocrelizumab IV600
Alemtuzumab IV12	0.36 (0.21, 0.63)										
Cladribine O3.5	0.98 (0.78, 1.22)	2.71 (1.49, 4.86)									
Fingolimod O0.5	0.71 (0.55, 0.90)	1.96 (1.09, 3.53)	0.72 (0.52, 1.00)								
Glatiramer acetate SC20	0.72 (0.57, 0.92)	2.01 (1.17, 3.50)	0.74 (0.53, 1.02)	1.02 (0.74, 1.41)							
Interferon beta 1a IM30	0.80 (0.61, 1.05)	2.22 (1.24, 3.87)	0.82 (0.58, 1.16)	1.13 (0.84, 1.55)	1.10 (0.85, 1.42)						
Interferon beta 1a SC22	0.55 (0.36, 0.87)	1.52 (0.74, 3.01)	0.56 (0.35, 0.92)	0.78 (0.47, 1.30)	0.76 (0.46, 1.28)	0.69 (0.41, 1.16)					
Interferon beta 1a SC44	0.71 (0.52, 0.96)	1.97 (1.25, 3.12)	0.73 (0.50, 1.07)	1.01 (0.70, 1.45)	0.98 (0.72, 1.33)	0.89 (0.65, 1.24)	1.30 (0.76, 2.21)				
Interferon beta 1b IM 250	0.83 (0.60, 1.15)	2.29 (1.27, 4.15)	0.85 (0.58, 1.24)	1.17 (0.81, 1.70)	1.14 (0.91, 1.43)	1.03 (0.76, 1.40)	1.51 (0.87, 2.57)	1.16 (0.81, 1.68)			
Natalizumab IV300	0.46 (0.33, 0.64)	1.28 (0.66, 2.44)	0.47 (0.32, 0.70)	0.65 (0.43, 0.98)	0.64 (0.42, 0.95)	0.58 (0.38, 0.88)	0.84 (0.48, 1.47)	0.65 (0.42, 1.03)	0.56 (0.35, 0.88)		
Ocrelizumab IV600	0.43 (0.27, 0.68)	1.19 (0.67, 2.08)	0.44 (0.26, 0.74)	0.61 (0.37, 1.00)	0.59 (0.38, 0.93)	0.54 (0.33, 0.86)	0.78 (0.42, 1.47)	0.60 (0.43, 0.85)	0.52 (0.32, 0.84)	0.93 (0.54, 1.62)	
Peginterferon beta 1a SC125	0.46 (0.27, 0.80)	1.29 (0.58, 2.82)	0.47 (0.26, 0.85)	0.66 (0.35, 1.19)	0.64 (0.35, 1.18)	0.58 (0.31, 1.10)	0.84 (0.42, 1.68)	0.65 (0.34, 1.23)	0.56 (0.30, 1.06)	1.01 (0.52, 1.93)	1.08 (0.53, 2.20)

Table 72 Probability that each intervention will rank in each position for CDP3 and CDP6 combined (fixed effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]	p_rank[12]
Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.09	0.51	1.00
Alemtuzumab IV12	0.53	0.74	0.87	0.95	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Cladribine O3.5	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.04	0.11	0.24	0.63	1.00
Fingolimod O0.5	0.00	0.00	0.00	0.04	0.16	0.42	0.62	0.78	0.90	0.99	1.00	1.00
Glatiramer acetate SC20	0.00	0.00	0.00	0.02	0.09	0.29	0.58	0.83	0.97	1.00	1.00	1.00
Interferon beta 1a IM30	0.00	0.00	0.00	0.00	0.02	0.08	0.20	0.39	0.66	0.91	0.97	1.00
Interferon beta 1a SC22	0.04	0.11	0.25	0.47	0.76	0.85	0.90	0.94	0.97	0.99	1.00	1.00
Interferon beta 1a SC44	0.00	0.00	0.00	0.03	0.15	0.39	0.61	0.76	0.89	0.97	0.99	1.00
Interferon beta 1b IM 250	0.00	0.00	0.00	0.01	0.02	0.07	0.15	0.29	0.51	0.82	0.91	1.00
Natalizumab IV300	0.10	0.32	0.59	0.85	0.97	0.99	0.99	1.00	1.00	1.00	1.00	1.00
Ocrelizumab IV600	0.16	0.47	0.73	0.88	0.98	0.99	1.00	1.00	1.00	1.00	1.00	1.00
Peginterferon beta 1a SC125	0.18	0.36	0.55	0.74	0.88	0.93	0.95	0.97	0.98	0.99	1.00	1.00

MRI Gd+ lesions (RRMS population)

Table 73 Comparison of results from fixed and random effects NMA for MRI Gd+ lesions (RRMS population)

	Fixed effects	Random Effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	0.20 (0.11, 0.35)	0.19 (0.10, 0.37)
Cladribine O3.5	0.24 (0.18, 0.33)	0.24 (0.16, 0.37)
Fingolimod O0.5	0.33 (0.27, 0.40)	0.33 (0.26, 0.42)
Glatiramer acetate SC20	0.77 (0.62, 0.95)	0.76 (0.58, 0.99)
Interferon beta 1a IM30	0.60 (0.47, 0.75)	0.61 (0.46, 0.81)
Interferon beta 1a SC44	0.53 (0.42, 0.67)	0.52 (0.38, 0.69)
Interferon beta 1b IM 250	0.28 (0.15, 0.51)	0.28 (0.15, 0.56)
Natalizumab biosimilar	0.11 (0.05, 0.22)	0.11 (0.05, 0.25)
Natalizumab IV300	0.14 (0.09, 0.21)	0.14 (0.09, 0.22)
Ocrelizumab IV600	0.09 (0.06, 0.13	0.09 (0.05, 0.14)
Tau (95%CrI)	NA	0.11 (0.006, 0.32)
Mean log odds ratio	-1.35	-1.35
Residual deviance	17.8 (on 19 data points)	16.5 (on 19 data points)
pD	10.2	12
DIC	27.9	28.5

Note: the random effects model had good convergence (all Rhat <1.01) and so informative priors were not needed.

Chosen model: Fixed effects model

Figure 33 Model fit for MRI Gd+ lesions combined assessed by individual study residual deviance (fixed effects analysis; RRMS population)

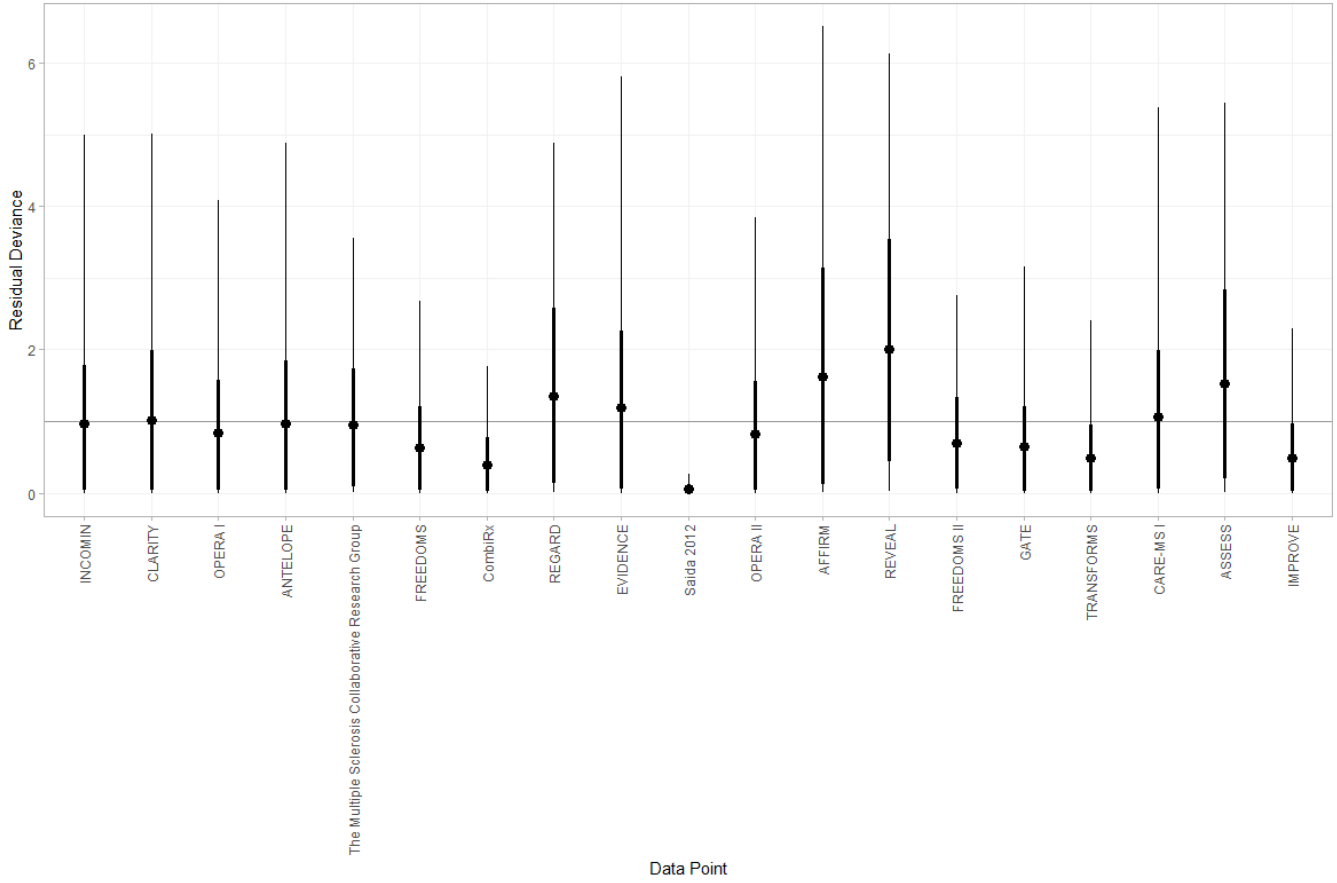

Table 74 Comparison (HR and 95% CrI) for each intervention pair for MRI Gd+ lesions (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab biosimilar	Natalizumab IV300
Alemtuzumab IV12	0.20 (0.11, 0.35)									
Cladribine O3.5	0.24 (0.18, 0.33)	1.23 (0.64, 2.39)								
Fingolimod O0.5	0.33 (0.27, 0.40)	1.66 (0.94, 2.99)	1.35 (0.94, 1.94)							
Glatiramer acetate SC20	0.77 (0.62, 0.95)	3.87 (2.16, 7.01)	3.14 (2.14, 4.56)	2.33 (1.83, 3.00)						
Interferon beta 1a IM30	0.60 (0.47, 0.75)	3.01 (1.76, 5.25)	2.45 (1.68, 3.60)	1.82 (1.42, 2.34)	0.78 (0.61, 0.99)					
Interferon beta 1a SC44	0.53 (0.42, 0.67)	2.69 (1.61, 4.66)	2.19 (1.51, 3.19)	1.62 (1.25, 2.11)	0.70 (0.55, 0.88)	0.89 (0.77, 1.04)				
Interferon beta 1b IM 250	0.28 (0.15, 0.51)	1.41 (0.65, 3.08)	1.15 (0.59, 2.20)	0.85 (0.47, 1.56)	0.36 (0.20, 0.67)	0.47 (0.27, 0.81)	0.52 (0.30, 0.93)			
Natalizumab biosimilar	0.11 (0.05, 0.22)	0.55 (0.22, 1.36)	0.44 (0.20, 0.98)	0.33 (0.16, 0.69)	0.14 (0.07, 0.30)	0.18 (0.09, 0.39)	0.20 (0.10, 0.43)	0.39 (0.15, 0.98)		
Natalizumab IV300	0.14 (0.09, 0.21)	0.70 (0.35, 1.44)	0.57 (0.35, 0.97)	0.42 (0.29, 0.64)	0.18 (0.12, 0.28)	0.23 (0.15, 0.36)	0.26 (0.17, 0.41)	0.50 (0.25, 1.00)	1.29 (0.69, 2.37)	
Ocrelizumab IV600	0.09 (0.06, 0.13)	0.44 (0.24, 0.83)	0.36 (0.22, 0.59)	0.27 (0.17, 0.41)	0.11 (0.08, 0.17)	0.15 (0.10, 0.21)	0.16 (0.12, 0.23)	0.31 (0.16, 0.62)	0.81 (0.35, 1.85)	0.63 (0.36, 1.10)

Table 75 Probability that each intervention will rank in each position for MRI Gd+ lesions (fixed effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]
Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	1.00
Alemtuzumab IV12	0.00	0.06	0.19	0.66	0.87	0.97	1.00	1.00	1.00	1.00	1.00
Cladribine O3.5	0.00	0.00	0.02	0.22	0.69	0.96	1.00	1.00	1.00	1.00	1.00
Fingolimod O0.5	0.00	0.00	0.00	0.00	0.04	0.36	1.00	1.00	1.00	1.00	1.00
Glatiramer acetate SC20	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.99	1.00
Interferon beta 1a IM30	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.08	0.98	1.00	1.00
Interferon beta 1a SC44	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.92	1.00	1.00	1.00
Interferon beta 1b IM 250	0.00	0.01	0.03	0.15	0.40	0.71	0.99	0.99	1.00	1.00	1.00
Natalizumab biosimilar	0.30	0.76	0.92	0.98	0.99	1.00	1.00	1.00	1.00	1.00	1.00
Natalizumab IV300	0.01	0.22	0.85	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ocrelizumab IV600	0.68	0.95	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

MRI T2 weighted lesions (RRMS population)

Table 76 Comparison of results from fixed and random effects NMA for MRI T2 weighted lesions (RRMS population)

