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Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809]

Assessment Report

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Produced by: Warwick Evidence

Division of Health Sciences

Warwick Medical School, University of Warwick

Coventry

CV4 7AL

Lead Author: Dr G.J. Melendez-Torres[1]

Co-authors: Mr Peter Auguste[1]

Dr Xavier Armoiry[1]

Dr Hendramoorthy Maheswaran[1]

Ms Rachel Court[1]

Dr Jason Madan[1]

Mr Alan Kan[1]

Ms Stephanie Lin[1]

Dr Carl Counsell[2]

Dr Jacoby Patterson[3]

Mr Jeremy Rodrigues[4]

Prof Olga Ciccarelli[5]

Ms Hannah Fraser[1]

Prof Aileen Clarke[1]

[1] Warwick Evidence, Warwick Medical School, University of Warwick, Coventry

[2] Divison of Applied Health Sciences, University of Aberdeen, Aberdeen

[3] Independent research consultant

[4] Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford

[5] Department of Neuroinflammation, Institute of Neurology, University College London, London

Correspondence to: G.J. Melendez-Torres, Warwick Evidence, Warwick Medical School, University of Warwick, Coventry, CV4 7AL

Tel: +44 (0) 24765 74877

Email: g.melendez-torres@warwick.ac.uk

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The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

GJMT coordinated the project, led the review of clinical effectiveness and led the drafting of the report. PA led the review of cost effectiveness, the critique of the RSS submission and the economic modelling and contributed to drafting the report. XA co-led the review of clinical effectiveness and contributed to the drafting of the report. HM and JM contributed to the economic evaluation work and contributed to drafting the report. RC contributed to the reviews of clinical and cost effectiveness through search and information specialist support and to the drafting of the report. AK and SL contributed to the review of clinical effectiveness and to the drafting of the report. CC and OC contributed as clinical experts and to the drafting of the report. JP and JR contributed to the review of clinical effectiveness and to the drafting of the report. HF contributed to drafting the report. AC supervised the project and contributed to the drafting of the report.

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1 ABSTRACT

Aims and objectives

To undertake:

a) systematic reviews of clinical and cost effectiveness of disease modifying therapies (DMTs) (Interferon β-1a, Pegylated interferon β-1a, Interferon β-1b and Glatiramer acetate) in relapsing remitting multiple sclerosis, secondary progressive multiple sclerosis and clinically isolated syndrome, against best supportive care (BSC) and each other investigating annualised relapse rate (ARR), and time to progression at 3 months (TTP3) and 6 months (TTP6);

b) cost effectiveness assessments of DMTs for CIS and RRMS against BSC and each other; to update NICE Technology Appraisal (TA) 32.

Methods

Searches were undertaken in January and February 2016. Databases included the Cochrane Library, MEDLINE, and the Science Citation Index. Two reviewers screened and assessed titles and abstracts with recourse to a third when needed. The Cochrane risk of bias tool and CHEERS and Phillips checklists were used for appraisal. Narrative synthesis and, where possible, random effects meta-analysis and network meta-analysis (NMA) were performed.

Cost effectiveness analysis used published literature, an updated RSS model (based on the UK Department of Health Risk Sharing Scheme observational study with historical comparator) and expert opinion. A de novo economic model was built for CIS. The base case used updated RSS data, an NHS and PSS perspective, 50-year time horizon, 2014/2015 prices and a discount rate of 3.5%. Outcomes are reported as incremental cost-effectiveness ratios (ICERs) as cost per quality-adjusted life year gained. Models were run deterministically with sensitivity analyses and probabilistically with 1,000 bootstrapped iterations.

Results

We included 63 publications relating to 35 RCTs. 83% had high risk of bias. There was very little difference between the different drugs in reducing moderate or severe relapse rates in RRMS. All were beneficial against BSC giving a pooled rate ratio of 0.65 (95% CI [0.56, 0.76]) for annualised relapse rate (ARR) and an HR of 0.70 (95% CI [0.55, 0.87]) for TTP3. NMA suggested Glatiramer acetate 20 mg SC had the highest probability of being the best in reducing ARR.

Three separate cost effectiveness searches resulted in > 2,500 publications with 26 included studies informing narrative synthesis and model inputs. The base case using a modified RSS gave mean incremental costs of £25,600 for pooled DMTs compared to BSC and 0.943 more QALYs to give an ICER of £27,200 per QALY. Probabilistic sensitivity analysis gave an ICER of £32,000 per QALY. AG inputs gave an ICER of £8,100 per QALY for pooled DMTs versus BSC. Pegylated IFN β-1a 125µg (Plegridy) was the most cost effective option of the individual DMTs with an ICER of £7000 compared to BSC. Glatiramer acetate 20 mg (Copaxone) was most cost effective treatment for CIS with an ICER of £12,900 per QALY gained.

Discussion and conclusions

DMTs both separately and together are clinically and cost effective for treatment of both RRMS and CIS. Both RCT evidence and the DH RSS data are at high risk of bias. Research priorities include comparative studies with longer follow up and systematic review and meta-synthesis of qualitative studies.

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2 LIST OF ABBREVIATIONSAND STATISTICAL GLOSSARY

Technical terms and abbreviations are used throughout this report.

ABN	Association of British Neurologists
AIC	Akaike information criterion
AMSTAR	Assessing the methodological qualities of systematic reviews
ANOVA	Analysis of variance
ARR	Annualised relapse rate
AUD	Austrailian dollars
BCMS	British Columbia Multiple Sclerosis Database
BIC	Bayesian information criterion
BNF	British National Formulary
BOI	Burden of illness
BSC	Best standard care
CDMS	Clinically definite multiple sclerosis
CEA	Cost-effectiveness analysis
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence interval
CIS	Clinically isolated syndrome
CSF	Cerebrospinal fluid
CNS	Central Nervous System
DH	UK Department of Health
DIS	Disseminated in space
DIT	Disseminated in time
DMF	Delayed-release dimethyl fumarate
DMTs	Disease modifying therapies
DSS	Disability Status Score
EBV	Epstein-Barr Virus
EDSS	Expanded disability status scale
ESG	European Study Group
EQ-5D	Euro Quality of Life 5 dimensions questionnaire
GA	Glatiramer Acetate
GPRD	General Practice Research Database
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
GWAS	Genome-wide association studies
HCHS	Hospital and Community Health Services
HLA	Human leucocyte
HR	Hazard ratio
HRQoL	Health related quality of life

HUI	Health Utility Index
ICER	Incremental cost-effectiveness ratio
IFN	Interferons
IM	Intramuscular
INHS	Italian National Health Service
LYG	Life-years gained
MBP	Myelin basic protein
MLY	Mono-symptomatic life years
MRI	Magnetic resonance imaging
MS	Multiple Sclerosis
MSCRG	Multiple Sclerosis Collaborative Research Group
MTA	Multiple Technology Appraisal
NABs	Neutralising antibodies
NASG	North American Study Group
NAWM	Normal-appearing white matter
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
ONS	Office of National Statistics
PASAT	Paced Auditory Serial Addition Test
PEG	Polyethylene glycol
pegIFN-β-1a	Pegylated IFN-β-1a
PPMS	Primary Progressive multiple sclerosis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRMS	Progressive relapsing multiple sclerosis
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALYs	Quality Adjusted Life Years
QoL	Quality of life
RR	Rate ratio
RCT	Randomised controlled trial
RePEC	Research Papers in Economics
RRMS	Relapsing remitting multiple sclerosis
RSS	Risk sharing scheme
SC	Subcutaneous
ScHARR	School of Health and Related Research
SEKs	Swedish Kroners
SMR	Standardized mortality rates

SNPs	Single-nucleotide polymorphisms
SPMS	Secondary progressive multiple sclerosis
S(t)	Survival at time t
SUCRA	Surface Under the Cumulative Ranking Curve
SWIMS	South West Impact of Multiple Sclerosis
TA32	Technology appraisal guidance 32
TTP	Time to progression
UK	United Kingdom
WTP	Willingness-to-pay

Statistical glossary

Annualised relapse rate (ARR). This indicates the number of relapses a patient would expect to have on average every year. Differences in the annualised relapse rate are measured as a rate ratio, which suggests the percentage difference in rate between two groups. That is, a rate ratio of 0.75 in group 1 as compared to group 2 means that group 1 has 25% fewer relapses than group 2. In contrast, a rate ratio of 1.25 suggests than group 1 has 25% more relapses than group 2. In MS, an improvement of one drug over another would be represented by a rate ratio of less than 1.

Time to disability progression (TTP). This indicates how quickly a patient would expect to have disability progression compared to another patient. This is measured as a hazard ratio. A hazard ratio less than 1 in group 1 as compared to group 2 means that group 1 will take longer to have disability progression. Conversely, a hazard ratio greater than 1 in group 1 as compared to group 2 means that group 1 will have disability progression faster on average. For example, a hazard ratio of 0.75 in group 1 as compared to group 2 means that at a point in the future, people without progression group 1 will have a 25% less chance of having disability progression as compared to people without progression in group 2. In MS, an improvement of one drug over another would be represented by a hazard ratio of less than 1.

Time to disability progression confirmed at 3 (or 6) months (TTP3 or TTP6). To reduce the effect of 'blips' in disability progression on estimates of effectiveness, many trials require than an initial sign of disability progression be confirmed at a repeat visit 3 (or 6) months later. Thus, time to disability progression confirmed at 3 months is simply the time to disability progression, when that disability progression has been subsequently confirmed 3 months after the visit where progression was first detected. Similarly, time to disability progression confirmed at 6 months is the time to progression when that progression has been subsequently confirmed 6 months after the visit where it was first detected.

Surface under the cumulative ranking curve (SUCRA). In network meta-analysis, it is possible to rank interventions on the size of their effect. This is done using the surface under the cumulative ranking curve, or the SUCRA. A higher SUCRA means a larger magnitude of effect. For clinical effectiveness outcomes, such as relapse rate and time to disability progression, interventions are ranked based on how much the intervention reduces relapse or slows down disability progression. For discontinuation due to adverse events, interventions are ranked on how much they increase the risk of discontinuation.

3 PLAIN ENGLISH SUMMARY

Multiple sclerosis (MS) causes inflammation of the nerves. It is a leading cause of disability in the UK. This study is about two types of MS. In relapsing remitting MS (RRMS) people have relapses, or attacks of more severe illness and recovery. In clinically isolated syndrome (CIS) people have just one episode but are thought to be at high risk of developing MS.

Various treatments are available for RRMS and CIS, including different types of beta interferons and glatiramer. These are known as disease-modifying therapies. In this study we looked at the clinical effectiveness and cost effectiveness of these drugs for RRMS and CIS.

We carried out systematic reviews of randomised controlled trials. We pooled the results on relapse rates and time to worsening of the disease. We drew on a Risk Sharing Scheme set up by the Department of Health to collect long-term information on the disease modifying therapies. We developed our own model for CIS.

We found that all the disease-modifying therapies were clinically and cost effective in both RRMS and CIS. The studies were at high risk of bias and had short follow up. A longer-acting interferon (Plegridy) was the most cost effective option for RRMS and glatiramer was the most cost effective for CIS.

We think that longer-term research is needed comparing these drugs with each other. A review of qualitative studies is also needed so we can understand more about the preferences and experiences of people living with MS.

4 SCIENTIFIC SUMMARY

4.1 *Background*

Multiple sclerosis (MS) is a neurodegenerative disorder characterized by inflammation and demyelination of neurons in the brain and spinal cord. It is a leading cause of disability in working-age adults, and affects over 100,000 people in the UK. The commonest form of MS is relapsing remitting MS or RRMS. A single demyelinating event thought to precede MS is known as clinically isolated syndrome (CIS) and RRMS can progress to secondary progressive MS (SPMS). Although there is currently no cure for MS, there are a number of disease-modifying therapies (DMTs) available to help reduce the frequency of relapses and the rate of disease progression. Beta interferons (IFN-β) and glatiramer acetate (GA) are two such drugs. At the time of the most recent NICE Technology Appraisal guidance on these drugs (TA32) in 2002, there was insufficient evidence of their clinical and cost-effectiveness. A risk-sharing scheme was put in place, allowing patients to access the drugs and the NHS to adjust prices based on cost-effectiveness data, as well as to monitor long-term outcomes. This current study aims to appraise the clinical and cost-effectiveness of IFN-β and glatiramer acetate, for MS integrating published evidence with data from the risk-sharing scheme and also to assess their role in CIS.

4.2 *Decision problem*

Our objectives were: a) to systematically review the evidence for the clinical effectiveness of

- IFN β-1a;
- Pegylated IFN β-1a;
- IFN β-1b; and
- GA

in people with

- relapsing multiple sclerosis (including people with relapsing remitting multiple sclerosis and people with secondary progressive multiple sclerosis with active disease, evidenced by relapses), and
- clinically isolated syndrome, that is, a single demyelinating event, who are considered at high risk of developing subsequent multiple sclerosis;

against the following comparators:

- best supportive care without disease modifying treatment, and
- beta interferons and glatiramer acetate compared with each other;

and investigating the following outcomes:

- relapse rate;
- transition to clinically definite MS, in the case of CIS;

- severity of relapse;
- disability (for example, expanded disability status scale [EDSS]);
- symptoms of multiple sclerosis such as fatigue, cognition and visual disturbance;
- freedom from disease activity;
- discontinuation due to neutralising antibodies;
- mortality;
- adverse effects of treatment; and
- health-related quality of life;

and b) to systematically review existing economic evaluations, including use of the existing RSS model; to develop a *de novo* economic model for CIS; to assess the cost effectiveness of the treatments (IFN β-1a, pegylated IFN β-1a, IFN β-1b, and GA) in treatment of CIS and RRMS against the stated comparators, expressed in incremental costs per quality-adjusted life year, with a time horizon sufficiently long to reflect any differences in costs or outcomes between the technologies being compared and from an NHS and Personal Social Services perspective; and to update model parameters and inputs to reflect available evidence from the literature, current costs, the NICE reference case, current practice, and new data from the risk sharing scheme.

4.3 *Methods*

4.3.1 Clinical and cost-effectiveness reviews

Searches were undertaken in January and February 2016. Several relevant systematic reviews were identified for some populations and study types, allowing some searches to be limited by publication date to 2012 onwards. For those populations and study types where no suitable systematic reviews were identified, database searches were undertaken from inception. Databases included were the Cochrane Library, the Cochrane MS specialized register; MEDLINE; Embase and the Science Citation Index. For the cost effectiveness reviews the NHS EED, Research Papers in Economics (RePEC) and the Cost-effectiveness Analysis (CEA) Registry were included. Online trials registers were searched as well as websites for Companies, Patient and carer, Professional and Research groups. Included designs were RCTs, systematic reviews, meta-analyses and cost-effectiveness studies. The population was people diagnosed with RRMS, SPMS, or CIS and the intervention was one of the designated drugs used within its marketing authorisation (and including the recommended dose regimen). Searches of reference lists and information provided by the manufacturers for the interventions were checked for additional eligible studies. Two reviewers screened and assessed titles and abstracts of all records for inclusion independently with recourse to a third reviewer in cases of disagreement. Systematic reviews used to locate primary studies were appraised using the AMSTAR checklist, primary clinical effectiveness studies were appraised using the Cochrane risk of bias assessment tool and health economic studies with the CHEERS and Phillips checklists. Narrative synthesis was undertaken. Where possible random effects meta-analyses and network meta-analyses were performed using Stata v14 for each outcome.

4.3.2 Cost-effectiveness methods

The RSS model is an economic analysis conducted to assess the cost-effectiveness of the combined treatment effect of disease modifying treatments included in the Risk Sharing Scheme (RSS) compared with best supportive care for people with relapsing-remitting multiple sclerosis. It is a Markov model based on the British Columbia multiple sclerosis (BCMS) cohort for natural history compared with cohorts of patients taking the intervention drugs. Drug prices were agreed with the Department of Health (DH) as part of the Risk Sharing Scheme. We based our cost effectiveness analysis on the RSS model, including data from the ten year follow up where available. For CIS we built a *de novo* economic model to assess the cost-effectiveness of the identified drugs. We used outcome values derived from our systematic reviews of the published literature, RSS pooled cost-effectiveness data, data submitted by the companies, expert opinion and NHS reference costs to input into the models in order to understand the relative costs and effectiveness of the different interventions and to explore the different assumptions made.

We used our modified RSS model with clinical effectiveness inputs derived from the Year 10 RSS analyses as the base case for RRMS with additional evidence on time to progression for the CIS base case. We estimated mean total costs and mean total QALYs for each intervention compared with best supportive care (BSC) and with each other and adopted an NHS and PSS perspective with a 50-year time horizon. Costs were in 2014/5 prices and a discount rate of 3.5% was used. Outcomes are reported as incremental cost-effectiveness ratios expressed in terms of cost per quality-adjusted life year gained. The models were run deterministically. We undertook sensitivity analyses and explored uncertainty to investigate key drivers. For RRMS we undertook probabilistic analyses with 1,000 bootstrapped iterations.

4.4 *Results*

4.4.1 Clinical effectiveness results

We identified 6,419 publications of which we included 63 relating to 35 primary studies. 83% (30/35) were at high risk of bias from either complete or partial participant unblinding and studies also suffered from relatively short follow-up times. Five studies investigated DMTs for CIS all demonstrating a benefit in time to progression to MS when compared against placebo or BSC. Three trials investigated SPMS indicating benefit from the interventions against placebo and 27 compared different DMTs with each other or placebo for RRMS using a variety of outcomes. In RRMS there was very little difference between the different drugs in reducing moderate or severe relapse rates. Random effects network meta-analysis gave a pooled rate ratio of 0.65 (95% CI 0.56, 0.76) for annualised relapse rate (ARR) for all intervention drugs compared to placebo and an HR of 0.70 (95% CI 0.55, 0.87) for disability progression confirmed at three months (TTP3). Rankings suggested that the drug which had the highest probability of being the best in reducing ARR was glatiramer acetate 20 mg SC once daily, followed by pegylated IFN β-1a 125 µg SC every two weeks. For TTP3 IFN β-1a 44 µg SC thrice weekly had the highest probability of being the most effective.

4.4.2 Cost effectiveness results

Our searches for systematic reviews identified 1566 records of which nine were economic evaluation studies. Searches for economic evaluations in CIS revealed 614 records of which 9 were selected. Searches for primary cost-effectiveness, HRQoL, costs and resource use studies for DMTs in RRMS yielded 2451 studies of which 8 matched inclusion criteria. The cost-effectiveness systematic review findings suggested that models were sensitive to time horizons. Most demonstrated an acceptable ICER for different formulations of IFN β-1b in relation BSC at standard levels of willingness to pay in a number of different countries. For RRMS however findings were often not generalizable and, studies were sensitive to time horizons used and starting distributions of disability.