	Fixed effects	Random Effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	0.61 (0.45, 0.81)	0.60 (0.41, 0.86)
Cladribine O3.5	0.52 (0.43, 0.64)	0.52 (0.39, 0.69)
Fingolimod O0.5	0.63 (0.55, 0.72)	0.63 (0.53, 0.73)
Glatiramer acetate SC20	0.80 (0.66, 0.98)	0.79 (0.61, 1.01)
Interferon beta 1a IM30	0.77 (0.64, 0.92)	0.75 (0.59, 0.95)
Interferon beta 1a SC22	0.88 (0.71, 1.10)	0.87 (0.66, 1.15)
Interferon beta 1a SC44	0.72 (0.61, 0.85)	0.71 (0.57, 0.86)
Interferon beta 1b IM 250	0.46 (0.29, 0.73)	0.46 (0.27, 0.76)
Natalizumab biosimilar	0.46 (0.30, 0.70)	0.46 (0.28, 0.74)
Natalizumab IV300	0.50 (0.42, 0.59)	0.49 (0.38, 0.62)
Ocrelizumab IV600	0.44 (0.36, 0.55)	0.43 (0.32, 0.57)
Tau	NA	0.07 (0.002, 0.25)
Mean log odds ratio	-0.51	-0.52
Residual deviance	15.4 (on 18 data points)	15.6 (on 18 data points)
pD	11	12.3
DIC	26.4	27.9

(all Rhat <1.01)

RE parameters:

seed	437219664
prior_intercept	normal(0, scale = 10)
prior_trt	normal(0, scale = 10)
prior_het	half_normal(scale = 2)
adapt_delta	0.999

Chosen model: Fixed effects model

Figure 34 Model fit for MRI T2 weighted lesions assessed by individual study residual deviance (fixed effects analysis; RRMS population)

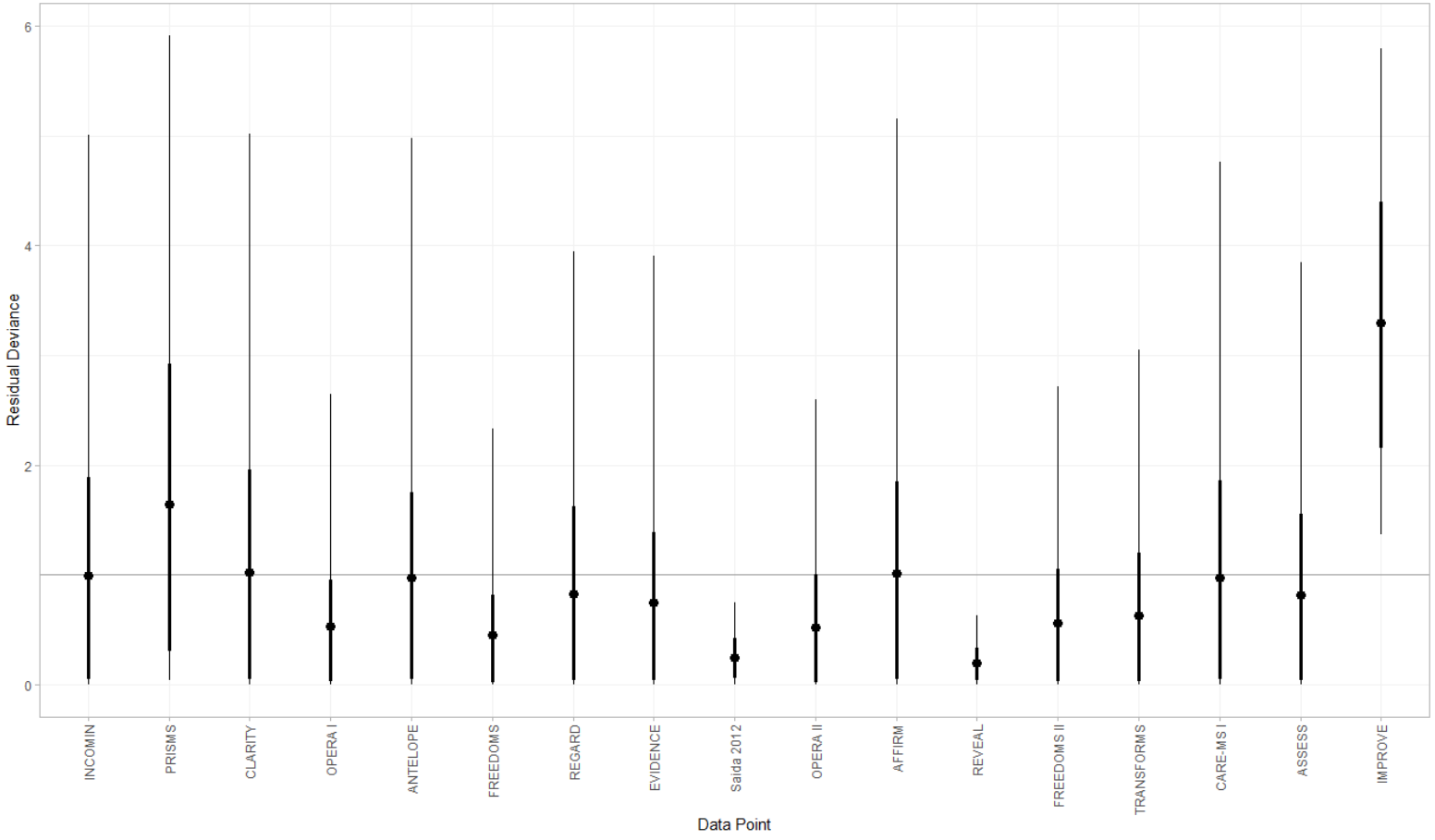

Table 77 Comparison (HR and 95% CrI) for each intervention pair for MRI T2 weighted lesions (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Interferon beta 1a IM30	Interferon beta 1a SC22	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab biosimilar	Natalizumab IV300
Alemtuzumab IV12	0.61 (0.45, 0.81)										
Cladribine O3.5	0.52 (0.43, 0.64)	0.86 (0.61, 1.23)									
Fingolimod O0.5	0.63 (0.55, 0.72)	1.04 (0.78, 1.40)	1.21 (0.96, 1.53)								
Glatiramer acetate SC20	0.80 (0.66, 0.98)	1.32 (0.99, 1.80)	1.53 (1.16, 2.03)	1.27 (1.07, 1.52)							
Interferon beta 1a IM30	0.77 (0.64, 0.92)	1.26 (0.95, 1.68)	1.46 (1.12, 1.92)	1.21 (1.03, 1.43)	0.95 (0.78, 1.17)						
Interferon beta 1a SC22	0.88 (0.71, 1.10)	1.45 (1.01, 2.09)	1.69 (1.25, 2.29)	1.40 (1.09, 1.79)	1.10 (0.83, 1.47)	1.15 (0.87, 1.52)					
Interferon beta 1a SC44	0.72 (0.61, 0.85)	1.19 (0.94, 1.50)	1.38 (1.06, 1.79)	1.14 (0.97, 1.34)	0.90 (0.75, 1.08)	0.94 (0.82, 1.09)	0.82 (0.62, 1.08)				
Interferon beta 1b IM 250	0.46 (0.29, 0.73)	0.76 (0.46, 1.29)	0.88 (0.52, 1.45)	0.73 (0.46, 1.15)	0.58 (0.36, 0.92)	0.60 (0.39, 0.92)	0.52 (0.31, 0.87)	0.64 (0.41, 1.00)			
Natalizumab biosimilar	0.46 (0.30, 0.70)	0.76 (0.46, 1.27)	0.88 (0.55, 1.41)	0.73 (0.47, 1.12)	0.57 (0.36, 0.90)	0.60 (0.38, 0.94)	0.52 (0.32, 0.83)	0.64 (0.41, 0.99)	1.00 (0.53, 1.83)		
Natalizumab IV300	0.50 (0.42, 0.59)	0.81 (0.58, 1.15)	0.94 (0.73, 1.22)	0.78 (0.64, 0.96)	0.62 (0.47, 0.79)	0.65 (0.50, 0.82)	0.56 (0.42, 0.74)	0.69 (0.54, 0.87)	1.07 (0.66, 1.75)	1.07 (0.73, 1.57)	
Ocrelizumab IV600	0.44 (0.36, 0.55)	0.73 (0.55, 0.96)	0.84 (0.63, 1.14)	0.70 (0.56, 0.86)	0.55 (0.44, 0.70)	0.58 (0.47, 0.71)	0.50 (0.37, 0.69)	0.61 (0.53, 0.71)	0.96 (0.60, 1.53)	0.96 (0.61, 1.55)	0.89 (0.68, 1.19)

Table 78 Probability that each intervention will rank in each position for MRI T2 weighted lesions (fixed effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]	p_rank[12]
Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.15	1.00
Alemtuzumab IV12	0.00	0.02	0.08	0.16	0.33	0.63	0.89	0.95	0.98	0.99	1.00	1.00
Cladribine O3.5	0.03	0.13	0.30	0.53	0.85	0.96	1.00	1.00	1.00	1.00	1.00	1.00
Fingolimod O0.5	0.00	0.00	0.00	0.01	0.11	0.51	0.94	0.99	1.00	1.00	1.00	1.00
Glatiramer acetate SC20	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.11	0.32	0.78	0.98	1.00
Interferon beta 1a IM30	0.00	0.00	0.00	0.00	0.00	0.00	0.04	0.21	0.63	0.92	1.00	1.00
Interferon beta 1a SC22	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.07	0.15	0.32	0.87	1.00
Interferon beta 1a SC44	0.00	0.00	0.00	0.00	0.00	0.02	0.14	0.70	0.94	0.99	1.00	1.00
Interferon beta 1b IM 250	0.32	0.50	0.62	0.74	0.86	0.93	0.97	0.99	0.99	1.00	1.00	1.00
Natalizumab biosimilar	0.31	0.49	0.65	0.78	0.88	0.95	0.98	0.99	0.99	1.00	1.00	1.00
Natalizumab IV300	0.04	0.20	0.49	0.81	0.96	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ocrelizumab IV600	0.30	0.67	0.86	0.96	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Any AEs (RRMS population)

Table 79 Comparison of results from fixed and random effects NMA for any AEs (RRMS population)

	Fixed Effects	Random effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	0.91 (0.55, 1.47)	0.91 (0.54, 1.51)
Cladribine O3.5	1.10 (0.94, 1.29)	1.10 (0.92, 1.31)
Fingolimod O0.5	1.02 (0.94, 1.11)	1.02 (0.93, 1.13)
Glatiramer acetate SC20	1.01 (0.90, 1.12)	1.01 (0.89, 1.14)
Glatiramer acetate SC40	1.06 (0.85, 1.30)	1.06 (0.83, 1.35)
Interferon beta 1a IM30	1.07 (0.93, 1.24)	1.07 (0.91, 1.25)
Interferon beta 1a SC44	0.88 (0.55, 1.40)	0.88 (0.54, 1.44)
Interferon beta 1b IM 250	0.77 (0.51, 1.19)	0.76 (0.49, 1.19)
Natalizumab biosimilar	0.92 (0.65, 1.28)	0.91 (0.64, 1.30)
Natalizumab IV300	0.97 (0.85, 1.11)	0.97 (0.83, 1.12)
Ocrelizumab IV600	0.88 (0.56, 1.38)	0.88 (0.55, 1.41)
Ofatumumab SC20	1.02 (0.73, 1.42)	1.03 (0.71, 1.49)
Peginterferon beta 1a SC125	1.12 (0.98, 1.27)	1.12 (0.97, 1.28)
Ponesimod O20	1.04 (0.77, 1.39)	1.04 (0.77, 1.42)
Teriflunomide O14	1.03 (0.74, 1.41)	1.03 (0.74, 1.47)
Tau (95% CrI)	NA	0.03 (0.002, 0.11)
Mean log odds ratio	-0.02	-0.02
Residual deviance:	17.8 (on 25 data points)	18.7 (on 25 data points)
pD	14.8	16.1
DIC	32.6	34.8

Note: the random effects model had good convergence (all Rhat <1.01) so informative priors were not needed.

Chosen model: Fixed effects model

Figure 35 Model fit for any AEs assessed by individual study residual deviance (fixed effects analysis; RRMS population)

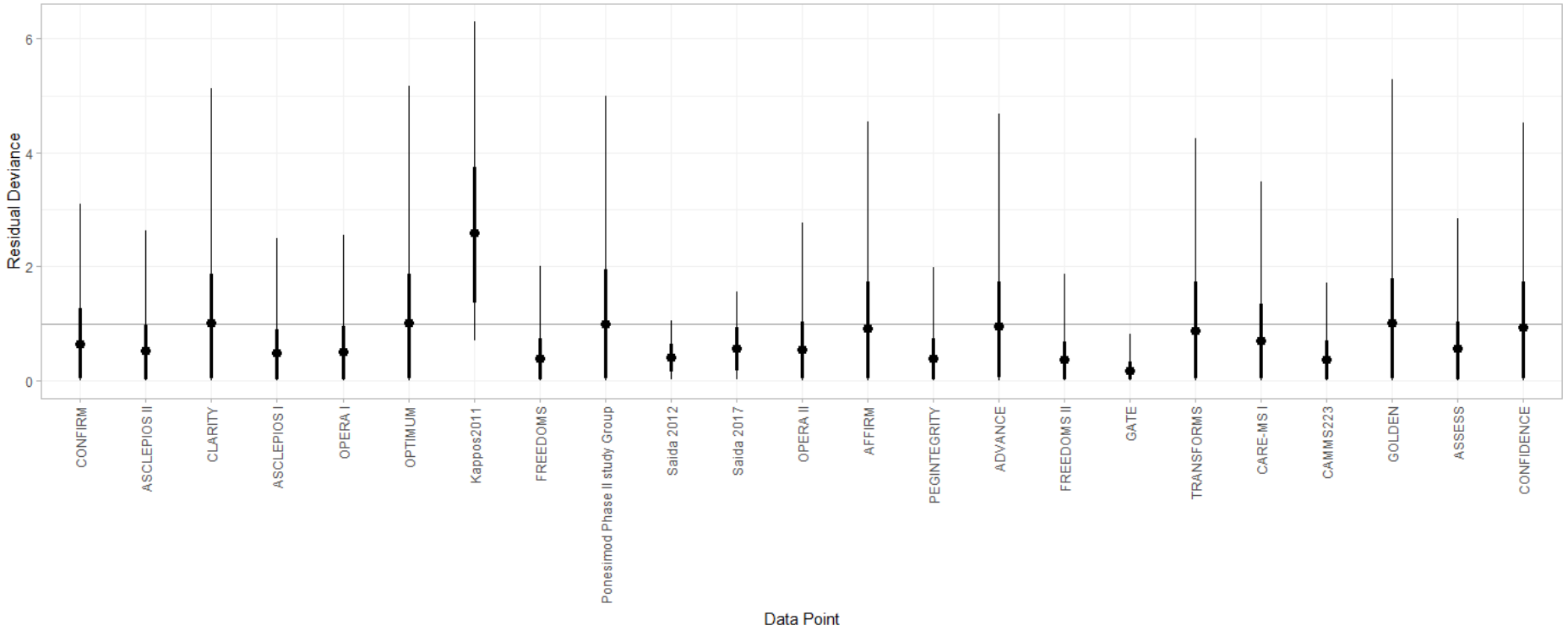

Table 80 Comparison (HR and 95% CrI) for each intervention pair for any AEs (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Glatiramer acetate SC40	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab biosimilar	Natalizumab IV300	Ocrelizumab IV600	Ofatumumab SC20	Peginterferon beta 1a SC125	Ponesimod O20
Alemtuzumab IV12	0.91 (0.55, 1.47)														
Cladribine O3.5	1.10 (0.94, 1.29)	1.21 (0.73, 2.05)													
Fingolimod O0.5	1.02 (0.94, 1.11)	1.13 (0.69, 1.88)	0.93 (0.78, 1.11)												
Glatiramer acetate SC20	1.01 (0.90, 1.12)	1.11 (0.67, 1.86)	0.92 (0.76, 1.11)	0.99 (0.88, 1.11)											
Glatiramer acetate SC40	1.06 (0.85, 1.30)	1.16 (0.68, 2.00)	0.96 (0.74, 1.25)	1.03 (0.83, 1.27)	1.05 (0.87, 1.26)										
Interferon beta 1a IM30	1.07 (0.93, 1.24)	1.18 (0.71, 2.00)	0.98 (0.79, 1.20)	1.05 (0.92, 1.19)	1.06 (0.90, 1.25)	1.02 (0.79, 1.31)									
Interferon beta 1a SC44	0.88 (0.55, 1.40)	0.97 (0.83, 1.13)	0.80 (0.49, 1.30)	0.86 (0.54, 1.38)	0.87 (0.54, 1.41)	0.84 (0.50, 1.39)	0.82 (0.50, 1.33)								
Interferon beta 1b IM 250	0.77 (0.51, 1.19)	0.84 (0.43, 1.64)	0.70 (0.44, 1.10)	0.75 (0.50, 1.14)	0.76 (0.50, 1.17)	0.73 (0.45, 1.17)	0.71 (0.47, 1.11)	0.87 (0.46, 1.64)							
Natalizumab biosimilar	0.92 (0.65, 1.28)	1.01 (0.55, 1.85)	0.83 (0.57, 1.20)	0.90 (0.63, 1.27)	0.91 (0.63, 1.28)	0.87 (0.58, 1.29)	0.85 (0.59, 1.24)	1.04 (0.58, 1.86)	1.20 (0.68, 2.11)						
Natalizumab IV300	0.97 (0.85, 1.11)	1.07 (0.64, 1.80)	0.89 (0.73, 1.09)	0.95 (0.81, 1.11)	0.97 (0.81, 1.14)	0.92 (0.72, 1.18)	0.91 (0.75, 1.10)	1.10 (0.67, 1.80)	1.27 (0.80, 1.97)	1.06 (0.79, 1.45)					
Ocrelizumab IV600	0.88 (0.56, 1.38)	0.97 (0.81, 1.16)	0.80 (0.49, 1.29)	0.86 (0.54, 1.36)	0.87 (0.54, 1.39)	0.83 (0.50, 1.38)	0.82 (0.51, 1.31)	1.00 (0.90, 1.11)	1.15 (0.63, 2.14)	0.96 (0.54, 1.71)	0.90 (0.56, 1.45)				
Ofatumumab SC20	1.02 (0.73, 1.42)	1.13 (0.62, 2.02)	0.93 (0.65, 1.35)	1.00 (0.71, 1.40)	1.01 (0.71, 1.43)	0.97 (0.65, 1.45)	0.95 (0.66, 1.36)	1.16 (0.65, 2.05)	1.33 (0.77, 2.29)	1.12 (0.70, 1.77)	1.05 (0.74, 1.49)	1.16 (0.67, 2.05)			
Peginterferon beta 1a SC125	1.12 (0.98, 1.27)	1.23 (0.75, 2.08)	1.02 (0.84, 1.24)	1.09 (0.94, 1.27)	1.11 (0.93, 1.31)	1.06 (0.83, 1.36)	1.04 (0.88, 1.24)	1.27 (0.79, 2.09)	1.46 (0.93, 2.25)	1.22 (0.84, 1.77)	1.15 (0.96, 1.39)	1.27 (0.80, 2.05)	1.09 (0.77, 1.56)		
Ponesimod O20	1.04 (0.77, 1.39)	1.14 (0.65, 2.01)	0.94 (0.68, 1.31)	1.01 (0.74, 1.37)	1.03 (0.75, 1.40)	0.98 (0.68, 1.42)	0.97 (0.69, 1.33)	1.18 (0.68, 2.04)	1.35 (0.80, 2.28)	1.13 (0.73, 1.76)	1.07 (0.78, 1.47)	1.18 (0.68, 2.03)	1.01 (0.87, 1.19)	0.93 (0.67, 1.28)	
Teriflunomide O14	1.03 (0.74, 1.41)	1.13 (0.63, 2.01)	0.94 (0.66, 1.32)	1.01 (0.71, 1.41)	1.02 (0.73, 1.42)	0.97 (0.66, 1.42)	0.96 (0.68, 1.36)	1.17 (0.66, 2.04)	1.34 (0.79, 2.29)	1.12 (0.71, 1.77)	1.06 (0.75, 1.48)	1.17 (0.67, 2.04)	1.01 (0.92, 1.11)	0.92 (0.66, 1.30)	0.99 (0.88, 1.12)

Table 81 Probability that each intervention will rank in each position for any AEs (fixed effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]	p_rank[12]	p_rank[13]	p_rank[14]	p_rank[15]	p_rank[16]
Placebo	0.00	0.01	0.03	0.07	0.14	0.25	0.42	0.57	0.73	0.85	0.92	0.97	0.99	1.00	1.00	1.00
Alemtuzumab IV12	0.09	0.21	0.36	0.47	0.54	0.59	0.63	0.66	0.68	0.71	0.74	0.78	0.82	0.86	0.91	1.00
Cladribine O3.5	0.00	0.01	0.02	0.03	0.06	0.08	0.12	0.17	0.23	0.30	0.38	0.49	0.60	0.71	0.84	1.00
Fingolimod O0.5	0.00	0.01	0.02	0.05	0.10	0.17	0.27	0.39	0.52	0.65	0.78	0.87	0.94	0.98	1.00	1.00
Glatiramer acetate SC20	0.00	0.02	0.06	0.11	0.18	0.28	0.38	0.50	0.61	0.72	0.81	0.89	0.94	0.98	1.00	1.00
Glatiramer acetate SC40	0.01	0.04	0.07	0.11	0.17	0.23	0.29	0.34	0.41	0.47	0.54	0.61	0.70	0.79	0.88	1.00
Interferon beta 1a IM30	0.00	0.01	0.03	0.05	0.08	0.13	0.17	0.23	0.31	0.40	0.52	0.62	0.73	0.82	0.92	1.00
Interferon beta 1a SC44	0.09	0.29	0.47	0.56	0.61	0.66	0.69	0.72	0.75	0.78	0.81	0.84	0.87	0.92	0.97	1.00
Interferon beta 1b IM 250	0.49	0.58	0.63	0.76	0.82	0.85	0.87	0.89	0.91	0.92	0.94	0.95	0.96	0.97	0.98	1.00
Natalizumab biosimilar	0.14	0.30	0.36	0.44	0.57	0.62	0.66	0.72	0.75	0.78	0.82	0.85	0.88	0.91	0.94	1.00
Natalizumab IV300	0.01	0.06	0.15	0.23	0.35	0.50	0.59	0.68	0.77	0.83	0.88	0.92	0.96	0.98	1.00	1.00
Ocrelizumab IV600	0.10	0.26	0.44	0.56	0.63	0.67	0.70	0.73	0.75	0.79	0.82	0.85	0.88	0.94	0.98	1.00
Ofatumumab SC20	0.03	0.10	0.15	0.22	0.29	0.35	0.42	0.46	0.51	0.55	0.60	0.67	0.74	0.82	0.91	1.00
Peginterferon beta 1a SC125	0.00	0.00	0.01	0.01	0.02	0.04	0.06	0.09	0.14	0.20	0.29	0.40	0.54	0.67	0.83	1.00
Ponesimod O20	0.01	0.04	0.08	0.15	0.21	0.27	0.33	0.40	0.45	0.50	0.57	0.64	0.73	0.85	0.92	1.00
Teriflunomide O14	0.02	0.07	0.12	0.18	0.24	0.32	0.38	0.44	0.49	0.54	0.60	0.66	0.72	0.81	0.93	1.00

Serious Adverse Events (RRMS population)

Table 82 Comparison of results from fixed and random effects NMA for SAEs (RRMS population)

	Fixed Effects	Random effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	1.06 (0.59, 1.90)	1.06 (0.55, 2.06)
Fingolimod O0.5	1.01 (0.78, 1.28)	1.02 (0.77, 1.39)
Glatiramer acetate SC20	0.83 (0.64, 1.07)	0.84 (0.63, 1.16)
Glatiramer acetate SC40	1.32 (0.51, 3.31)	1.35 (0.52, 3.58)
Interferon beta 1a IM30	0.92 (0.64, 1.32)	0.92 (0.61, 1.41)
Interferon beta 1a SC44	0.92 (0.59, 1.45)	0.92 (0.56, 1.54)
Interferon beta 1b IM 250	0.71 (0.48, 1.05)	0.71 (0.42, 1.18)
Natalizumab IV300	0.77 (0.58, 1.00)	0.75 (0.51, 1.05)
Ocrelizumab IV600	0.72 (0.41, 1.28)	0.72 (0.38, 1.41)
Ofatumumab SC20	1.58 (0.48, 4.99)	1.60 (0.47, 5.30)
Peginterferon beta 1a SC125	0.71 (0.50, 1.00)	0.71 (0.47, 1.12)
Ponesimod O20	1.46 (0.49, 4.22)	1.49 (0.50, 4.32)
Teriflunomide O14	1.37 (0.44, 4.15)	1.39 (0.43, 4.32)
Tau (95% CrI)	NA	0.11 (0.004, 0.32)
Mean log odds ratio	-0.01	-0.01
Residual deviance:	23.7 (on 31 data points)	23.1 (on 31 data points)
pD	13.1	14.8
DIC	36.8	37.8

Note: the random effects model had good convergence (all Rhat <1.01) so informative priors were not needed.

Chosen model: Fixed effects model

Figure 36 Model fit for SAEs assessed by individual study residual deviance (fixed effects analysis; RRMS population)