In the RSS model submission, a mean RR of 0.72 (95%CI Not reported) for ARR and a hazard ratio of 0.7913 (95%CI [0.7705, 0.8122]) for disability progression (equivalent to our TTP3 value) were given for patients taking DMTs compared to placebo based on year 10 analyses. Our base case using a modified RSS gave mean incremental costs of DMTs compared to BSC of approximately £25,600 more than BSC and produced 0.943 more QALYs to give an ICER of approximately £27,200 per QALY. Probabilistic sensitivity analysis gave similar values with an ICER of approximately £32,000 per QALY gained. DMTs were approximately £14,800 more costly than BSC using our clinical effectiveness results whilst conferring 1.822 more QALYs, equating to an ICER of approximately £8100 per QALY. Using the RSS base case model and with individual hazard ratios, we found that pegylated IFN β-1a 125 µg (Plegridy) was the most cost effective option with incremental costs of £17,800 and QALYs of 2.559 giving an ICER of £7000 compared to BSC. We explored varying key model input parameters, finding that changes to the hazard ratio for disability progression had the greatest impact on the cost-effectiveness results. A decrease in treatment effect (increase in hazard ratio by 10%) resulted in an ICER of approximately £64,000 per QALY gained.

For CIS we found that compared to BSC the optimal strategy was treatment with glatiramer acetate 20 mg (Copaxone) followed by DMTs for progression to RRMS. This was associated with incremental costs of £76,600 and incremental QALYs of 5.95 giving an ICER of £12,900 per QALY gained. Sensitivity analyses show that the model was most sensitive to change in the utility of the CIS health state. A 10% increase would however still give an ICER for glatiramer acetate 20 mg (Copaxone) of £14,500 versus best supportive care, well within the normal expected levels of willingness to pay.

4.5 Discussion and conclusion

We undertook systematic reviews, appraised the RSS model and designed a de novo model for CIS, to assess the clinical and cost effectiveness of DMTs in MS. From our systematic reviews we found that DMTs are effective when used for both RRMS and CIS. From our network meta-analysis glatiramer acetate is the most effective in reducing annualised relapse rate. For RRMS we found that overall DMTs are cost effective at current levels of willingness to pay at £27,200 per QALY. The individual drug with the lowest ICER against BSC at £7,000 was IFN β-1a 125 µg (Plegridy). We found that for CIS if DMTs are subsequently used for RRMS, the most cost effective option for CIS is glatiramer acetate.

4.5.1 Strengths and limitations

Strengths of the work include rigorous and comprehensive systematic reviews and a large number of network meta-analyses alongside careful assessment of company submissions and the RSS model. We built a de novo decision tree model to assess cost-effectiveness in CIS and for each investigation undertook a number of sensitivity analyses. Limitations include the limitations of the underlying studies, in that heterogeneity of definitions e.g. of progression, or of subgroups and of sparse networks limit our ability to synthesise our findings fully. More importantly we consider that the RCT evidence is problematic in that 30/35 studies were at high risk of bias and this along with short follow up times may not allow for adequate assessment of DMT effects. It is for these reasons that we elected to use a modified RSS model with appropriate adjustments, even though it is based on an observational design with a non-contemporaneous control cohort, as our base case for asssessment of cost effectiveness of the DMTs. In addition, in the cost effectiveness review we were unable to identify reliable estimates of utilities for CIS although we were able to take account of this in sensitivity analyses. The economic model represents the care pathway to the best of our knowledge, but practice and management may vary.

4.5.2 Implications for healthcare

We did not include formulations outside the recommended usage in the UK. Also we should recognise here that our study was specifically designed to exclude the clinical and cost-effectiveness of newer MS treatments such as newer monoclonal antibodies (alemtuzumab, daclizumab). This review should be considered in conjunction with newer NICE and other guidance on the clinical and cost-effectiveness of these agents.

4.5.3 Research priorities

One key flaw in the assembled clinical effectiveness evidence was the lack of long-term follow-up. We consider that the distinctiveness of the different stages of MS is open to question. Additionally, valuation of health benefits continues to be a vexing area for MS and this was an issue identified in the original guidance resulting from TA32. Additional priorities include:

- How and under what circumstances does MS progress through different types (CIS, RRMS, SPMS)? How do these transitions relate to changing imaging technologies and changes in clinical practice?
- Further research that does not concentrate on the lower end of the EDSS scale may be of value for populations with MS as survival and advances in support and aids for those with disabilities improve.
- The RSS was designed to collect longer-term observational data in this area, however a large-scale, longitudinal randomised trial comparing active first-line agents would contribute meaningfully towards resolving uncertainty about the remaining relative benefits of different IFN or GA formulations.
- We consider that a systematic review and meta-synthesis of qualitative studies relating to the lived experience of MS, with particular attention to the dominant clinical features, e.g. relapse and disability progression would be of value. This would provide a basis for an understanding of relevant health states and benefits that more closely matches the preferences and experiences of people living with the target condition.

5 BACKGROUND

5.1 *Introduction*

Multiple sclerosis (MS) is a progressive, degenerative disease affecting the central nervous system. It is characterised by inflammation and demyelination of the neurons, mediated by an autoimmune response by T-cells to white matter.

Although not yet fully understood, the aetiology of MS involves major genetic components[1] with two or more genes active in causing its development.[2, 3] There is also a body of literature linking the development of MS with environmental factors, or hypothesising the involvement of viral infections such as Epstein-Barr virus.[4-8]

Within the United Kingdom, prevalence is around 203/100,000 person-years, whilst incidence was 9.6/100,000 person-years between 1990 and 2010, with a female to male ratio of 2.4.[9] Peak incidence is at around 40 and 45 years of age (men and women, respectively) with peaks in prevalence at 56 and 59 years for men and women respectively.

5.2 *Types of MS*

The disease can develop and progress in three major forms: (i) relapsing remitting (RRMS); (ii) Primary progressive (PPMS); and (iii) Secondary progressive (SPMS);, of which RRMS originates from a single demyelinating event, known as clinically isolated syndrome (CIS).[10]

CIS events are isolated events of neurological disturbance lasting more than 24 hours, which indicate the first clinical demyelination of the central nervous system,[11] with clinical syndromes that are monofocal in nature (for example, optic neuritis and transverse myelitis) or multifocal (sucha s optical neuritis, limb weakness from transverse myelitis and cerebellar signs). Patients presenting with a clinical history of 1 attack are given a diagnosis of CIS. In these cases, MRI helps to confirm whether a diagnosis of MS can be given instead at the onset of symptoms. A diagnosis of MS requires that DIT and DIS criteria are fulfilled, and these can be checked using the MRI scan performed at onset of CIS. Patients with CIS who fulfil the DIS criteria, need evidence of DIT to become MS; and if DIT is not met at the baseline scan, it is necessary either to repeat the MRI scan to check whether there is a new lesion, or wait for a second clinical attack. Notably, then, delays in the onset to a second “relapse” for patients with CIS are equivalent to delays of MS progression

In 80% of cases, RRMS is the form of MS at time of diagnosis. In RRMS patients experience an exacerbation of symptoms followed by periods of remission. RRMS, as defined in research protocols, is characterised by episodes of relapses that last more than 24 to 48 hours. RRMS can be subtyped as rapidly evolving or highly active MS, and although these terms have not been precisely defined, they usually indicate two or more relapses within one year with evidence of increasing lesion frequency on MRI scans.[12] This classification is mainly used in reference to newer therapies like natalizumab and fingolimod.[13]

PPMS has an older age of onset, with greater susceptibility in men,[14] and is typically characterised by occasional plateaus in disease progression, with temporary minor improvements from onset.[15] Some PPMS patients experience relapses alongside disease progression.

SPMS follows on from RRMS but the disease course is progressive, with or without temporary relapses, remissions and plateaus in symptoms.[15] The transition is

The natural course of the disease is highly variable, with early stages of MS potentially developing into any of subtypes. However, each subtype is associated with cumulative neurological dysfunction, which is often measured using the Expanded Disability Status Scale (EDSS).[16] Transition from RRMS to SPMS occurs in 60% to 70% of patients initially diagnosed with RRMS, approximately 10 to 30 years from disease onset. About 15% of RRMS patients may be diagnosed with 'benign' MS, thus avoiding the progression of disability and conversion to SPMS.[17]

To date, there is no cure for MS. Currently approved drugs for MS act as immunomodulators or immunosuppressants with the aim of reducing the pathological inflammatory reactions and reducing the frequency and severity of relapses, and the rate of disease progression. Immunomodulation and immunosuppressing drugs used in MS are called disease-modifying therapies (DMTs).

5.3 *Disease modifying therapies*

5.3.1 Beta interferons

There are currently five licensed beta interferon (IFN-β) drugs in MS: two IFN β-1a (Avonex, Rebif), one pegylated IFN β-1a (Plegridy), and two IFN-β-1b (Betaferon, Extavia). These five drugs are recombinant forms of natural IFN-β, which is a 166 amino-acid glycoprotein which can be produced by most body cells in response to viral infection or other biologic inducers.[21] IFN β-1a are structurally indistinguishable from natural IFN-β whereas IFN β-1b are non-glycosylated forms that carry two structural changes compared to natural IFN-β (Met-1 deletion and Cys-17 to Ser mutation).

Depending on the formulation, the dose regimen is one intramuscular injection once a week (Avonex), one subcutaneous injection three times per week (Rebif), or one subcutaneous injection every other day (Betaferon, Extavia). The two IFN β-1b are the same drug (both are manufactured on the same production line). Pegylated IFN β-1a is a long-acting formulation of IFN β-1a obtained by adding methoxy-PEG-O-2-methylpropionaldehyde to IFN β-1a which allows less frequent administration (one subcutaneous injection every 2 weeks).