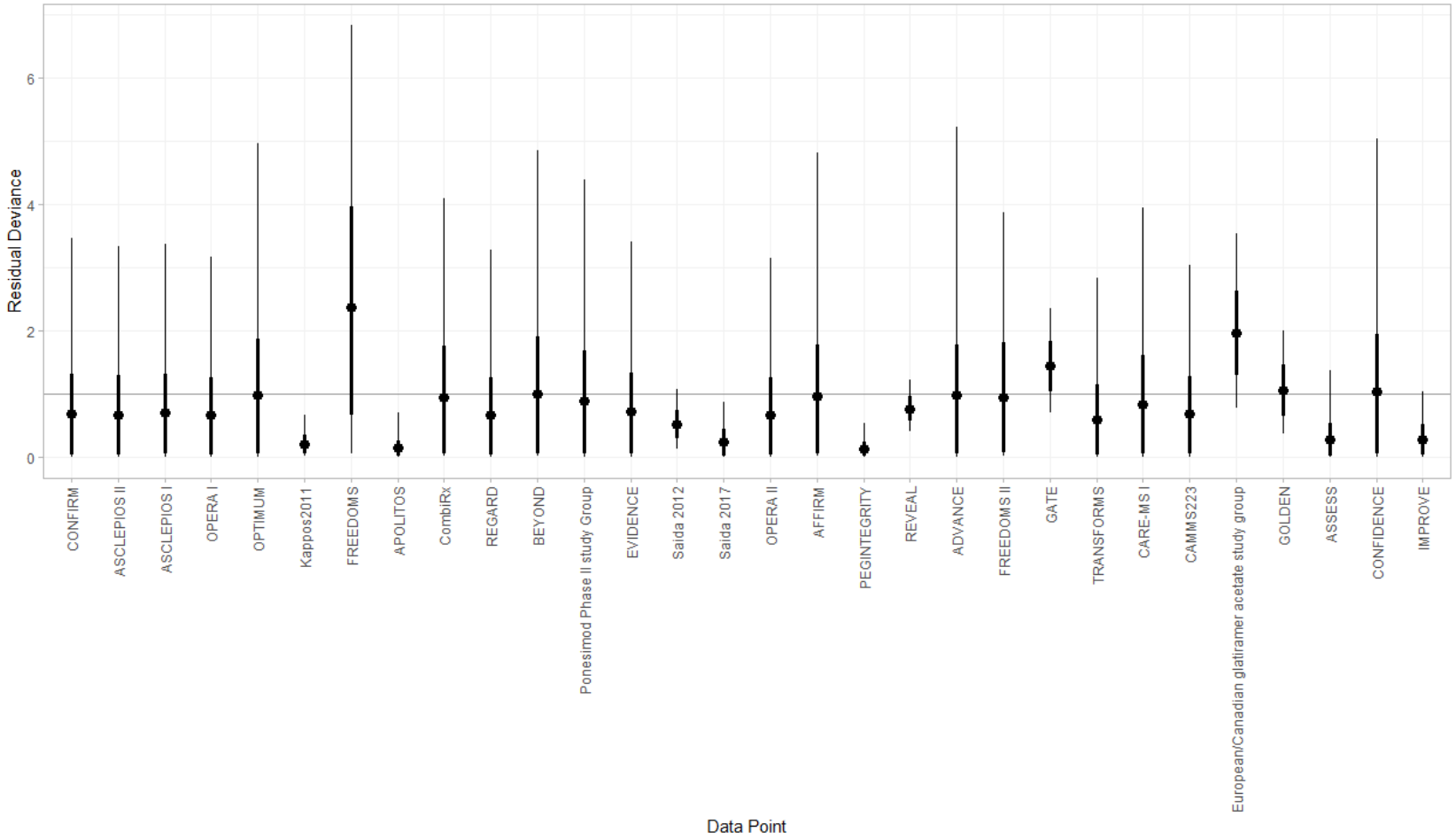

Table 83 Comparison (HR and 95% CrI) for each intervention pair for SAEs (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Fingolimod O0.5	Glatiramer acetate SC20	Glatiramer acetate SC40	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab IV300	Ocrelizumab IV600	Ofatumumab SC20	Peginterferon beta 1a SC125
Alemtuzumab IV12	1.06 (0.59, 1.90)											
Fingolimod O0.5	1.01 (0.78, 1.28)	0.95 (0.53, 1.72)										
Glatiramer acetate SC20	0.83 (0.64, 1.07)	0.78 (0.45, 1.35)	0.82 (0.61, 1.12)									
Glatiramer acetate SC40	1.32 (0.51, 3.31)	1.25 (0.43, 3.50)	1.32 (0.52, 3.34)	1.60 (0.65, 3.98)								
Interferon beta 1a IM30	0.92 (0.64, 1.32)	0.86 (0.49, 1.56)	0.91 (0.63, 1.30)	1.11 (0.80, 1.55)	0.69 (0.26, 1.82)							
Interferon beta 1a SC44	0.92 (0.59, 1.45)	0.87 (0.61, 1.23)	0.92 (0.58, 1.48)	1.11 (0.74, 1.69)	0.70 (0.26, 1.87)	1.00 (0.65, 1.57)						
Interferon beta 1b IM 250	0.71 (0.48, 1.05)	0.67 (0.36, 1.24)	0.71 (0.46, 1.09)	0.86 (0.62, 1.18)	0.54 (0.20, 1.40)	0.77 (0.49, 1.22)	0.77 (0.45, 1.28)					
Natalizumab IV300	0.77 (0.58, 1.00)	0.72 (0.38, 1.38)	0.76 (0.54, 1.10)	0.93 (0.64, 1.36)	0.58 (0.22, 1.50)	0.83 (0.53, 1.33)	0.83 (0.48, 1.41)	1.08 (0.67, 1.75)				
Ocrelizumab IV600	0.72 (0.41, 1.28)	0.68 (0.41, 1.12)	0.72 (0.40, 1.29)	0.88 (0.51, 1.51)	0.55 (0.20, 1.55)	0.79 (0.44, 1.39)	0.79 (0.55, 1.11)	1.02 (0.55, 1.94)	0.95 (0.50, 1.79)			
Ofatumumab SC20	1.58 (0.48, 4.99)	1.48 (0.37, 5.34)	1.57 (0.47, 5.03)	1.91 (0.56, 6.01)	1.19 (0.26, 5.15)	1.72 (0.50, 5.74)	1.71 (0.47, 5.83)	2.22 (0.64, 7.43)	2.06 (0.61, 6.68)	2.17 (0.58, 7.86)		
Peginterferon beta 1a SC125	0.71 (0.50, 1.00)	0.67 (0.34, 1.30)	0.71 (0.47, 1.07)	0.86 (0.57, 1.31)	0.54 (0.20, 1.42)	0.77 (0.48, 1.26)	0.77 (0.44, 1.34)	1.00 (0.61, 1.64)	0.93 (0.60, 1.43)	0.98 (0.50, 1.90)	0.45 (0.13, 1.52)	
Ponesimod O20	1.46 (0.49, 4.22)	1.38 (0.39, 4.65)	1.46 (0.47, 4.28)	1.77 (0.57, 5.13)	1.11 (0.26, 4.50)	1.59 (0.50, 4.79)	1.59 (0.49, 5.05)	2.06 (0.64, 6.27)	1.91 (0.63, 5.75)	2.02 (0.60, 6.81)	0.93 (0.56, 1.53)	2.06 (0.66, 6.27)
Teriflunomide O14	1.37 (0.44, 4.15)	1.29 (0.35, 4.46)	1.36 (0.42, 4.26)	1.66 (0.50, 5.16)	1.03 (0.22, 4.37)	1.49 (0.44, 4.78)	1.49 (0.43, 4.83)	1.93 (0.58, 6.04)	1.79 (0.56, 5.59)	1.89 (0.52, 6.63)	0.87 (0.63, 1.18)	1.92 (0.59, 6.24)

Table 84 Probability that each intervention will rank in each position for SAEs (fixed effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]	p_rank[12]	p_rank[13]	p_rank[14]
Placebo	0.00	0.00	0.00	0.02	0.05	0.13	0.24	0.40	0.59	0.78	0.89	0.95	0.99	1.00
Alemtuzumab IV12	0.01	0.04	0.07	0.11	0.16	0.21	0.28	0.35	0.44	0.61	0.75	0.82	0.91	1.00
Fingolimod O0.5	0.00	0.01	0.02	0.04	0.09	0.16	0.26	0.40	0.57	0.76	0.86	0.93	0.98	1.00
Glatiramer acetate SC20	0.01	0.05	0.16	0.35	0.55	0.70	0.83	0.91	0.96	0.98	0.99	1.00	1.00	1.00
Glatiramer acetate SC40	0.05	0.08	0.10	0.12	0.16	0.19	0.22	0.26	0.30	0.36	0.56	0.62	0.70	1.00
Interferon beta 1a IM30	0.01	0.04	0.09	0.16	0.27	0.39	0.52	0.64	0.77	0.86	0.93	0.96	0.99	1.00
Interferon beta 1a SC44	0.00	0.04	0.11	0.19	0.29	0.40	0.52	0.63	0.76	0.85	0.91	0.96	1.00	1.00
Interferon beta 1b IM 250	0.23	0.44	0.60	0.72	0.80	0.88	0.92	0.95	0.97	0.99	0.99	1.00	1.00	1.00
Natalizumab IV300	0.10	0.27	0.44	0.57	0.69	0.79	0.87	0.93	0.96	0.98	0.99	1.00	1.00	1.00
Ocrelizumab IV600	0.28	0.42	0.54	0.64	0.72	0.79	0.85	0.90	0.94	0.96	0.98	0.99	1.00	1.00
Ofatumumab SC20	0.01	0.05	0.08	0.10	0.12	0.14	0.16	0.19	0.21	0.25	0.30	0.42	0.65	1.00
Peginterferon beta 1a SC125	0.23	0.43	0.58	0.70	0.79	0.86	0.91	0.95	0.97	0.99	0.99	1.00	1.00	1.00
Ponesimod O20	0.02	0.04	0.08	0.11	0.13	0.16	0.18	0.22	0.25	0.29	0.38	0.62	0.83	1.00
Teriflunomide O14	0.06	0.10	0.13	0.16	0.19	0.22	0.24	0.27	0.31	0.35	0.47	0.74	0.96	1.00

Discontinuation due to AEs (RRMS population)

Table 85 Comparison of results from fixed and random effects NMA for discontinuation due to AEs (RRMS population)

	Fixed Effects	Random effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	0.42 (0.14, 1.14)	0.45 (0.13, 1.54)
Cladribine O3.5	1.68 (0.75, 3.78)	1.68 (0.56, 5.11)
Fingolimod O0.5	1.54 (1.16, 2.02)	1.63 (1.08, 2.64)
Glatiramer acetate SC20	2.15 (1.43, 3.27)	2.21 (1.25, 3.99)
Glatiramer acetate SC40	1.84 (1.00, 3.32)	1.86 (0.83, 4.16)
Interferon beta 1a IM30	1.53 (0.89, 2.59)	1.70 (0.87, 3.77)
Interferon beta 1a SC44	2.10 (1.19, 3.73)	2.29 (1.04, 5.29)
Interferon beta 1b IM 250	2.22 (1.04, 4.71)	2.41 (1.02, 6.19)
Natalizumab biosimilar	2.87 (0.67, 12.07)	2.63 (0.47, 14.21)
Natalizumab IV300	1.37 (0.75, 2.47)	1.27 (0.53, 2.85)
Ocrelizumab IV600	1.24 (0.59, 2.54)	1.37 (0.52, 3.88)
Peginterferon beta 1a SC125	3.48 (1.46, 8.36)	3.50 (1.24, 9.82)
Tau (95% CrI)	NA	0.27 (0.01, 0.69)
Mean log odds ratio	0.52	0.55
Residual deviance:	29.2 (on 28 data points)	26 (on 28 data points)
pD	12	15.7
DIC	41.2	41.7

Note: the random effects model had good convergence (all Rhat <1.01) so informative priors were not needed.

Chosen model: Fixed effects model

Figure 37 Model fit for discontinuation due to AEs assessed by individual study residual deviance (fixed effects analysis; RRMS population)

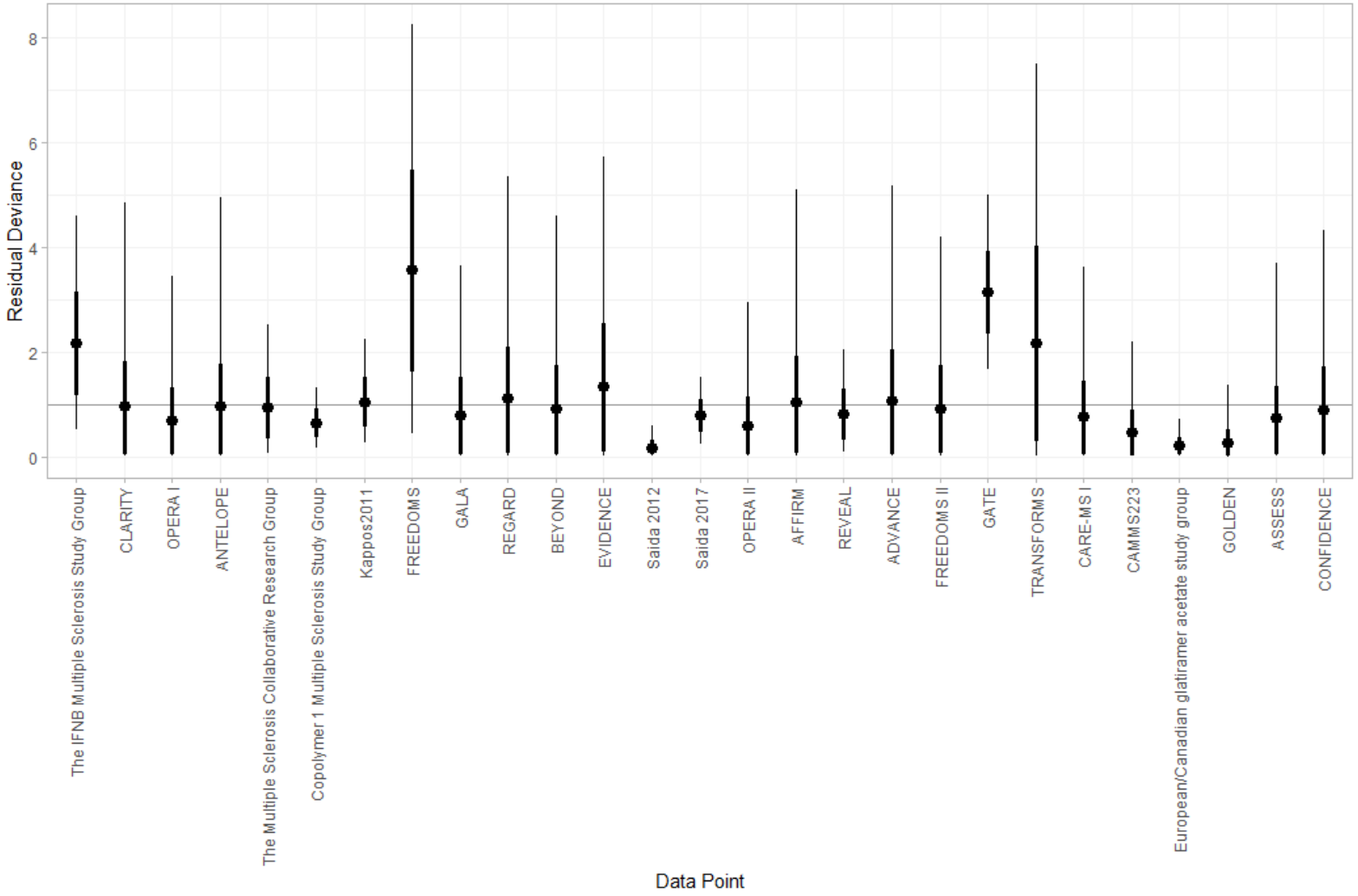

Table 86 Comparison (RR and 95% CrI) for each intervention pair for discontinuation due to AEs (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Glatiramer acetate SC40	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab biosimilar	Natalizumab IV300	Ocrelizumab IV600
Alemtuzumab IV12	0.42 (0.14, 1.14)											
Cladribine O3.5	1.68 (0.75, 3.78)	4.04 (1.14, 14.59)										
Fingolimod O0.5	1.54 (1.16, 2.02)	3.71 (1.37, 10.17)	0.92 (0.39, 2.16)									
Glatiramer acetate SC20	2.15 (1.43, 3.27)	5.18 (1.86, 14.34)	1.28 (0.53, 3.21)	1.40 (0.97, 2.00)								
Glatiramer acetate SC40	1.84 (1.00, 3.32)	4.42 (1.39, 13.89)	1.09 (0.40, 2.96)	1.19 (0.65, 2.21)	0.85 (0.47, 1.52)							
Interferon beta 1a IM30	1.53 (0.89, 2.59)	3.67 (1.28, 10.45)	0.91 (0.36, 2.36)	0.99 (0.58, 1.61)	0.71 (0.41, 1.22)	0.83 (0.40, 1.74)						
Interferon beta 1a SC44	2.10 (1.19, 3.73)	5.06 (2.16, 12.11)	1.25 (0.49, 3.42)	1.36 (0.79, 2.36)	0.98 (0.58, 1.64)	1.15 (0.55, 2.39)	1.38 (0.81, 2.31)					
Interferon beta 1b IM 250	2.22 (1.04, 4.71)	5.35 (1.55, 18.48)	1.33 (0.46, 3.99)	1.44 (0.69, 3.00)	1.03 (0.52, 2.10)	1.21 (0.49, 2.97)	1.46 (0.63, 3.32)	1.06 (0.45, 2.43)				
Natalizumab biosimilar	2.87 (0.67, 12.07)	6.91 (1.14, 42.03)	1.71 (0.33, 8.88)	1.86 (0.44, 8.19)	1.33 (0.31, 5.82)	1.56 (0.35, 7.52)	1.88 (0.44, 9.02)	1.36 (0.30, 6.44)	1.29 (0.26, 6.37)			
Natalizumab IV300	1.37 (0.75, 2.47)	3.30 (1.00, 11.22)	0.82 (0.30, 2.24)	0.89 (0.46, 1.74)	0.64 (0.32, 1.30)	0.75 (0.32, 1.74)	0.90 (0.40, 2.04)	0.65 (0.29, 1.48)	0.62 (0.24, 1.62)	0.48 (0.13, 1.76)		
Ocrelizumab IV600	1.24 (0.59, 2.54)	2.97 (1.15, 7.98)	0.74 (0.25, 2.19)	0.80 (0.40, 1.63)	0.57 (0.29, 1.12)	0.67 (0.29, 1.58)	0.81 (0.42, 1.62)	0.59 (0.38, 0.94)	0.56 (0.22, 1.43)	0.43 (0.09, 2.06)	0.90 (0.35, 2.29)	
Peginterferon beta 1a SC125	3.48 (1.46, 8.36)	8.38 (2.24, 31.99)	2.08 (0.63, 6.89)	2.26 (0.90, 5.66)	1.62 (0.62, 4.43)	1.90 (0.66, 5.66)	2.28 (0.83, 6.29)	1.66 (0.58, 4.76)	1.57 (0.50, 5.00)	1.21 (0.22, 6.28)	2.54 (0.90, 7.53)	2.82 (0.92, 8.82)

Table 87 Probability that each intervention will rank in each position for discontinuation due to AEs (fixed effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]	p_rank[12]	p_rank[13]
Placebo	0.03	0.49	0.84	0.96	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Alemtuzumab IV12	0.92	0.97	0.98	0.99	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Cladribine O3.5	0.01	0.09	0.17	0.27	0.36	0.45	0.53	0.62	0.70	0.79	0.88	0.97	1.00
Fingolimod O0.5	0.00	0.00	0.04	0.15	0.37	0.60	0.81	0.92	0.98	0.99	1.00	1.00	1.00
Glatiramer acetate SC20	0.00	0.00	0.00	0.00	0.01	0.03	0.10	0.22	0.44	0.69	0.89	0.98	1.00
Glatiramer acetate SC40	0.00	0.01	0.05	0.12	0.21	0.31	0.42	0.56	0.69	0.81	0.92	0.98	1.00
Interferon beta 1a IM30	0.00	0.03	0.11	0.26	0.42	0.58	0.73	0.84	0.92	0.97	0.99	1.00	1.00
Interferon beta 1a SC44	0.00	0.00	0.00	0.02	0.05	0.11	0.20	0.33	0.49	0.67	0.85	0.97	1.00
Interferon beta 1b IM 250	0.00	0.01	0.03	0.07	0.11	0.17	0.24	0.32	0.43	0.56	0.74	0.91	1.00
Natalizumab biosimilar	0.01	0.06	0.09	0.13	0.17	0.21	0.24	0.28	0.33	0.39	0.46	0.65	1.00
Natalizumab IV300	0.01	0.11	0.27	0.44	0.58	0.70	0.79	0.86	0.92	0.96	0.99	1.00	1.00
Ocrelizumab IV600	0.01	0.23	0.41	0.58	0.71	0.80	0.88	0.93	0.97	0.98	1.00	1.00	1.00
Peginterferon beta 1a SC125	0.00	0.00	0.01	0.01	0.03	0.04	0.07	0.10	0.13	0.18	0.28	0.55	1.00

ARR (HARR MS population)

Table 88 Comparison of results from fixed and random effects NMA for ARR (HARRMS population)

	Fixed Effects	Random effects
Intervention	**RR (95% Credible interval)**	**RR (95% Credible interval)**
Alemtuzumab IV12	0.53 (0.30, 0.92)	0.64 (0.00, 200.49)
Cladribine O3.5	0.57 (0.33, 0.97)	0.57 (0.02, 22.18)
Fingolimod O0.5	0.52 (0.39, 0.69)	0.56 (0.02, 18.53)
Interferon beta 1a	1.03 (0.64, 1.67)	1.23 (0.02, 143.02)
Natalizumab IV300	0.31 (0.15, 0.63)	0.32 (0.01, 11.88)
Ocrelizumab IV600	0.33 (0.15, 0.69)	0.38 (0.00, 102.99
Tau (95% CrI)	NA	1.40 (0.05,3.95)
Mean log odds ratio	-0.69	-0.58
Residual deviance:	8.1 (on 8 data points)	8 (on 8 data points)
pD	8.1	8
DIC	16.2	16.1

Note: all Rhat <1.01

RE parameters:

seed	437219664
trt_effects	"random"
prior_intercept	normal(0, scale = 10)
prior_trt	normal(0, scale = 5)
prior_het	half_normal(scale = 2)
control = list	max_treedepth = 12
adapt_delta	0.99

Chosen model: Fixed effects model

Figure 38 Model fit for ARR assessed by individual study residual deviance (fixed effects analysis; HARRMS population)

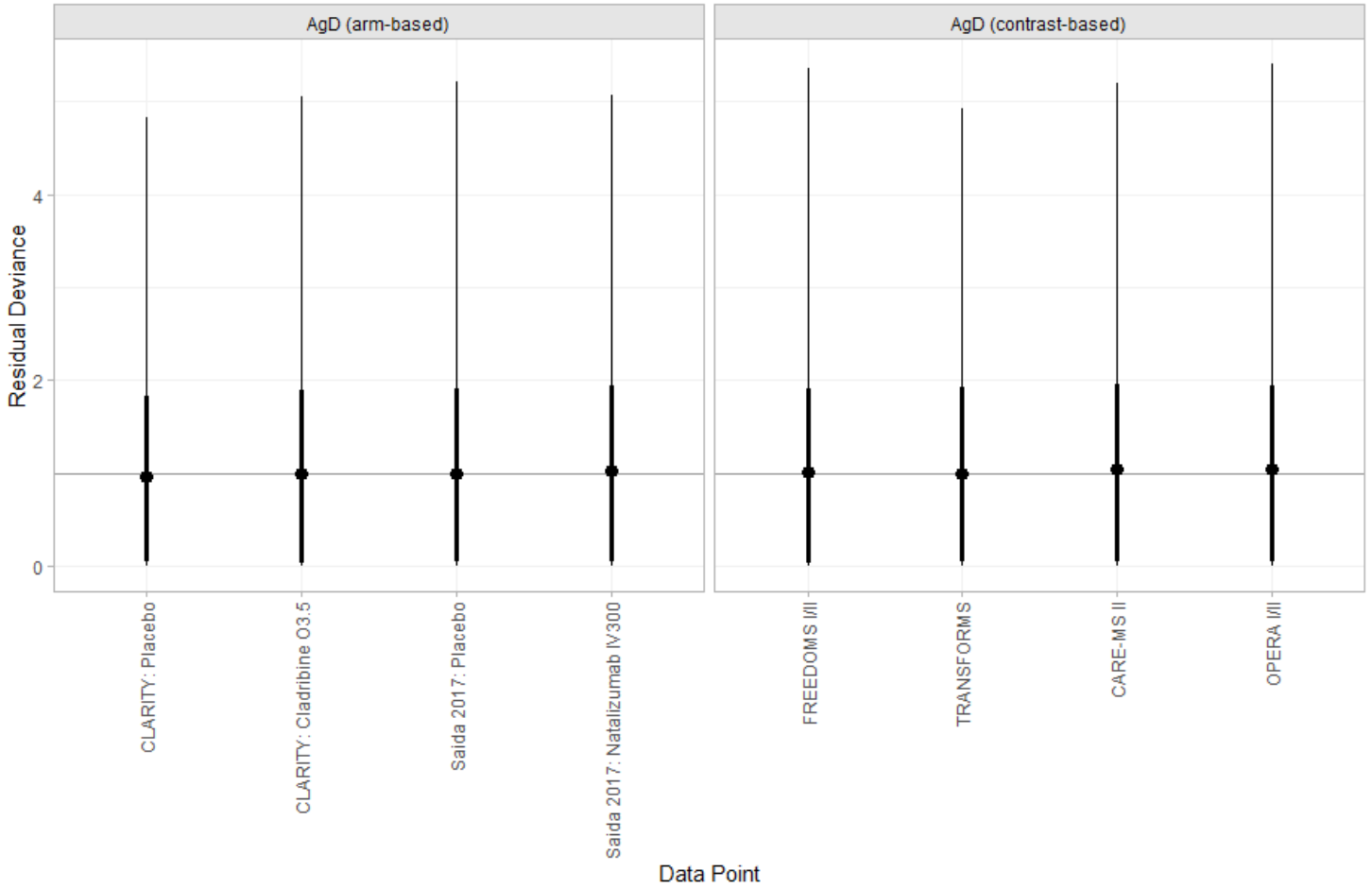

Table 89 Comparison (RR and 95% CrI) for each intervention pair for ARR (random effects analysis; HARRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Interferon beta 1a	Natalizumab IV300
Alemtuzumab IV12	0.53 (0.30, 0.92)					
Cladribine O3.5	0.57 (0.33, 0.97)	1.08 (0.49, 2.39)				
Fingolimod O0.5	0.52 (0.39, 0.69)	0.99 (0.61, 1.60)	0.91 (0.50, 1.69)			
Interferon beta 1a	1.03 (0.64, 1.67)	1.97 (1.52, 2.56)	1.82 (0.87, 3.83)	1.99 (1.33, 2.97)		
Natalizumab IV300	0.31 (0.15, 0.63)	0.59 (0.24, 1.43)	0.54 (0.22, 1.39)	0.59 (0.28, 1.29)	0.30 (0.13, 0.70)	
Ocrelizumab IV600	0.33 (0.15, 0.69)	0.62 (0.33, 1.17)	0.58 (0.23, 1.43)	0.63 (0.31, 1.29)	0.32 (0.18, 0.56)	1.06 (0.38, 3.00)

Table 90 Probability that each intervention will rank in each position for ARR (random effects analysis; HARRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]
Placebo	0.00	0.00	0.00	0.00	0.02	0.57	1.00
Alemtuzumab IV12	0.01	0.12	0.43	0.70	0.99	1.00	1.00
Cladribine O3.5	0.02	0.13	0.33	0.53	0.94	0.99	1.00
Fingolimod O0.5	0.00	0.09	0.39	0.83	1.00	1.00	1.00
Interferon beta 1a	0.00	0.00	0.00	0.00	0.05	0.45	1.00
Natalizumab IV300	0.53	0.83	0.92	0.96	1.00	1.00	1.00
Ocrelizumab IV600	0.44	0.84	0.93	0.97	1.00	1.00	1.00

Appendix 6
Details on economic models in previous relevant TAs

Table 91 Summary of economic evaluations of Highly Active Relapse Remitting Multiple Sclerosis technologies with marketing authorisation in the UK

TA (year) Intervention	Model type	Time horizon	Discount Rate	Population	Comparators	Outcomes and sources of data
TA767 (2022) Ponesimod (Ponvory, Janssen)[42]	Markov Cohort Model	Lifetime 50 years (annual cycles)	3.5 %	RRMS *Subgroup:* HA RRMS	RRMS • Beta interferons, • Dimethyl fumarate, • Glatiramer acetate, • Teriflunomide, • Ocrelizumab, • Peginterferon beta-1a • Ofatumumab. HA RRMS • Alemtuzumab • Fingolimod • Cladribine, • Ofatumumab and • Ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable)	Intervention: ARR, CDP-3, CDP-6, AEs from OPTIMUM, OPTIMUM-LT Comparators: ARR, DCP-3, CDP-6, All cause discontinuation from NMA (RRMS), NMA (HA RRMS) Natural History: RRMS transitions from the British Columbia Multiple Sclerosis registry,[126] HA RRMS transitions from the AFFIRM trial. Converting from RRMS to SPMS from the London, Ontario MS database.[127] ARR by EDSS[127] Relative risk of relapse from the AFFIRM trial. Relative risk of death applied to EDSS states.[337]

TA (year) Intervention	Model type	Time horizon	Discount Rate	Population	Comparators	Outcomes and sources of data
TA699 (2021) Ofatumumab (Kesimpta, Novartis)[41]	Markov Cohort Model	Lifetime 62 years (annual cycles)	3.5 %	RRMS *Subgroups:* HA RRMS & RES RRMS were not considered suitable for decision making	RRMS • Beta interferons, • Dimethyl fumarate, • Glatiramer acetate, • Teriflunomide, • Peginterferon beta-1a	Intervention: ARR, CDP-3, CDP-6, AEs , EQ-5D from ASCLEPIOS I, ASCLEPIOS II Comparators: ARR, DCP-3, CDP-6, All cause discontinuation from NMA (RRMS) Natural History: RRMS transitions from the British Columbia Multiple Sclerosis registry,[126]. Converting from RRMS to SPMS from the London, Ontario MS database[127] supplemented by the EXPAND trial. ARR by EDSS[127] Relative risk of relapse from the AFFIRM trial. Relative risk of death applied to EDSS states.[337]
TA616 (2019) Cladribine tablets (Mavenclad, Merck Serono)[38]	Markov Cohort Model	Lifetime 50 years (annual cycles)	3.5 %	RES RRMS SOT RRMS	RES RRMS • Alemtuzumab • Natalizumab • Daclizumab (contra indicated to alemtuzumab) SOT RRMS • Alemtuzumab • Fingolimod • Daclizumab (contra indicated to alemtuzumab)	Intervention & Comparators relative treatment effects: ARR, DCP-3, CDP-6, relapse free patients, AEs (grades 3 or 4), discontinuation due to AEs, all cause discontinuation from NMA & Meta-regressions per sub-group (RES RRMS, SOT RRMS) Intervention: EQ-5D from ASCLEPIOS I Natural History: RRMS transitions from the British Columbia Multiple Sclerosis registry,[126]. Faster rates of progression for the SOT RRMS & RES RRMS groups based on CLARITY. Converting from RRMS to SPMS from the London, Ontario MS database[127] supplemented by the EXPAND trial. ARR independent of EDSS, year1 pbo arm of CLARITY, subsequent years as a function of time from the British Columbia Multiple Sclerosis registry.[170] Relative risk of death from a meta-analysis of SMRs.[338]