The precise mechanism of action of IFN-β in MS is not fully understood. The immunologic effects of IFN-β that are thought to have a potential action on MS are inhibition of T-cell co-stimulation/ activation processes, modulation of anti-inflammatory and pro-inflammatory cytokines, and decrease of aberrant T-cell migration.[22]

The main indication for IFN-β is the treatment of RRMS. For some patients IFN-β is indicated in response to a single demyelinating event with an active inflammatory process where there is determined to be a high risk of development of clinically definite MS. IFN β-1b is also licensed for use in SPMS, as is IFN β-1a SC 44µg three

times weekly (Rebif) in cases where SPMS remains with ongoing relapse activity. IFN-β drugs are not indicated for PPMS.

The most common reported adverse events of IFN-β are irritation at injection-site reactions and flu-like syndrome.[23] Other adverse events include pain, fatigue, headache and liver function abnormalities; a rare but important side effect is nephrotic syndrome. Adverse events may result in treatment discontinuation. Given the biological nature of recombinant IFN-β, patients are at risk of developing neutralising antibodies (NABs) against IFN-β. NABs are thought to increase relapse rates and the rate of disease progression.

Depending on the formulation, the current annual cost per patient of the beta interferons in the UK, assuming BNF list prices and considering a continuous treatment at standard dose, is between £7,264 and £10,572.[24]

5.3.2 Disease modifying therapies (glatiramer acetate)

There are two licensed formulations of glatiramer acetate (GA) (Copaxone). GA is the acetate salt of synthetic polypeptides, containing four naturally occurring amino acids. The mechanisms by which GA exerts its effects in patients with MS are not fully understood but it is now thought that GA induces a broad immunomodulatory effect that modifies immune processes which are currently believed to be responsible for the pathogenesis of MS.

According to the summary of product characteristics, GA is indicated for the treatment of RRMS, but not for PPMS or SPMS. The dose regimen is 20 mg daily (formulation of 20mg/mL) or 40 mg three times a week (formulation of 40mg/mL) by subcutaneous injection. The most common adverse events of GA are reaction of flushing, chest tightness, sweating, palpitations, headache and anxiety.[25] Injection-site reactions are observed in up to a half of patients.

The current annual cost per patient of GA in the UK, assuming BNF list prices and considering a continuous treatment at standard dose, can be estimated at £6,681-£6,704.[24]

5.3.3 Current use in the UK

IFN-β and GA are currently not recommended by NICE (Technology Appraisal 32, 'Beta interferon and glatiramer acetate for the treatment of multiple sclerosis', published January 2002) as they were considered not to be cost-effective. However, IFN-β and GA have been available in the NHS through a risk-sharing scheme, with the exception of one new brand of IFN-β-1b (Extavia) and of pegylated IFN-β-1a (Plegridy), which were released after the publication of TA 32. Within the risk-sharing scheme (RSS), a registry has been set up to record long term clinical outcomes of patients receiving IFN-β and GA. This review will consider the final data from this scheme alongside the clinical effectiveness evidence, and its implications for the clinical and cost-effectiveness of GA and IFN-β.

5.4 *Description of the health problem*

Multiple sclerosis (MS) is a neurodegenerative disorder characterized by inflammation and demyelination of neurons in the brain and spinal cord. It is a leading cause of non-traumatic disability in working-age adults, and affects over 100,000 people in the UK. Although there is currently no cure for MS, there are a number of disease-modifying drugs available to help reduce the frequency of relapses and the rate of disease progression. IFN-β and GA are two such groups of drugs; at the time of the technology appraisal guidance 32 (2002), however, there was insufficient evidence of their clinical and cost-effectiveness. A risk-sharing scheme was put in place, allowing patients to access the drugs and the NHS to adjust prices based on cost effectiveness data, as well as monitor for long-term outcomes. This current study aims to appraise the clinical and cost-effectiveness of IFN-β and glatiramer, integrating evidence from the literature with data on long-term outcomes collected from the risk-sharing scheme. This introduction will summarize the pathogenesis, clinical course, epidemiology, and current service provision for MS.

5.4.1 Pathogenesis

Although the precise pathogenesis of MS is unclear, our current understanding is that it stems from auto-reactive inflammatory responses targeting the myelin sheaths of CNS neurons. This inflammatory response begins in the periphery with activation of T-helper cells that recognize CNS antigens. The subsequent inflammatory cascade leads and responds to disruption of the blood-brain barrier, allowing for increased transepithelial migration of activated immune cells, cytokines, and chemokines into the CNS. Once in the CNS, the autoimmune response leads to demyelination and axonal degeneration.

More recently, MS has been recognised as consisting of both neurodegenerative and inflammatory processes.[26, 27] Although neurodegeneration in MS is even less understood than inflammation, it is thought to be mediated by degeneration of transected axons, defects in ion balance, and loss of nutritional support to glial cells surrounding neurons.[28] Notably, investigations of autopsy specimens have shown that axonal loss can occur even in areas without acute inflammation, including in grey matter and normal-appearing white matter (NAWM).[29] These neurodegenerative processes are thought to be responsible for progressive and permanent disability.

5.4.2 Aetiology

A large body of evidence suggests a multifactorial aetiology of MS, with some interaction of genetic and environmental triggers causing the peripheral immune system to become activated against CNS antigens. Although the precise interaction remains unknown, a number of risk factors for MS have been identified.

Genetic

Unsurprisingly, genetic polymorphisms linked to MS have been identified primarily in immune response proteins. The first and most significant genetic locus was identified in the 1970s on the human leucocyte antigens (HLA) complex.[30, 31] HLAs encode part of the class II major histocompatibility complex (MHC) in humans, which presents processed foreign antigens to T cells for recognition.[31, 32] Variations within the HLA region have been consistently associated with a risk of MS, with the HLA-DRB1*15:01 allele particularly

implicated[33-36]. It is also thought that the HLA complex carries genetic determinants of MS clinical progression.[31]

Although the HLA complex has the strongest and most long-standing linkage with MS, other genes are suspected of increasing disease susceptibility, age of onset and poorer prognoses for specific types of MS.[33] These genes have been identified based on evidence from genetic linkage studies, microarray studies, and, more recently, genome-wide association studies (GWAS).[37] A seminal GWAS study performed by the International Multiple Sclerosis Consortium and the Wellcome Trust Case Control Consortium studied 465,434 single-nucleotide polymorphisms (SNPs) in 9,772 cases and 17,376 controls, implicating at least 59 non-HLA genes as associated with MS inheritance. These genes include those in cytokine, immune stimulation, and immunological signal transduction pathways.[33]

Despite substantial data on genetic risk for MS, the rate of concordance between monozygotic twins is modest at about 25%.[38] Additionally, a study reporting genome, epigenome, and RNA sequences in MS-discordant monozygotic twins was able to find no substantial difference accounting for MS-discordance. Such evidence points to the involvement of other causes in MS pathogenesis.[39]

Viral

Among all environmental risk factors investigated in MS aetiology, Epstein-Barr Virus infection has shown the strongest consistent evidence of association.[40] EBV was first suggested as a potential causative agent of MS because of the similarity in epidemiological distribution across age, geography, ethnicity, and socioeconomic status.[41] 99.5% of patients with MS test seropositive for EBV antibodies, compared to 94.2% of the general population.[42] The current evidence for EBV's role in MS is multifaceted: prospective studies note increased serum anti-EBV antibody titres before onset of MS;[43] a meta-analysis found that for both adults and children testing negative for EBV, the OR for developing MS was 0.18 (for adults, 95% CI [0.13, 0.26]) compared to people who tested positive;[44] and at the molecular level, EBV can be isolated from B-cell infiltrates in meninges.[45] Although EBV is a demonstrated risk factor for MS, its role in causation remains unproven.

Other environmental risk factors

Populations living farther from the equator, both native and foreign-born, have consistently shown increased MS risk[46-50].[51] In one meta-analysis, this correlation persisted even after adjusting for regional differences in genetic HLA-DRB1 alleles,[51] though it was not replicated in a separate meta-analysis using incidence instead of prevalence.[52] One hypothesis is that this effect is mediated by sun exposure and vitamin D levels, with one supporting meta-analysis of 11 studies finding lower mean serum 25(OH)D levels in patients with MS [46-50].[53] Other possible explanations include confounding by socioeconomic factors or the 'hygiene hypothesis'. Smoking is also implicated as a modest but consistent risk factor for MS, with smoking cessation suggested as an effective public health intervention that carries numerous other benefits.[40]

5.4.3 Presentation

Clinical symptoms

Although the initial signs of MS are variable between patients, they classically present with focal neurological symptoms and signs of CNS dysfunction around the third decade of life. Relapses may present as painful loss of vision in one eye (optic neuritis), unilateral motor or sensory disturbance (cortico-bulbar/spinal tract involvement), double vision/vertigo/unsteadiness (brainstem or cerebellar syndrome), Lhermitte's phenomenon (pain down the spine/body on flexing the neck, from a cervical cord lesion), or bilateral leg and bladder dysfunction (spinal cord syndrome). Fatigue is a common but non-specific symptom. As MS progresses in severity, it can also lead to cognitive decline as well as changes in mobility, bladder/bowel function, and sexual function.

Imaging features

MRI modalities have an advantage over other imaging techniques with the ability to dampen resonance signals from the cerebrospinal fluid and intensify signals from sites of inflammation.[54] In sites of active inflammation, disruption of the blood-brain barrier allows lesions to be enhanced' with the administration (and take-up) of contrast, while chronic lesions are generally non-enhancing. MRI formally joined the diagnostic criteria for MS in 2001, and has rapidly become a primary tool for characterizing MS severity and progression. The characteristic MRI lesion is a cerebral or spinal plaque with high T2 signal, representing a region of demyelination with axon preservation. In the brain, plaques representing perivenular inflammation (and potential blood-brain barrier disruption) are known as 'Dawson's Fingers', and they are seen inthe periventricular regions radiating perpendicularly away from ventricles. Outside the periventricular region, plaques are also commonly found in the corpus callosum, sub/juxta-cortical region, optic nerves, and visual pathway.[55] Spinal cord lesions are nearly as common, though they more likely to be noticed clinically before MRI identification.