TA (year) Intervention	Model type	Time horizon	Discount Rate	Population	Comparators	Outcomes and sources of data
TA533 (2018) Ocrelizumab (Ocrevus, Roche)[33]	Multi-state Markov Cohort Model	Lifetime 50 years (annual cycles)	3.5 %	RRMS *Subgroups:* HA RRMS RES RRMS	RRMS • Alemtuzumab, • Beta interferons, • Dimethyl fumarate, • Glatiramer acetate, • Natalizumab, • Fingolimod. HA RRMS • Alemtuzumab • Fingolimod RES RRMS • Alemtuzumab • Natalizumab	Intervention: ARR, DCP-3, CDP-6, AEs, EQ-5D from OPERA I - OPERA II - OPERA OLE Comparators: ARR, DCP-3, CDP-6, All cause discontinuation, NMA (RRMS) - NMA (HA RRMS) - NMA (RES RRMS) Natural History: RRMS transitions from the British Columbia Multiple Sclerosis registry,[126] HA RRMS transitions from the AFFIRM trial. Converting from RRMS to SPMS from the London, Ontario MS database.[127] ARR by EDSS.[127] Relative risk of relapse from the AFFIRM trial. Relative risk of death applied to EDSS states[337]
TA312 (2014, update 2020) Alemtuzumab (Lemtrada, Sanofi)[39]	Multi-state Markov Cohort Model	Lifetime 50 years (annual cycles)	3.5 %	RRMS *Subgroups:* HA RRMS RES RRMS	RRMS • Beta interferons, • Glatiramer acetate, HA RRMS • Fingolimod RES RRMS • Natalizumab	Intervention & Comparators relative treatment effects: ARR, SAD-3, SAD-6, relapse free patients, discontinuation due to AEs from NMAs per group / sub-group (RRMS, HA RRMS and RES RRMS) Intervention: AEs, SAEs, EQ-5D from CAMMS223, CARE-MS I & II Natural History: RRMS transitions EDSS (1-9) and converting from RRMS to SPMS were sourced from the London Ontario MS database.[127] RRMSEDSS 0 from the placebo arms of TOWER & TEMSO trials ARR by EDSS[127] Relative risk of death applied to EDSS states[337]

TA (year) Intervention	Model type	Time horizon	Discount Rate	Population	Comparators	Outcomes and sources of data
TA254 (2012) Fingolimod (Gilenya, Novartis)[40]	Markov Cohort Model	Lifetime 50 years (annual cycles)	3.5 %	Main analysis: 1b)HA RRMS In DP not in CE analysis: 1a)HA RRMS 2)RES RRMS	1b)HA RRMS • beta interferon-1a (Avonex) • Rebif-22 • Rebif-44 • Betaferon • Extavia	Intervention ARR, SAD-3, SAD-6 from the TRANSFORMS & FREEDOMS trials. Comparators: ARR, SAD-3, SAD-6 from NMAs (HA RRMS) Natural History: RRMS transitions EDSS (1-9) and converting from RRMS to SPMS from the London, Ontario MS database .[115] ARR by EDSS[127] Relative risk of death applied to EDSS states.[337]
TA127 (2007) (Tysabri, Biogen Inc)[34]	Multi-state Markov Cohort Model	Lifetime 20 years (annual cycles)	3.5 %	RES RRMS SOT RRMS	• Beta interferons, • Glatiramer acetate.	Intervention ARR, SAD-3, SAD-6 from AFFIRM. Comparators: ARR, SAD-3, SAD-6 from pairwise meta-analyses Natural History: RRMS transitions EDSS (1-9) and converting from RRMS to SPMS from the London, Ontario MS database .[115] } HA RRMS transitions from the AFFIRM trial. ARR by EDSS[127] Relative risk of death applied to EDSS states[337]

Table 92 (continued) Summary of economic evaluations of Highly Active Relapse Remitting Multiple Sclerosis technologies with marketing authorisation in the UK

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
TA767 (2022) Ponesimod (Ponvory, Janssen)[42]	20 in total: • 10 EDSS RRMS • 9 EDSS SPMS • Death	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement • Caregiver disutilities • Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	**Treatment switching or sequencing** – The EAG acknowledged the availability of data a limitation on modelling this aspect of clinical practice, leading to an oversimplified model. **Implausible no. of patients in high EDSS states** – Contrary to the expert opinion of clinical advisors a higher proportion of patients than would be observed in practice progressed to EDSS 8 and 9 where they accumulated negative QALYs. The EAG was critical of this aspect of the model, despite it being broadly in line with other appraisals. The committee concluded that this model, as with other multiple sclerosis models, was limited in its ability to accurately reflect the course of the condition. **More appropriate data on mortality** - Clinical experts considered the mortality data was outdated and that managing acute infection and nursing has fundamentally reduced mortality with MS. That new standardised mortality rates by EDSS state had been recently published. The committee concluded that in future appraisals in MS, it would like to see more appropriate sources of mortality data in a model with plausible distributions of people in EDSS states.	The committee concluded that overall, the cost-effectiveness results were acceptable and the most likely estimates were below what NICE considers an acceptable use of NHS resources
TA699 (2021) Ofatumumab (Kesimpta, Novartis)[41]	21 in total: • 10 EDSS RRMS • 10 EDSS SPMS	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement	**loss of treatment effectiveness** – The committee refereed to TA533 (Ocrelizumab) which had accepted treatment discontinuation as proxy for loss of effectiveness over time, despite lack of evidence on waning from the key trials.	The committee referred to the appraisal guidelines stating that, above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
	• Death	• Caregiver disutilities • Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	**Implausible relapse rates in higher EDSS states** – Contrary to clinical advice the company modelled increasing relapse rates at the higher EDSS SPMS states. The EAG went with values that were decreasing as severity increased, reported in TA 527. **Conflicting approaches to converting from RRMS to SPMS** – the company used transition matrices from the British Columbia longitudinal multiple sclerosis dataset (TA254). The EAG preferred to use transition matrices from the London Ontario multiple sclerosis dataset (TA624) Both data sources had been accepted previously by NICE technology appraisal committees and were found to have minimal impact on the ICERs.	will take into account the degree of certainty around the ICER. The committee noted that, with the exception of waning of treatment effect, changes to each assumption had a minor impact on the base-case ICER. The committee concluded that it could recommend ofatumumab as an additional treatment option for relapsing–remitting multiple sclerosis.
TA616 (2019) Cladribine tablets (Mavenclad, Merck Serono)[38]	21 in total: • 10 EDSS RRMS • 10 EDSS SPMS • Death	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement • Caregiver disutilities • Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	**Inaccurate RES RRMS & SOT RRMS natural history** - The company calculating different rates of disability progression in the subgroups. The clinical experts and the EAG explained that, although assuming different rates of disease progression for each subgroup was reasonable, the company's approach was simplistic and potentially inaccurate. The committee appreciated that there was no clear alternative data source or method, and was aware that such adjustment had not been used in previous technology appraisals. **loss of treatment effectiveness** – The company used treatment switching analysis to support their assumption; treatment waning for Cladribine to begin 2 years later than comparators. The committee noted that there was no statistically significant evidence to support different waning effects and that patient numbers used for the analysis in the subgroups were very small. It concluded that the company's evidence	Cladribine dominated all other treatments in both RES RRMS and SOT RRMS groups. Cladribine was more effective and cheaper than fingolimod and natalizumab. It was less effective and cheaper than alemtuzumab. The ICERs vs. alemtuzumab were: • £219,549 gained per QALY lost (RES RRMS) • £372,802 gained per QALY lost SOT (RRMS) The committee concluded that cladribine was a cost-effective use of NHS resources for rapidly evolving severe relapsing–remitting multiple sclerosis and sub optimally treated relapsing–remitting multiple sclerosis.

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
			was insufficient to justify using a different treatment waning assumption for cladribine. **Treatment stopping rates are not constant** - The EAG explained that people are more likely to stop treatment during the first year of treatment than in a subsequent year. Therefore, the company's approach of applying trial-based discontinuation rates to subsequent years would overestimate the number of people stopping treatment.	
TA533 (2018) Ocrelizumab (Ocrevus, Roche)[33]	31 in total: • 20 EDSS RRMS • 10 EDSS SPMS • Death	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement • Caregiver disutilities • Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	**loss of treatment effectiveness** – In clinical practice, when a drug is no longer effective, patients switch on to alternative treatments. Treatment switching was not included in the model. The EAG accepted treatment discontinuation as proxy for loss of effectiveness over time, despite lack of evidence on waning from the key trials.	The most plausible ICERs were below £30,000 per QALY gained in the relapsing–remitting multiple sclerosis population compared with all relevant comparators, apart from alemtuzumab, which dominated all comparisons. In the highly active subgroup, the most plausible ICER for ocrelizumab compared with fingolimod was below £20,000 per QALY gained. In the rapidly evolving severe subgroup, ocrelizumab was cheaper and less effective than natalizumab. The most plausible ICER for ocrelizumab compared with natalizumab was In the range of £350,000 to £125,000 saved per QALY lost .
TA312 (2014, update 2020) Alemtuzumab (Lemtrada, Sanofi)[39]	20 in total: • 10 EDSS RRMS • 9 EDSS SPMS	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement	**loss of treatment effectiveness** – The company assumed treatment with Alemtuzumab would persist indefinitely. The clinical specialists also stated that people who experience a relapse soon after treatment with	The most plausible ICER for alemtuzumab compared with glatiramer acetate for people with active relapsing-remitting multiple sclerosis is likely to lie between £13,600

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
	• Death	• Caregiver disutilities • Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	alemtuzumab will probably be offered alternative treatment. The Committee stated that, for some people, alemtuzumab might not provide long-term enduring effect and other treatments might be required. The Committee concluded that because of the uncertainty about the long-term treatment effects it was appropriate to incorporate waning effects into the model.	and £24,500 per QALY gained active relapsing–remitting multiple sclerosis. The most plausible ICER for patients with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment was £8900 per QALY gained for alemtuzumab compared with fingolimod. Alemtuzumab dominated natalizumab (that is, less expensive and more effective) for patients with rapidly evolving severe relapsing-remitting multiple sclerosis.
TA254 (2012) Fingolimod (Gilenya, Novartis)[339]	21 in total: • 10 EDSS RRMS • 10 EDSS SPMS • Death	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement • Caregiver disutilities • Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	**Uncertainty in the analysis on the population of interest -** analysis of population 1b that excluded people who also met the criteria for population 2 (that is, a population in which people with rapidly evolving severe disease were excluded) was provided. The Committee noted that this analysis generated lower ICERs than those for the whole of population 1b, but was aware of reservations expressed by the manufacturer and the EAG about the small samples on which the subgroup analysis was based **Uncertainty around the improvements in quality of life** - There weren't statistically significant changes from baseline for EQ-5D measures observed for people with relapsing–remitting multiple sclerosis treated with fingolimod or placebo in the	The Committee acknowledged that there was variation in current practice and therefore concluded that fingolimod should be compared with a weighted average of the comparators used in UK clinical practice of RRMS. That the most plausible ICER for fingolimod compared with the weighted average of the comparators was likely to be in the range of £25,000 to £35,000 per QALY gained from the main analysis on population 1b. In supplementary analyses For population 1b, excluding those who also met the criteria for population 2, the EAG concluded that the incremental analysis shows that in both populations Avonex is either dominated or extendedly dominated. The EAG therefore advised

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
			FREEDOMS trial. A slight, non-statistically significant improvement in the PRIMUS-QoL scale was observed for people treated with fingolimod or Avonex in the TRANSFORMS trial. **Loss of treatment effectiveness** – The Committee preferred a 50% waning of treatment effect after 5 years be included in the base-case analysis. **Unrealistic disability progression** – The Committee noted the concerns of the clinical specialists that the model may not reflect the natural history of multiple sclerosis, because it does not allow for improvement in EDSS scores. **Call for an economic model that reflects clinical practice in UK** - The Committee emphasised that it is important that a new model for multiple sclerosis is developed for any future appraisals of treatments for multiple sclerosis. The new model should ideally be based on UK patient cohorts, should use the best available evidence (including experience to date from the risk-sharing scheme) and should include all currently available treatments for multiple sclerosis, so that future appraisals of treatments for multiple sclerosis are directly relevant to UK clinical practice.	that the cost effectiveness of fingolimod should be derived from incremental analysis.
TA127 (2007) (Tysabri, Biogen Inc.)[34]	21 in total: • 10 EDSS RRMS	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement	**Uncertainty in the analysis on the population of interest -** The EAG was critical that the data for the comparators derived from people with RRMS rather than HA RRMS . The company excluded the SENTINEL	The Committee noted that the base case ICERs estimated by the manufacturer for the suboptimal therapy group were £43,400 per QALY gained or higher. It therefore concluded that natalizumab

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
	• 10 EDSS SPMS • Death	• Caregiver disutilities • Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	trial SOT RRMS subgroup data from the model, especially that these was relied on for the marketing authorisation. **Loss of treatment effectiveness** – The EAG expressed concern about the extrapolation of 2-year data from the AFFIRM study to a 20-year time horizon. **Unrealistic disability progression** – the EAG expressed concern that, although the transition probabilities in the manufacturer's model were based on data from AFFIRM, the model appeared to predict a higher rate of sustained disability progression at 2 years than reported in AFFIRM. **Treatment effects on progression from RRMS to SPMS** – There wasn't evidence to support the assumption that Natalizumab reduces progression from RRMS to SPMS	would not be a cost-effective use of NHS resources in this group of people. The Committee concluded that the ICER of £32,000 per QALY for natalizumab compared with beta interferon presented by the manufacturer was more likely to be an overestimate. They concluded natalizumab for the treatment of RES RRMS patients was a cost-effective use of NHS resources.