Pathology

Early acute stage lesions are active plaques characterised by breakdown of myelin, which may appear oedematous and inflamed histologically. Sub-acute stage lesions appear paler in colour and have higher focal regions of macrophages. Chronic stage lesions are inactive plaques with low activity of myelin breakdown, but characterised by gliosis, leading to the production of scar tissue.[56-58] Within the chronic stages of the lesions, attempts at remyelination occur but the process may be hampered and unsuccessful due to the scar tissue formed by gliosis.[59, 60]

5.5 *Diagnostic Criteria*

The diagnosis of MS is a clinical one, with supportive roles for neuroimaging and paraclinical findings. The fundamental requirement is for demonstrated CNS lesions disseminated in time and space (DIT and DIS, respectively). Initially this demonstration was purely based on clinical findings and history; over time,

laboratory results (such as CSF oligoclonal bands) and paraclinical evidence (such as neuroimaging) have been included as possible bases of diagnosis.[61]

The McDonald criteria, newly revised in 2010,[62] continue to form the standard diagnostic tool for investigating suspected MS in research settings and, to a more flexible degree, in clinical practice.[63] An MS attack, relapse, or episode is defined by 'patient-reported symptoms or objectively observed signs typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection'.

The most 'secure' diagnoses are supported by 2+ MS attacks, with objective clinical evidence of at least 1 lesion and 'reasonable historical evidence' of the second. Patients who have had 2+ attacks with associated clinical signs of 2 or more separate lesions in the CNS are said to have clinically definite MS (CDMS). If objective clinical evidence for only 1 lesion is found, evidence for DIS can come from T2 lesions on MRI if they occur in at least 2 of 4 locations characteristic for MS (juxtacortical, periventricular, infratentorial, spinal cord). Evidence for DIT can be provided by new T2 or contrast-enhancing lesions on MRI appearing after disease onset, or the simultaneous presence of contrast-enhancing (active) and non-enhancing (chronic) lesions on the scan performed at onset of CIS. Patients presenting with a clinical history of 1 attack and objective clinical evidence of 1 lesion, but without sufficient evidence of either DIS or DIT, are diagnosed with CIS.

5.5.1 Recent trends in the McDonald diagnostic criteria

The Poser et al. criteria for MS diagnosis were published in 1983, and included two major categories of 'definite' or 'probable' MS, each with subgroups of 'clinical' or 'laboratory-supported'.[64] Diagnosis was made based on number of attacks, and lesions with clinical evidence, paraclinical evidence, and laboratory evidence. CIS or 'possible MS' was not included in the criteria, as those patients were not yet involved in research studies. The McDonald 2001 diagnostic criteria did away with the previous categories and instead focused on evidence for DIT and DIS. For the first time, it also explicitly allowed for MRI data to serve as evidence for DIS and DIT. Originally, demonstration of DIS meant meeting the Barkhol/Tintoré criteria[65] (or showing 2 MRI lesions and positive CSF), and demonstration of DIT could only be done by enhancing lesions appearing 3 months after a clinical event. With a 2005 revision to the criteria, DIT could also be demonstrated by appearance of new T2 lesions 1 month after a 'reference scan' (which was required to be 3 months post clinical onset).[66]

The McDonald 2010 revision further simplified previous diagnostic criteria. It allowed for lesions at 2 of 4 areas to provide evidence of DIS, as opposed to the previous Barkhol/Tintoré criteria.[65] It also simplified the DIT criteria by removing the requirement that the baseline MRI be at least 30 days post clinical event, and allowing for presence of simultaneous enhancing and non-enhancing lesions on the scan at onset of CIS to serve for DIT. After this revision, a diagnosis of MS could be confirmed based on just a single MRI (with enhancing and non-enhancing lesions disseminated in space). Because more patients meet the DIS and DIT criteria under the 2010 revision as opposed to the original guidelines or 2005 revision, more recently diagnosed patients are more likely to have a diagnosis of confirmed MS instead of CIS.

5.6 *Prognosis*

5.6.1 Disability as part of prognosis

Quantification of disability in multiple sclerosis has been used extensively to standardise characterizations of functional disease progression. The three Kurtzke scales have commonly been used to describe MS progression. First, the functional systems scale is comprised of measures of functionality in 8 pre-chosen systems[16]; second, the Disability Status Score (DSS) is an eleven-point scale measuring global disability[71]; and third, the Expanded Disability Status Score (EDSS) is a modification of DSS measuring 20 points of disability.[72] The EDSS is currently used as the standard to measure disease progression in MS.

The EDSS quantifies disability in eight functional systems, specifically focusing on pyramidal, cerebellar, brain stem, sensory, bowel & bladder, visual, and cerebral/mental function (Scoring is detailed in Appendix 2).[16] An EDSS score of 0.0 would indicate normal neurology with no impairment in any system; an EDSS score of 4 suggests full ambulation without aid despite relatively severe disability; a score of 6 suggests needing unilateral support (ex. cane, crutch) to walk 100m; and a score of 7 suggests wheelchair confinement, with inability to walk >5m with support.[16]

5.6.2 Prognoses for disease progression

Prognostic data is primarily taken from longitudinal cohort studies, many of which can patients both on and off treatment. Patients who present with CIS have a 60-80% risk of developing clinically definite MS within 10 years if they have MRI lesions at the time of presentation, and ~20% risk if they do not (note that this prognosis will likely change with the revised McDonald 2010 diagnostic criteria for CIS) (reviewed in [73]). RRMS is thought to last for around 2 decades before transition to SPMS.[74] Up to 15% of patients with RRMS may be retrospectively diagnosed with 'benign' MS.[17] There is significantly less consensus about the natural history of disability in the progressive phase of MS, with median times to EDSS 6 ranging from 15-32 years.[74] Very generally, progression to EDSS 4 is suspected to occur after 1 decade, EDSS 6 after 2 decades, and EDSS 7 after 3 decades.[75, 76] Median ages for EDSS 4, 6, and 7 were 42, 53, and 63, respectively, for a cohort study of 1844 patients in Lyon.[77]

Risk factors for disease progression

MS is notoriously heterogeneous, and even when all known risk factors are combined, they provide only moderate prognostic value. Generally, observational data have found male gender, older age of onset, progressive state at onset, and higher number of MRI lesions to be predictive of a poor prognosis with faster disability progression.[78, 79] A recent systematic review has identified several key factors related to relapse frequency and recovery.[79] Relapse activity appears to decrease with age and disease duration, and cohort studies suggest that women experience relapses more frequently. Modifiable risk factors, including smoking, exposure to infectious disease and discontinuation of DMTs, also are associated with increased relapse frequency.

Relapse rates

There is some controversy over whether increased rates of relapse events represent an independent risk for disability progression in MS. Short-term studies suggest that relapses do not entirely regress, so that when EDSS scores are eleveated during relapses pateints do not return to their previous baseline.[80] Authors of these studies would conclude that a greater number of relapses, then, would lead to earlier increases in EDSS scores. Longer cohort studies, however, have noted that number of relapses is not associated with time to SPMS or EDSS 6.[75, 81] A study examining placebo groups from two large phase III trials also noted that half of patients satisfying criteria for 'confirmed progression' (definitions ranging from 1.0 EDSS increase for 3 months, to 2.0 EDSS increase for 6 months) were erroneously diagnosed, as their EDSS scores did not sustain progression even through the end of the trial.[82] Thus, in short-term studies, EDSS scores measured months after relapse may still be reflecting changes of active, not progressive, disease. These longer time scales for recovery from relapse may need greater recognition.

Most recently, a longitudinal cohort study by Leray et al. suggested that MS may be characterized by 2 distinct phases, with Phase 1 lasting from diagnosis until irreversible EDSS 3, and Phase 2 from EDSS 3 until EDSS 6. Notably, disability progression in Phase 1 did not influence Phase 2, and, similarly to previous studies, increased relapse during the first 2 years of MS only influenced time in Phase 1. Relapses after EDSS 3 were not associated with continued disability progression. Previously-characterized risk factors of gender, age of onset, and relapse history were not related to disability progression in phase 2.[83] These data are in line with previous studies suggesting that while rates of relapse early in disease predicts disease progression, relapses later in RRMS or during SPMS may not significantly predict or influence disability progression.[84, 85]

Prognoses for mortality

Patients with MS have an average lifespan 7-14 years shorter than matched controls.[86] A meta-analysis of standardized mortality rates (SMR) found that patients overall had a 2.81 SMR compared to controls, which suggests 181% more mortality per year than anticipated at any age.[87] This was especially increased for those with EDSS>7.5, who, in a separate study, were found to have a 4.0 SMR compared to controls.[88] One review notes that in most cohort studies of people with MS, MS is cited as a cause of between half and three-quarters of deaths. It also notes wide variation in the proportion of deaths ascribed to MS, resulting from variations in assessment, interpretation, and coding practices. In particular, death from suicide is inconsistently reported as MS-related, though there is a substantially increased risk of suicide among people with MS. [86]

5.6.3 Epidemiology

Prevalence and incidence

An international survey including data from 92 countries estimated the median global prevalence of MS to be 33/100,000, or about 2.3 million people worldwide.[63] This prevalence has been increasing in the past few decades, primarily because of increased survival and diagnosis, but a meta-regression analysis suggested that there is also likely a true increase in MS incidence.[52] This analysis also suggested that the increase is primarily in women, who already face double the burden of MS compared to men.[52, 89-92 93]

A recent systematic review reported estimates for MS prevalence in the UK ranging from 97.26 in England in 1998[94] to 230.60 per 100,000 in Scotland in 2008.[89, 95] Incidence estimates were less common, and ranged from 4.4 to 12.2 per 100,000 person-years.[89] Analysis of the UK General Practice Research Database between 1990-2010[9], similarly, showed an estimated prevalence of 258.5/100,000 women and 113.1/100,000 men, with incidence of 11.52/100,000 women per year and 4.84/100,000 men per year. Incidences peaked in women of age 40 and men of age 45. Although no systematic reviews of longitudinal incidence trends specifically look at the UK, the analysis of the UK GPRD estimates that while overall prevalence of MS is increasing due to increased survival, incidence has decreased by 1.5% per year (though this may be due to decreased false positive diagnoses). This analysis estimates that 126,669 people with MS were living in the UK in 2010, though the number may be inflated about 20% with inaccurate diagnoses.[96]

Burdens of disease.

The effects of MS have major ramifications for the patient and carers, as well as financial implications for the patient and the state.

Disability

MS has a wide range of effects, ranging from mobility problems to bladder/bowel dysfunction, sexual dysfunction, fatigue, visual disturbances, pain, depression, and memory changes.[97] Interviews with 301 patients in Wales found that weakness, sensory changes, and ataxia were the most commonly-reported symptoms of MS,[98] while a postal survey of 223 unrepresentative MS patients found fatigue, bladder/bowel problems, balance problems, and muscle weakness to be the 'worst' symptoms.[97, 99] In terms of functional impacts, mobility, ability to use stairs, and outdoor transport were cited as the most significantly impacted by disease, whereas activities like dressing and feeding were more preserved.[100] Surveys of mobility in randomly-sampled populations of patients with MS note that slightly less than half (41.4%-53%) require walking aids or a wheelchair (EDSS 6+).[100-102]

Quality of life

A survey based on the EuroQoL 5 dimensions questionnaire (EQ-5D) suggested that 82.5% of 4516 patients had experienced difficulty in their daily activities, and 76% experienced pain and problems with mobility, with patients rating their mean health state as 5.97 out of 10[103] (cf. UK general population 8.3[104]). Another study with 2708 participants living with MS established a mean utility of 0.49 (perfect health equal to 1.00), with an inverse relationship between EDSS score and quality of life.[105] The study established that quality of life was affected by type of disease, recent relapse and length of time since diagnosis, with SPMS demonstrating lowest quality of life across subtypes.

The lifetime prevalence of depression patients with MS is ~50%, with an estimated annual prevalence of 20%.[106] Meta-analysis showed a 2.13 SMR for suicide compared to the general population,[87] though accuracy is difficult to assess because reporting of suicide as a cause of death continues to be heavily influenced by cultural biases.[86] Risk factors for suicide in patients with MS may include depression, social isolation, younger age, advanced disease subtype, low socio-economic status and higher EDSS score.[107]

Cost

A number of cost estimates for MS exist, most of them based on cost-of-illness analyses (which are contested)[108] with significant variation in methodologies and costs accounted for.[97] Most recently, analyses estimated an average of between £30,460 - £39,500 per person-year.[109, 110] Overall indirect costs, including those from lost employment, are projected to be greater than direct costs of care, and costs are greater for those in later stages of disease.[97] Estimated cost of relapse range from £519[111] to £2115,[112] depending on level of care required.

Cross-sectional surveys of disability in patients with MS demonstrate substantial changes to employment. Surveys with an average age of 50 have noted that most patients are not working,[100, 113] and most early or partial retirement is due to MS.[102, 113] In a study of 301 patients in England in the 1980s, 27% of patients report decreased standard of living because of employment changes and care costs, and 36% of carers interviewed also had their careers impacted.[113] Lost employment is estimated to currently account for 34%-40% of the total cost of MS.[109, 110]

Patient expectations and perceptions of disease

The literature describing qualitative experiences of patients is not as comprehensive as that surrounding pharmacological treatments and pathology of MS. Collectively, however, what does exist unsurprisingly describes the experience of symptom onset and diagnosis as a negative one.[114-116] Patients inevitably experience distress and anxiety as they become aware of symptoms[116], and this can continue or be amplified as they learn of their diagnosis; the diagnosis can, however, also be a source of relief because it provides an explanation for symptoms.[115] Receiving adequate information from healthcare professionals at the time of diagnosis can have a positive effect on patients' wellbeing and self-identification of relevant support services,[115] while a lack of information or empathy can be linked to frustration, anxiety, and fear.[116] The transition from RRMS to SPMS is also a challenging time for patients, as this requires adjusting to new 'realities' and preparing for forthcoming challenges in a declining trajectory.[117] A recent qualitative systematic review emphasizes the importance of support from healthcare providers, and an accessible healthcare system.[118] Comprehensive care plans including patient and carer support alongside therapeutics are described as key for successful management of MS.[119]

Current service provision

At present there is no cure for MS, but treatment options exist based on the stage and subtype of disease. Currently approved drugs for MS act as immunomodulators or immunosuppressants, with the aim of reducing the pathological inflammatory reactions occurring in MS, and thus the frequency and severity of relapses and the rate of disease progression.[120] Management of MS also includes non-pharmacological options such as lifestyle adjustments and rehabilitation, which are also included in the NICE guidelines for MS management.[19]

Treatments to reduce the risk of relapses

Drugs aimed at reducing the risk of relapses are called disease-modifying therapies (DMTs). In addition to the DMTs introduced in section 5.3, several newer drugs are licenced for use in the UK. Five newer drugs are recommended by NICE for the treatment of MS: natalizumab, teriflunomide, alemtuzumab, fingolimod and

dimethyl fumarate. A summary of these recommendations is provided in Table 1. DMTs are indicated in the treatment of classic RRMS, with the exception of natalizumab and fingolimod, which are recommended only in patients with highly active RRMS. Among DMTs, interferon beta-type drugs and GA are indicated for patients with CIS.

Immunosuppressive agents, such as azathioprine, cyclophosphamide, mitoxantrone, and methotrexate, can also be used in the management of MS. These agents can provide potential benefit through downregulating pathogenic mediators of MS, but can also induce severe adverse effects on the immune system. Consequently, those drugs are only indicated in patients with aggressive forms of MS, including patients who experience very frequent and severe relapses. They are not included in any NICE guidelines currently, though they continue to be used for MS[121] and a systematic review suggests their effectiveness in preventing relapse recurrence.[122]

Table 1: NICE technology appraisal guidelines and recommendations for DMTs

Treatment	Technology appraisal	NICE recommendation
Alemtuzumab	TA312, 05/2014	recommended as an option, within its marketing authorisation, for treating adults with active RRMS
Dimethyl fumarate*	TA320, 08/2014	recommended as an option for treating adults with active RRMS, only if they do not have highly active or RES RRMS
Fingolimod*	TA254, 04/2012	recommended as an option for the treatment of highly active RRMS in adults, only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon
Natalizumab	TA127, 08/2007	recommended as an option for the treatment only of rapidly evolving severe RRMS (RES)
Teriflunomide*	TA303, 01/2014	recommended as an option for treating adults with active RRMS only if they do not have highly active or RES RRMS

Active RRMS: defined as 2 clinically significant relapses in the previous 2 years
RES RRMS: rapidly evolving severe RRMS, defined by two or more disabling relapses in 1 year, and one or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.
*available with discount agreed to by manufacturer in a patient access scheme

Treatment of acute relapses

Steroids are commonly used and recommended to treat acute relapses. Steroids are aimed at reducing duration of relapses by shutting down production of inflammatory cytokines and destroying activated lymphocytes that cause demyelination; these drugs are not, however, thought to induce long-term benefit in the course of the disease.[123] NICE guidelines[124] recommend use of oral methylprednisolone 0.5g daily for 5 days in the first instance and to consider intravenous methylprednisone 1g daily for 3-5 days as an alternative if oral steroids are not tolerated or have failed, or if hospital admission for severe relapse or monitoring is required. Patients should not be offered a supply of steroids to administer at home for prophylactic use for future relapses. Lastly, patient education should target management of potential complications, such as mental health changes or irregularities in blood glucose. NICE guidelines[124]

Pharmacological treatment of symptoms

Current NICE guidelines offer advice to healthcare professionals, patients and families on the management of MS symptoms.[19] Recommendations include amantadine use for fatigue (though it does not have marketing authorisation in this indication), and baclofen or gabapentin for spasticity, with combinations of baclofen and gabapentin possible if individual drugs cannot reach a dosage for adequate relief.[124] Other drugs such as tizanidine, dantrolene, or benzodiazepines should be considered as second or third-line options. NICE guideines also noted that fampridine, recently approved in Europe to improve walking ability in people with MS, has not been recommended by NICE as a cost effective treatment. A systematic review, however, concluded that the absolute and comparative efficacy and tolerability of anti-spasticity agents in MS was poorly documented, and no recommendations could be made to guide prescription.[125]

For treatment of psychological changes, rivastigmine, donepezil and memantine, which are classically used in Alzheimer's disease, have been tested to improve cognitive impairment, but overall evidence for their efficacy in MS patients has proved inconclusive.[126] The treatment of depression includes consideration of both psychotherapy and antidepressant medication. Commonly used medications are selective serotonin reuptake inhibitors such as fluoxetine, paroxetine and sertraline. A recent systematic review showed that depression severity was improved in three pharmacological studies of depression treatment in MS.[127] NICE guidelines state that amitriptyline can be considered to treat emotional liability.