Abbreviations: **AE:** Adverse Events, **ARR:** Annualised Relapse Rate, **CDP**: Confirmed Disability Progression, EAG: External Assessment Group; **EDSS:** Expanded Disability Scale Status, **EQ-5D**: EuroQol five dimensions quality of life index, **GBP £:** Great Britain Pound, **HA RRMS:** Highly Active Relapse Remitting Multiple Sclerosis, **HDA RRMS:** High Disease Activity Relapse Remitting Multiple Sclerosis, **HS:** Health State, **ICER:** Incremental Cost-Effectiveness Ratio, **NHS:** National Health Service, **NMA:** Network Meta-Analysis, **QALY**: Quality Adjusted Life, **RES RRMS:** Rapidly Evolving Severe Relapse Remitting Multiple Sclerosis, **RRMS:** Relapse Remitting Multiple Sclerosis, **SAD**: Sustained Accumulation of Disability, **SOT RRMS:** Sub-Optimally Treated Relapse Remitting Multiple Sclerosis, **SPMS:** Secondary Progressive Multiple Sclerosis,

Appendix 7
Additional MS Registry results

Sample sizes for events in the MS registry are summarized in the tables Table 93 (those that depend on treatment) and

Table 94 (those that do not depend on treatment). The sample sizes for those that do not depend on treatment were considerably lower than for those that did depend on treatment, indicating that modelling their treatment dependence would result in poorly informed models.

Table 93 Samples sizes for events in the MS registry that were modelled to depend on treatment

Group	N	.Alemtuzumab	N.Beta.Interferon	N.Cladribine	N.Fingolimod	N.Glatiramer.Acetate	N.Natalizumab	N.Ocrelizumab	N.Ofatumumab	N.Ponesimod	N.Female
Time to EDSS Increase (RRMS Highly Active)	224	12	9	23	65	20	23	43	25	4	186
Time to EDSS Increase (All RRMS)	1016	41	168	35	158	158	177	203	69	7	838
Time to Relapse (RRMS Highly Active)	50	1	11	1	13	11	7	4	1	1	40
Time to Relapse (All RRMS)	191	9	56	2	34	44	28	15	2	1	150

Table 94 Samples sizes for events in the MS registry that were not modelled to depend on treatment

Group	N	N.Alemtuzumab	N.Beta.Interferon	N.Cladribine	N.Fingolimod	N.Glatiramer.Acetate	N.Natalizumab	N.Ocrelizumab	N.Ofatumumab	N.Ponesimod	N.Female
Time to EDSS Decrease (All RRMS)	793	29	159	12	93	138	156	160	43	3	652
Time to EDSS Increase (SPMS)	181	4	69	7	31	21	29	16	4	0	133
Time to Relapse (SPMS)	164	2	79	1	31	28	19	4	0	0	121
Time to SP Conversion (RRMS Highly Active)	66	2	23	0	20	14	3	4	0	0	46
Time to SP Conversion (All RRMS)	222	3	107	2	37	40	29	4	0	0	164

The covariance matrices for the coefficients (on log scale) of the exponential survival models estimated by the MS registry are reported below. These covariances were used when sampling the log rates used for the economic model, although only the coefficient for natalizumab was used from the DMT dependent models.

Table 95 Covariance matrix for coefficients of exponential survival model for Time to EDSS Increase (RRMS Highly Active)

	rate	EDSS	Alemtuzumab	Cladribine	Fingolimod	Glatiramer Acetate	Natalizumab	Ocrelizumab	Ofatumumab	Ponesimod
rate	0.26316339	-0.0188753	-0.2004151	-0.2160293	-0.2131976	-0.2207916	-0.2001307	-0.2067891	-0.1979965	-0.2045135
EDSS	-0.0188753	0.00564056	0.00012407	0.00479009	0.0039439	0.00621322	3.9063E-05	0.00202883	-0.0005987	0.00134879
Alemtuzumab	-0.2004151	0.00012407	0.34285982	0.20010533	0.20008672	0.20013663	0.20000083	0.20004459	0.1999868	0.20002964
Cladribine	-0.2160293	0.00479009	0.20010533	1.20406765	0.20334921	0.20527638	0.20003314	0.20172289	0.19949154	0.20114539
Fingolimod	-0.2131976	0.0039439	0.20008672	0.20334921	0.34561467	0.20434427	0.20002728	0.20141853	0.19958135	0.20094304
Glatiramer Acetate	-0.2207916	0.00621322	0.20013663	0.20527638	0.20434427	0.37351063	0.200043	0.20223477	0.19934048	0.20148569
Natalizumab	-0.2001307	3.9063E-05	0.20000083	0.20003314	0.20002728	0.200043	0.40000021	0.20001402	0.19999582	0.20000931
Ocrelizumab	-0.2067891	0.00202883	0.20004459	0.20172289	0.20141853	0.20223477	0.20001402	0.28406303	0.19978462	0.20048511
Ofatumumab	-0.1979965	-0.0005987	0.1999868	0.19949154	0.19958135	0.19934048	0.19999582	0.19978462	0.53339679	0.1998568
Ponesimod	-0.2045135	0.00134879	0.20002964	0.20114539	0.20094304	0.20148569	0.20000931	0.20048511	0.1998568	1.20032233

Table 96 Covariance matrix for coefficients of exponential survival model for Time to EDSS Increase (All RRMS)

	rate	EDSS	Alemtuzumab	Cladribine	Fingolimod	Glatiramer Acetate	Natalizumab	Ocrelizumab	Ofatumumab	Ponesimod
rate	0.0379168	-0.0042253	-0.0256477	-0.0264687	-0.0245772	-0.0253309	-0.0225739	-0.0250133	-0.024759	-0.0238234
EDSS	-0.0042253	0.00153897	-0.0002433	5.5707E-05	-0.0006332	-0.0003587	-0.0013629	-0.0004744	-0.000567	-0.0009078
Alemtuzumab	-0.0256477	-0.0002433	0.13746535	0.02630698	0.02641591	0.0263725	0.02653128	0.02639079	0.02640544	0.02645932
Cladribine	-0.0264687	5.5707E-05	0.02630698	0.35965108	0.02629286	0.0263028	0.02626645	0.02629861	0.02629526	0.02628292
Fingolimod	-0.0245772	-0.0006332	0.02641591	0.02629286	0.07005459	0.02646338	0.02687657	0.02651098	0.02654909	0.02668931
Glatiramer Acetate	-0.0253309	-0.0003587	0.0263725	0.0263028	0.02646338	0.06639939	0.02663346	0.02642636	0.02644795	0.02652738
Natalizumab	-0.0225739	-0.0013629	0.02653128	0.02626645	0.02687657	0.02663346	0.05191298	0.0267359	0.02681792	0.02711971
Ocrelizumab	-0.0250133	-0.0004744	0.02639079	0.02629861	0.02651098	0.02642636	0.0267359	0.04820114	0.02649057	0.02659561
Ofatumumab	-0.024759	-0.000567	0.02640544	0.02629526	0.02654909	0.02644795	0.02681792	0.02649057	0.12652468	0.02665025
Ponesimod	-0.0238234	-0.0009078	0.02645932	0.02628292	0.02668931	0.02652738	0.02711971	0.02659561	0.02665025	1.0268511

Table 97 Covariance matrix for coefficients of exponential survival model for Time to Relapse (RRMS Highly Active)

	rate	EDSS	Alemtuzumab	Cladribine	Fingolimod	Glatiramer Acetate	Natalizumab	Ocrelizumab	Ofatumumab	Ponesimod
rate	0.1760278	-0.0212619	-0.09098	-0.112242	-0.1078575	-0.1035607	-0.0569426	-0.0976834	-0.112242	-0.133504
EDSS	-0.0212619	0.00885927	-0.0141752	-0.0053159	-0.0071428	-0.0089332	-0.0283577	-0.0113821	-0.0053159	0.00354338
Alemtuzumab	-0.09098	-0.0141752	1.14768071	0.13350564	0.13642877	0.13929343	0.17037343	0.14321177	0.13350564	0.11933043
Cladribine	-0.112242	-0.0053159	0.13350564	1.12818956	0.12928594	0.13036023	0.14201567	0.13182966	0.12818972	0.12287382
Fingolimod	-0.1078575	-0.0071428	0.13642877	0.12928594	0.20768195	0.13220238	0.14786343	0.13417681	0.12928594	0.12214312
Glatiramer Acetate	-0.1035607	-0.0089332	0.13929343	0.13036023	0.13220238	0.24511877	0.15359423	0.13647701	0.13036023	0.12142704
Natalizumab	-0.0569426	-0.0283577	0.17037343	0.14201567	0.14786343	0.15359423	0.35862733	0.16143293	0.14201567	0.11365796
Ocrelizumab	-0.0976834	-0.0113821	0.14321177	0.13182966	0.13417681	0.13647701	0.16143293	0.38962324	0.13182966	0.12044757
Ofatumumab	-0.112242	-0.0053159	0.13350564	0.12818972	0.12928594	0.13036023	0.14201567	0.13182966	1.12818956	0.12287382
Ponesimod	-0.133504	0.00354338	0.11933043	0.12287382	0.12214312	0.12142704	0.11365796	0.12044757	0.12287382	1.12641703

Table 98 Covariance matrix for coefficients of exponential survival model for Time to Relapse (All RRMS)

	rate	EDSS	Alemtuzumab	Cladribine	Fingolimod	Glatiramer Acetate	Natalizumab	Ocrelizumab	Ofatumumab	Ponesimod
rate	0.0531041	-0.0074094	-0.0248499	-0.0294932	-0.0219009	-0.0251326	-0.0169087	-0.0198371	-0.0335028	-0.0382852
EDSS	-0.0074094	0.00191196	0.0001186	0.0013168	-0.0006423	0.00019157	-0.0019306	-0.0011749	0.00235144	0.00358552
Alemtuzumab	-0.0248499	0.0001186	0.14939758	0.02447193	0.02435039	0.02440212	0.02427048	0.02431736	0.02453611	0.02461266
Cladribine	-0.0294932	0.0013168	0.02447193	0.52529706	0.02394784	0.02452217	0.02306063	0.02358107	0.02600972	0.02685964
Fingolimod	-0.0219009	-0.0006423	0.02435039	0.02394784	0.05686411	0.02432588	0.02503884	0.02478496	0.02360024	0.02318564
Glatiramer Acetate	-0.0251326	0.00019157	0.02440212	0.02452217	0.02432588	0.04940943	0.02419681	0.02427252	0.02462584	0.02474949
Natalizumab	-0.0169087	-0.0019306	0.02427048	0.02306063	0.02503884	0.02419681	0.06480111	0.02557657	0.02201592	0.02076985

Ocrelizumab	-0.0198371	-0.0011749	0.02431736	0.02358107	0.02478496	0.02427252	0.02557657	0.10844554	0.02294528	0.02218694
Ofatumumab	-0.0335028	0.00235144	0.02453611	0.02600972	0.02360024	0.02462584	0.02201592	0.02294528	0.52728212	0.02879993
Ponesimod	-0.0382852	0.00358552	0.02461266	0.02685964	0.02318564	0.02474949	0.02076985	0.02218694	0.02879993	1.03111405

Table 99 Covariance matrix for coefficients of exponential survival model for Time to EDSS Decrease (All RRMS)

	rate	EDSS
rate	0.048537	-0.0099457
EDSS	-0.0099457	0.00242531

Table 100 Covariance matrix for coefficients of exponential survival model for Time to EDSS Increase (SPMS)

	rate	**EDSS**
rate	0.41327905	-0.0685228
EDSS	-0.0685228	0.01220504

Table 101 Covariance matrix for coefficients of exponential survival model for Time to Relapse (SPMS)

	rate	**EDSS**
rate	0.86895777	-0.1357356
EDSS	-0.1357356	0.02188323

Table 102 Covariance matrix for coefficients of exponential survival model for Time to SP Conversion (RRMS Highly Active)

	rate	**EDSS**
rate	0.45009625	-0.0734639
EDSS	-0.0734639	0.01242186

Table 103 Covariance matrix for coefficients of exponential survival model for Time to SP Conversion (All RRMS)

	rate	**EDSS**
rate	0.13046351	-0.0207383
EDSS	-0.0207383	0.0034233

The results of fitting the multistate model to the All RRMS population are provided in Table 104 with standard errors in Table 105.

Table 104 MS registry log rates of transition between EDSS states based on multistate model

	0	1	2	3	4	5	6	7	8
0	0	5.33192944	0	0	0	0	0	0	0
1	6.21287963	0	2.06546476	0	0	0	0	0	0
2	0	-0.714375	0	3.94007716	0	0	0	0	0
3	0	0	3.89699664	0	-0.3884832	0	0	0	0
4	0	0	0	-0.3449541	0	0.16070213	0	0	0
5	0	0	0	0	0.59315005	0	0.31408698	0	0
6	0	0	0	0	0	-1.191966	0	-1.9983354	0
7	0	0	0	0	0	0	-1.1958821	0	-1.4518141
8	0	0	0	0	0	0	0	1.25944346	0

Table 105 Standard errors for MS registry log rates of transition between EDSS states based on multistate model

	0	1	2	3	4	5	6	7	8
0	0	2.10122434	0	0	0	0	0	0	0
1	2.08691526	0	0.345469	0	0	0	0	0	0
2	0	0.30187187	0	1.61466577	0	0	0	0	0
3	0	0	1.61681602	0	0.1488902	0	0	0	0
4	0	0	0	0.16046662	0	0.17763808	0	0	0
5	0	0	0	0	0.19043778	0	0.16388654	0	0
6	0	0	0	0	0	0.15350255	0	0.16672652	0
7	0	0	0	0	0	0	0.20999212	0	0.70836177
8	0	0	0	0	0	0	0	0.78283474	0

Appendix 8
Additional economic results

The total costs, total QALYs, and net benefits from the sensitivity analyses are presented below.

Table 106 Costs, QALYs and Net Benefit for treatments in comparison to Natalizumab IV (publicly available list prices) for Scenario 1 (All RRMS MS Registry population)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab-IV	598795.89 (541344.80, 668003.78)	9.39 (7.23, 12.17)	-410973.22 (-507725.34, -328395.74)	-317061.89 (-435024.42, -208253.29)
Natalizumab-SC	598390.47 (548051.13, 675501.89)	9.40 (7.12, 11.93)	-410458.67 (-512092.84, -336732.27)	-316492.77 (-434697.06, -225168.41)
Natalizumab biosimilar-IV	579908.89 (523045.16, 652685.77)	9.48 (7.08, 12.23)	-390247.57 (-495770.40, -309160.37)	-295416.90 (-415763.27, -201317.59)
Natalizumab biosimilar-SC	582183.63 (529485.06, 660590.52)	9.44 (7.34, 12.33)	-393354.55 (-488369.63, -317375.00)	-298940.01 (-405165.50, -204396.00)
Fingolimod	554644.56 (506013.91, 605241.50)	9.07 (6.74, 11.89)	-373332.15 (-439292.78, -293001.89)	-282675.94 (-366349.33, -174048.65)
Alemtuzumab	392265.32 (339307.14, 442588.68)	9.58 (7.28, 12.22)	-200663.61 (-279920.30, -126785.15)	-104862.75 (-200969.95, -11332.86)
Cladribine	388725.14 (342211.85, 436994.17)	8.76 (6.27, 11.39)	-213531.13 (-291153.75, -150969.01)	-125934.13 (-225773.91, -42879.73)
Ponesimod	482553.79 (439545.43, 555432.90)	8.95 (6.61, 11.37)	-303468.40 (-398720.43, -221229.76)	-213925.71 (-326068.53, -112605.33)
Ofatumumab	581498.65 (524699.05, 673961.13)	9.48 (7.18, 11.71)	-391816.87 (-516957.99, -301301.26)	-296975.98 (-438103.52, -191451.79)
Ocrelizumab	610973.28 (550077.19, 688108.24)	9.48 (7.22, 12.12)	-421311.97 (-517712.16, -341047.50)	-326481.32 (-435151.70, -224920.07)
Peginterferon-beta-1 SC 125µg	378806.29 (333919.20, 440357.27)	9.29 (7.04, 11.77)	-192936.46 (-267297.66, -127636.15)	-100001.55 (-196554.26, -14198.13)
Interferon-beta-1a SC 22µg	397488.66 (350587.74, 453451.67)	9.23 (6.98, 11.82)	-212813.70 (-284706.94, -139697.08)	-120476.22 (-215635.75, -24732.19)
Interferon-beta-1a SC 44µg	378381.40 (329630.26, 424331.74)	9.05 (6.15, 11.75)	-197470.92 (-280882.90, -132525.87)	-107015.68 (-215978.35, -29124.46)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Interferon-beta-1a IM 30µg	387836.50 (339638.11, 448683.70)	8.82 (5.92, 11.53)	-211489.18 (-294277.50, -132080.67)	-123315.52 (-232329.70, -17747.86)
Interferon-beta-1b SC 250µg	377187.75 (326714.14, 428150.07)	8.83 (6.48, 11.68)	-200597.82 (-281996.00, -127701.81)	-112302.86 (-215219.01, -16976.85)
Glatiramer Acetate 20mg	368533.08 (318421.90, 424950.62)	9.04 (6.67, 11.99)	-187774.06 (-269458.79, -120769.00)	-97394.54 (-191000.77, -11625.21)
Glatiramer Acetate 40mg	367001.59 (323298.80, 423995.21)	9.00 (6.79, 11.74)	-187043.11 (-261447.24, -121999.46)	-97063.88 (-189595.24, -10080.72)

Table 107 Costs, QALYs and Net Benefit for treatments in comparison to Natalizumab IV (publicly available list prices) for Scenario 2 (base-case w/ random effects NMA)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab-IV	598372.81 (546324.59, 673317.57)	9.58 (7.19, 12.63)	-406861.30 (-503937.23, -332801.32)	-311105.55 (-422956.65, -210429.32)
Natalizumab-SC	594613.77 (544928.33, 667468.89)	9.65 (7.29, 12.75)	-401652.27 (-490794.21, -335379.62)	-305171.52 (-415156.58, -206711.84)
Natalizumab biosimilar-IV	578589.43 (516709.91, 650346.20)	9.56 (7.17, 12.94)	-387487.40 (-484230.09, -302809.47)	-291936.39 (-413491.22, -173319.17)
Natalizumab biosimilar-SC	577461.75 (519695.59, 650792.03)	9.59 (7.05, 12.70)	-385640.28 (-491843.00, -301175.40)	-289729.55 (-413548.83, -185442.23)
Fingolimod	548613.06 (512651.42, 614318.67)	9.37 (6.83, 12.23)	-361304.77 (-435943.23, -301588.96)	-267650.63 (-350307.96, -190427.15)
Alemtuzumab	395735.19 (349536.35, 463348.50)	9.79 (7.02, 13.10)	-199964.30 (-291544.28, -106482.27)	-102078.85 (-208802.63, 13607.02)
Cladribine	388510.58 (342885.39, 443015.67)	8.91 (6.14, 11.54)	-210374.01 (-293864.41, -137535.89)	-121305.73 (-232011.97, -34532.84)
Ponesimod	480555.51 (427234.29, 547633.22)	9.10 (6.27, 11.50)	-298589.89 (-406677.15, -218011.39)	-207607.07 (-344500.87, -106979.46)
Ofatumumab	583003.39 (528763.35, 657647.34)	9.41 (6.84, 12.76)	-394781.13 (-494840.15, -307948.05)	-300670.01 (-415571.15, -188608.84)
Ocrelizumab	608513.00 (561119.72, 669324.12)	9.66 (7.61, 12.40)	-415333.26 (-497062.28, -347017.17)	-318743.39 (-411116.00, -229319.80)
Peginterferon-beta-1 SC 125µg	376669.86 (326404.56, 445471.06)	9.52 (7.25, 12.34)	-186209.50 (-271379.16, -104614.15)	-90979.31 (-200229.96, 19391.44)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Interferon-beta-1a SC 22µg	398806.56 (346242.70, 457440.61)	9.35 (7.09, 12.51)	-211717.04 (-309743.62, -126530.35)	-118172.29 (-237616.66, -5062.01)
Interferon-beta-1a SC 44µg	374019.28 (322168.34, 426849.54)	9.35 (6.85, 12.41)	-186928.25 (-276500.32, -107158.27)	-93382.73 (-200596.19, 12988.73)
Interferon-beta-1a IM 30µg	386799.83 (338733.28, 445194.14)	8.97 (6.29, 12.07)	-207340.72 (-298670.32, -127009.53)	-117611.17 (-230676.28, -10687.99)
Interferon-beta-1b SC 250µg	364990.86 (313505.86, 430970.20)	9.29 (6.59, 12.66)	-179248.16 (-284117.16, -76551.06)	-86376.81 (-219162.58, 44489.20)
Glatiramer Acetate 20mg	362912.60 (306509.82, 416675.82)	9.11 (6.60, 12.28)	-180623.98 (-267384.96, -94989.34)	-89479.67 (-200441.97, 11212.71)
Glatiramer Acetate 40mg	367784.97 (318208.39, 432781.53)	9.11 (6.36, 12.11)	-185545.43 (-266212.66, -101760.69)	-94425.67 (-205747.54, 9151.66)

Table 108 Costs, QALYs and Net Benefit for treatments in comparison to Natalizumab IV (publicly available list prices) for Scenario 3 (base-case & assuming JCV testing provided free of charge by manufacturers)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab-IV	562443.81 (511510.68, 641789.27)	11.18 (8.22, 14.43)	-338935.69 (-473880.31, -251626.66)	-227181.64 (-388596.81, -112286.13)
Natalizumab-SC	562682.85 (511613.14, 654456.97)	11.20 (8.23, 14.73)	-338667.64 (-471536.84, -261249.30)	-226660.03 (-384668.83, -118997.45)
Natalizumab biosimilar-IV	544207.05 (498616.93, 626417.06)	11.14 (8.20, 14.49)	-321369.48 (-437442.09, -242310.50)	-209950.69 (-358348.65, -98012.69)
Natalizumab biosimilar-SC	541662.28 (488163.66, 618771.01)	11.16 (8.18, 14.55)	-318498.59 (-446802.32, -235714.80)	-206916.75 (-362445.55, -89314.51)
Fingolimod	515561.88 (465834.49, 592723.88)	10.90 (7.84, 14.58)	-297463.95 (-431552.97, -211288.35)	-188414.98 (-357264.51, -77028.43)
Alemtuzumab	360937.84 (314526.46, 415502.63)	11.32 (8.49, 14.61)	-134570.29 (-212319.32, -68298.46)	-21386.52 (-125960.31, 73934.23)
Cladribine	348440.03 (304305.36, 414499.40)	10.66 (7.41, 14.59)	-135228.91 (-254511.61, -61569.08)	-28623.35 (-173771.00, 66301.37)
Ponesimod	444057.70 (395803.91, 518072.17)	10.90 (7.24, 14.25)	-226084.60 (-344152.07, -141369.99)	-117098.04 (-273087.09, -4807.75)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Ofatumumab	549680.95 (496084.71, 626940.15)	11.08 (8.02, 14.48)	-328052.89 (-462936.26, -251872.52)	-217238.85 (-380934.32, -116838.53)
Ocrelizumab	576608.50 (525932.16, 658066.04)	11.28 (8.05, 14.57)	-351082.95 (-481370.01, -276591.86)	-238320.18 (-397492.63, -137618.56)
Peginterferon-beta-1 SC 125µg	343178.10 (296942.17, 398482.75)	11.09 (8.13, 14.37)	-121352.36 (-235653.66, -40747.38)	-10439.50 (-154336.51, 95596.30)
Interferon-beta-1a SC 22µg	358910.56 (312218.91, 417588.57)	11.02 (7.92, 14.47)	-138446.88 (-237720.76, -65451.34)	-28215.03 (-153811.30, 69279.58)
Interferon-beta-1a SC 44µg	341087.60 (298992.52, 413554.46)	10.85 (8.16, 14.29)	-124118.66 (-224930.42, -38395.37)	-15634.19 (-141681.51, 101602.13)
Interferon-beta-1a IM 30µg	348343.06 (296631.36, 414106.34)	10.73 (7.07, 14.23)	-133825.37 (-266131.81, -49270.63)	-26566.52 (-189372.65, 83927.33)
Interferon-beta-1b SC 250µg	336548.87 (291412.61, 413549.07)	10.78 (7.29, 14.16)	-121033.61 (-249343.45, -35322.27)	-13275.99 (-181840.36, 96667.75)
Glatiramer Acetate 20mg	328795.83 (288931.79, 394107.22)	10.91 (7.44, 14.37)	-110671.59 (-232424.76, -34809.97)	-1609.46 (-155847.98, 99754.61)
Glatiramer Acetate 40mg	328710.26 (279774.89, 393415.70)	10.88 (7.53, 14.23)	-111206.41 (-233044.31, -25103.97)	-2454.49 (-160987.35, 114599.29)

Table 109 Costs, QALYs and Net Benefit for treatments in comparison to Natalizumab IV (publicly available list prices) for Scenario 4 (base-case & assuming lowest generic prices)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab-IV	567206.62 (515989.58, 646969.91)	11.18 (8.22, 14.43)	-343698.51 (-478923.66, -256427.65)	-231944.45 (-393640.16, -116759.62)
Natalizumab-SC	567460.49 (515964.10, 659385.70)	11.20 (8.23, 14.73)	-343445.28 (-476538.97, -266378.65)	-231437.68 (-389729.42, -123532.80)
Natalizumab biosimilar-IV	548995.60 (503066.35, 631754.31)	11.14 (8.20, 14.49)	-326158.04 (-442264.89, -247021.95)	-214739.25 (-363107.98, -102724.15)
Natalizumab biosimilar-SC	546412.78 (492243.98, 623904.43)	11.16 (8.18, 14.55)	-323249.09 (-451680.81, -240479.30)	-211667.25 (-367304.79, -94079.01)
Fingolimod	335804.52 (290819.35, 393084.47)	10.90 (7.84, 14.58)	-117706.59 (-223030.88, -36799.35)	-8657.63 (-139474.60, 101895.35)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Alemtuzumab	362426.34 (315802.47, 417204.72)	11.32 (8.49, 14.61)	-136058.79 (-213370.79, -69826.47)	-22875.02 (-127011.78, 72508.05)
Cladribine	349930.51 (305487.25, 415856.20)	10.66 (7.41, 14.59)	-136719.39 (-255990.66, -62870.99)	-30113.83 (-175250.05, 64626.55)
Ponesimod	445558.21 (397147.44, 519340.02)	10.90 (7.24, 14.25)	-227585.10 (-345288.63, -142929.03)	-118598.55 (-274455.67, -6467.86)
Ofatumumab	551178.38 (497587.54, 628450.25)	11.08 (8.02, 14.48)	-329550.31 (-464446.36, -253257.69)	-218736.28 (-382444.42, -118410.09)
Ocrelizumab	578096.88 (527458.10, 659330.20)	11.28 (8.05, 14.57)	-352571.33 (-482590.32, -277846.93)	-239808.56 (-398649.45, -139338.35)
Peginterferon-beta-1 SC 125µg	344691.51 (298364.16, 399694.49)	11.09 (8.13, 14.37)	-122865.78 (-236905.31, -42009.03)	-11952.91 (-155588.17, 94057.25)
Interferon-beta-1a SC 22µg	360394.11 (313452.66, 419105.16)	11.02 (7.92, 14.47)	-139930.42 (-239309.88, -66790.88)	-29698.58 (-155045.02, 67744.35)
Interferon-beta-1a SC 44µg	342581.14 (300199.52, 415208.40)	10.85 (8.16, 14.29)	-125612.20 (-226249.01, -39863.25)	-17127.73 (-143208.54, 100029.18)
Interferon-beta-1a IM 30µg	349838.95 (297790.59, 415484.27)	10.73 (7.07, 14.23)	-135321.26 (-267410.99, -50722.21)	-28062.41 (-190651.83, 82461.43)
Interferon-beta-1b SC 250µg	338035.98 (292809.83, 414894.48)	10.78 (7.29, 14.16)	-122520.73 (-250728.60, -36668.90)	-14763.10 (-183228.83, 95326.42)
Glatiramer Acetate 20mg	324077.33 (283831.26, 388513.07)	10.91 (7.44, 14.37)	-105953.08 (-227710.21, -30270.14)	3109.04 (-149580.17, 104585.66)
Glatiramer Acetate 40mg	324036.70 (274440.80, 388793.61)	10.88 (7.53, 14.23)	-106532.85 (-226977.80, -20437.00)	2219.07 (-154920.84, 119387.08)