Managing disability

Non-pharmacological treatment options are directed towards a rehabilitative approach with specialist assistance from a multidisciplinary team.

There is evidence that physical activity alone can improve fatigue, and it has been linked to improvement in aerobic capacity, gait parameters and QoL[128, 129]. Suggestions for an effective rehabilitation regime include progression of physical activity from basic to integrated functions,[130] to utilize working muscles while avoiding muscle overload. Although RCTs have shown some evidence of improved mobility and QoL from exercise interventions, however, systematic reviews have not reached consensus on whether the studies – which are especially limited by small samples and risk of bias from lack of blinding – are enough to make guided exercise prescriptions.[131-133] Urinary incontinence affects approximately 75% of patients and can substantially impact quality of life.[134] NICE guidelines on lower urinary tract dysfunction in neurological disease are available, and should be used to inform treatment.[135]

Care should also be taken in the management of mental health of patients. Interventions should be aimed at regular monitoring of any depressive states and mental health services should be offered routinely to encourage participation.[136] Education for all healthcare providers and the patient in coping mechanisms may help improve QoL.[137]

6 DESCRIPTION OF TECHNOLOGY UNDER ASSESSMENT

In accordance with the NICE scope, this MTA focuses on IFN-β (including pegylated IFN β-1a) and glatiramer acetate.

6.1 *Beta interferons (IFN-β)*

Interferons (IFNs) are proteins that bind to cell surface receptors, initiating a cascade of signaling pathways ending with the secretion of antiviral, antiproliferative, and immunomodulatory gene products.[138] Natural IFN-β is a 166 amino-acid glycoprotein that can be produced by most cells in response to viral infection or other biologic inducers.[21] There are two types of recombinant IFN-β, known as IFN β-1a and IFN β-1b. IFN β-1a is a glycosylated form structurally undistinguishable from natural IFN-β;[21] recombinant IFN β-1b is a non-glycosylated form that carries one amino- acid substitution.[139]. Several in-vitro studies have concluded that biologic activity of some IFN-β-1a formulations is greater than that of IFN β-1b [21, 139, 140] but the clinical implications of such differences are unknown. Furthermore, those studies have not compared all the approved formulations of recombinant IFN β.

The precise mechanism of action of IFN-β in MS is not fully understood, but some potential actions include inhibition of T-cell activation, modulation of inflammatory cytokines, and decrease of aberrant T-cell migration into the CNS. [22]

There are currently five licensed IFN-β: two IFN β-1a (Avonex, Rebif), one pegylated IFN β-1a (Plegridy), and two IFN β-1b (Betaferon, Extavia):

- One formulation of IFN β-1a (Avonex) is given at the recommended dosage of 30 μg (6 million IU), administered by intramuscular injection once a week.
- The other formulation of IFN β-1a (Rebif) is given at the recommended posology of 22 μg (6 million IU) or 44 micrograms (12 million IU) three times per week by subcutaneous injection.
- IFN β-1b (Betaferon, Extavia) is given at the recommended posology of 250 μg every other day by subcutaneous injection.
- Pegylated IFN β-1a (Plegridy) has polyethylene glycol (PEG) added to the N-terminus of IFN β-1a, allowing for less frequent administration. Its recommended dosage is 125 μg injected subcutaneously every 2 weeks.

The current licensed indications of IFN-β are listed in Table 2. Their main indication is for treatment of patients with relapsing-remitting MS (RRMS); most (Avonex, Rebif, Betaferon/Extavia) also have indications indicated in patients with a single demyelinating event with an active inflammatory process and at high-risk of developing CDMS. IFN β-1b is licenced for use in patients with secondary progressive MS (SPMS). IFN β-1a (Rebif) is licensed with SPMS with ongoing relapse activity. IFN-β are not indicated for primary progressive MS (PPMS).

The most commonly reported adverse events of IFN-β are injection-site reactions (mainly inflammation) and flu-like syndrome (including fever, chills and myalgias, and headache) but these generally decline markedly after the first year of treatment.[23] Other adverse events include hypersensitivity reactions, blood disorders

(mainly leucopenia), menstrual disorders, mood and personality changes. Adverse events may be responsible for treatment discontinuation.

Because of its biological nature, recombinant IFN-β also carries a risk for patients of developing neutralizing antibodies (NABs),[141] and this is thought to reduce the treatment efficacy.[142] The occurrence of NABs depends on patient-specific factors but also treatment-specific factors like formulation, route of administration, dosage, and frequency of administration. Given their different natures and routes of administration, the immunogenicity of IFN-β varies among the formulations of IFN-β. A recently published systematic review of randomised trials showed that the rate of patients developing NABs was 2.0%-18.9% for Avonex, 16.5%–35.4% for Rebif, and 27.3%–53.3% for Betaferon.[143] Some guidelines recommend testing patients treated with IFN-β for the presence of NABs after 12 and 24 months of treatment.[141, 144]. In the UK, the monitoring of NABs is not performed in routine practice.

According to net prices listed in the British National Formulary, the current annual cost per patient of beta interferons in the UK can be estimated at £8,502 for Avonex, £7,976/ £10,572 for lower dose/higher doses of Rebif, and £7,264 for Betaferon/Extavia. Estimated costs in 2013-14 for IFN-β in England were £52,000,000 with 27.6% growth from 2012-13.[145].

As of July 2016, no biosimilar version of IFN-β is available in the UK.

6.2 *Glatiramer acetate (GA)*

Glatiramer acetate is a synthetic molecule containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine and L-lysine. It was initially created to mimic myelin basic protein (MBP), a suspected autoimmune antigen, and induce a mouse form of MS. Surprisingly, it prevented MS induction in mice, triggering clinical studies of glatiramer as a treatment for MS.[138] It is now thought that glatiramer induces a broad immunomodulatory effect, with actions including competition for the binding of antigen presenting cells; antagonism at specific T-cell receptors; and promotion of anti-inflammatory responses in dendritic cells, monocytes, and B-cells.[146]

Two formulations of GA are currently used: 20mg/mL and 40mg/mL (Copaxone, TEVA UK), equivalent to 18 mg or 36 of glatiramer base respectively. The dose regimen is 20 mg daily (formulation of 20mg/mL) or 40 mg three times a week (formulation of 40mg/mL) by subcutaneous injection. See Table 2. As of February 2016, no generic version of Copaxone is available in the UK.

GA is indicated for the treatment of patients with RRMS. It is not indicated for PPMS or SPMS. The most common adverse events of glatiramer are flushing, chest tightness, sweating, palpitations and anxiety,[25] and injection site reactions are observed in up to a half of patients.

The current annual cost per patient of glatiramer acetate in the UK can be estimated at £6,681-£6,704.[145] Generic prices are not yet available.

Table 2: Licensed indications for interferon beta and glatiramer acetate (as reflected in the NICE scope)

Brand name	INN	Recommended Usage	Indications
Avonex	IFN β-1a	Dose: 30 µg (6 million IU) Administration: intramuscular injection Frequency: once a week	• RRMS. 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. • 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. • Should be discontinued in patients who develop progressive MS.
Rebif	IFN β-1a	Dose: 22 µg (6 million IU) or 44 µg (12 million IU) Administration: subcutaneous injection. Frequency: Three times weekly	• RRMS. In clinical trials, this was characterised by two or more relapses in the previous two years. • Patients with a single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis. • Efficacy has not been demonstrated in patients with SPMS without ongoing relapse activity
Betaferon Extavia	IFN β-1b	Dose: 250 µg (8 million-IU) Administration: subcutaneous injection. Frequency: 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 CDMS • Patients with RRMS and two or more relapses within the last two years. • Patients with SPMS with active disease, evidenced by relapses.
Plegridy	Pegylated IFN β-1a	Dose: 125 µg Administration: subcutaneous injection: Frequency: every 2 weeks	• Adult patients for the treatment of RRMS
Copaxone	Glatiramer acetate (GA)	Dose: 20mg or 40mg Administration: subcutaneous injection. Frequency: daily (20 mg) or three times weekly (40 mg)	• Treatment of relapsing forms of multiple sclerosis (MS). It is not indicated in primary or secondary progressive MS. • Glatiramer acetate in the 20 mg formulation has been studied in both RRMS and CIS.

6.3 *Care pathways for IFN- β and GA*

IFN-β and GA are considered first-line treatments for RRMS, except for patients with highly active RRMS, in which more advanced treatments (e.g. natalizumab) are considered most appropriate. Though some patients prefer dimethyl fumarate or teriflunomide because of their oral mode of administration, IFN-β and GA both have well-established long-term safety profiles that avoid some of the more severe side effects presented by other drugs, e.g. the rare but serious complications of progressive multifocal leukoencephalopathy associated with the reactivation of the John Cunningham virus (JCV) in dimethyl fumarate. Additionally, some patients may choose not to take IFN-β or GA, especially after CIS, or if the course of MS appears to be benign. Patients receive specialist advice, including from neurologists and nurses specialist in MS care, in choosing which DMT to initiate. It is common for MS patients to see a neurologist about once a year for maintenance, and MRIs are administered generally not more than once a year. Exacerbations may be managed by local GPs or by specialist neurology services depending on severity and complexity.

Switching between first-line treatments mainly occurs because of side effects. Patients may escalate to a second-line treatment if MS is highly active, i.e. characterised by multiple disabling relapses in a year, or unchanged relapse rate during first-line treatment.

Upon transition to SPMS—a diagnosis which is made retrospectively—patients are supposed to cease use of drugs that are not licenced for SPMS. However, there is anecdotal evidence that patients may continue on these drugs because of perceived benefits for relapse rate and the absence of any other treatment for SPMS.

6.4 *The UK Multiple Sclerosis Risk Sharing Scheme*

The last technology appraisal for beta interferons and glatiramer in the treatment of MS (TA32) did not find sufficient evidence of clinical and cost-effectiveness to recommend treatment.[147] The Department of Health set up a risk-sharing scheme (RSS) to provide the then-licenced formulations of interferon β-1a (Avonex, Rebif), interferon β-1b (Rebif) and glatiramer (Copaxone) to patients.[148] Under this arrangement, the benefit of each drug would be regularly assessed using target outcomes agreed upon with manufacturers. Price for each drug would be scaled, as necessary, to reach a target level of cost-effectiveness, set at the start of the scheme as £36,000/quality-adjusted life-year (QALY). As part of the RSS, patients meeting the criteria for treatment were enrolled in a cohort and monitored regularly for evidence of disability progression and treatment benefit. Analysis of the six-year data of this clinical cohort[149] compared disease progression against a historical comparator and suggested that, on the whole, the DMTs included in the RSS reduced disability progression and did so to the agreed level of cost-effectiveness.

Because all patients in the RSS received treatment, a comparator cohort including patients with measurement of disease progression without access to DMTs was needed. Several natural history cohorts meeting these criteria exist. The six-year interim analyses used the British Columbia cohort, which was initiated in 1980, before DMTs were made routinely available in Canada. The cohort has prospectively recorded EDSS scores and covers about 80% of the relevant MS population in that area, providing a rich source of data about the natural history of

MS.[150, 151] Patients from the British Columbia cohort who would have met the criteria for prescribing interferon or glatiramer were selected for comparison to those in the UK risk-sharing scheme.[149, 151, 152]

7 DEFINITION OF THE DECISION PROBLEM

7.1 *Decision problem and aim*

To appraise the clinical and cost-effectiveness of beta interferons and glatiramer acetate within their marketing authorisation for treating multiple sclerosis, as an update to technology Technology Appraisal guidance 32.

In this assessment, we will appraise beta interferon and glatiramer acetate using published data and taking account of additional data on long-term outcomes from the risk sharing scheme.

As requested by NICE, we have included beta interferons and glatiramer acetate to be compared with best supportive care. NICE commented that, 'Since Technology Appraisal 32 was published another interferon 1b (Extavia, Novartis), a pegylated interferon beta 1a (Plegridy, Biogen Idec) and a new formulation of glatiramer acetate (Copaxone, Teva pharmaceuticals) have been granted marketing authorisations. These technologies were not included in the risk sharing scheme because they were not appraised in Technology Appraisal 32. It has been determined by NICE that it is relevant to include these technologies in this appraisal so that guidance can be issued for all beta interferons and formulations of glatiramer acetate currently licensed for MS in the UK. Further active treatments that have been licensed and recommended by NICE (including teriflunomide, fingolimod, natalizumab, alemtuzumab and dimethyl fumerate) will not be considered in this appraisal.'

In addition, people with CIS will be considered in this appraisal.

7.2 *Objectives*

Our objectives were: a) to systematically review the evidence for the clinical effectiveness of

- IFN β-1a;
- Pegylated IFN β-1a;
- IFN β-1b; and
- GA

in people with

- relapsing multiple sclerosis (including people with relapsing remitting multiple sclerosis and people with secondary progressive multiple sclerosis with active disease, evidenced by relapses), and
- clinically isolated syndrome, that is, a single demyelinating event, who are considered at high risk of developing subsequent multiple sclerosis;

against the following comparators:

- best supportive care without disease modifying treatment, and
- beta interferons and glatiramer acetate compared with each other;

and investigating the following outcomes:

- relapse rate;
- transition to clinically definite MS, in the case of CIS;
- severity of relapse;
- disability (for example, expanded disability status scale [EDSS]);
- symptoms of multiple sclerosis such as fatigue, cognition and visual disturbance;
- freedom from disease activity;
- discontinuation due to neutralising antibodies;
- mortality;
- adverse effects of treatment; and
- health-related quality of life;

and b) to systematically review existing economic evaluations, including use of the existing RSS model; to develop a *de novo* economic model for CIS; to assess the cost effectiveness of the treatments (IFN β-1a, pegylated IFN β-1a, IFN β-1b, and GA) in treatment of CIS and RRMS against the stated comparators, expressed in incremental costs per quality-adjusted life year, with a time horizon sufficiently long to reflect any differences in costs or outcomes between the technologies being compared and from an NHS and Personal Social Services perspective; and to update model parameters and inputs to reflect available evidence from the literature, current costs, the NICE reference case, current practice, and new data from the risk sharing scheme.

8 METHODS FOR ASSESSMENT OF CLINICAL EFFECTIVENESS

8.1 *Protocol registration*

We presented our protocol to a Stakeholder Information Meeting on 29 February 2016 and subsequently registered it on PROSPERO as CRD42016043278.

8.2 *Identification of studies*

Initial scoping searches were undertaken in MEDLINE and the Cochrane Library in October 2015 to assess the volume and type of literature relating to the assessment question and to inform further development of the search strategy. Several relevant systematic reviews from the Cochrane Database of Systematic Reviews were identified.[153-157]

The following search strategy was designed to capture randomised controlled trials (RCTs) of DMTs for patients with RRMS, SPMS or CIS. An iterative procedure was used to develop the planned searches with reference to previous systematic reviews.[153-158] Clinical searches were restricted to RCT evidence. The included and excluded study lists from previous relevant Cochrane systematic reviews were checked.[155, 156] The main database searches for multiple sclerosis were undertaken in January and February 2016 and limited by date to the beginning of 2012 (the year the searches were undertaken for the broad review and network meta-analysis (NMA) by Filippini, et al., 2013[156]) onwards. This review was chosen because of the breadth of its scope, search strategy and eligibility criteria. Other more recent reviews were considered to be more limited in terms of the types of MS covered and the types of studies included. An additional targeted search for RCTs in CIS, not limited by date, was performed. A full record of searches is provided in Appendix 1. These searches were developed for MEDLINE and adapted as appropriate for the other databases.

The search strategy comprised the following main sources:

- Searching of electronic bibliographic databases including trials in progress
- Scrutiny of references of included studies and relevant systematic reviews
- Contact with experts in the field
- Screening of websites for relevant publications

We ran electronic searches on the following databases:

- Cochrane Multiple Sclerosis and Rare Diseases of the CNS group specialized register
- MEDLINE (Ovid)
- MEDLINE In-Process & Other Non-Indexed Citations (Ovid)
- Embase (Ovid)
- Cochrane Library (Wiley), including Cochrane Database of Systematic Reviews, CENTRAL, DARE, NHS EED, and HTA databases
- Science Citation Index and Conference Proceedings - Science (Web of Science)
- UKCRN Portfolio Database

We also searched the trial registers at ClinicalTrials.gov and WHO ICTRP.

All bibliographic records identified through the electronic searches were collected in a managed reference database. The reference lists of included studies and relevant review articles were checked and the companies' websites were screened for relevant publications. The included studies and reference lists of company submissions were checked for relevant unpublished studies and any additional published studies. Other grey literature searches were undertaken using the online resources of the following organisations (see Table 3). More details of these website searches are provided in Appendix 1.

Table 3: Online resources searched for relevant literature

Companies	Bayer	http://www.bayer.co.uk/ http://pharma.bayer.com/
	Biogen Idec	https://www.biogen-international.com/ https://www.biogen.uk.com/
	Merck Serono	http://biopharma.merckgroup.com/en/index.html
	Novartis	https://www.novartis.com https://www.novartis.co.uk/
	Teva Pharmaceuticals	http://www.tevapharm.com/research_development/ http://www.tevauk.com/
Patient carer groups	Brain and Spine Foundation	http://www.brainandspine.org.uk
	Multiple Sclerosis National Therapy Centres	http://www.msntc.org.uk
	MS UK	http://www.ms-uk.org
	Multiple Sclerosis Society	https://www.mssociety.org.uk
	Multiple Sclerosis Trust	https://www.mstrust.org.uk
	Neurological Alliance	http://www.neural.org.uk
	The Brain Charity (formally known as Neurosupport)	http://www.thebraincharity.org.uk
	Sue Ryder	http://www.sueryder.org
Professional groups	Association of British Neurologists	http://www.theabn.org
	British Neuropathological Society	http://www.bns.org.uk
	Institute of Neurology	https://www.ucl.ac.uk/ion https://www.ucl.ac.uk/ion/departments/neuroinflammation http://discovery.ucl.ac.uk
	Primary Care Neurology Society	http://www.p-cns.org.uk
	Therapists in MS	https://www.mstrust.org.uk/health-professionals/professional-networks/therapists-ms-tims/research
	United Kingdom Multiple Sclerosis Specialist Nurse Association	http://www.ukmssna.org.uk
Research groups	Brain Research Trust	http://www.brt.org.uk/research
	British Neurological Research Trust	http://www.ukscf.org http://www.ukscf.org/about-us/bnrt.html
	Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System	http://www.cochranelibrary.com http://msrdcns.cochrane.org/our-reviews
	National Institute for Health Research	http://www.nihr.ac.uk/research/ http://www.nihr.ac.uk/industry/ http://www.nihr.ac.uk/policy-and-standards/

8.3 *Inclusion criteria*

We included studies that met the following criteria.

The **study design** was a randomised controlled trial, a systematic review, or a meta-analysis.

The **population** was people diagnosed with RRMS, SPMS, or CIS.

The **intervention** was one of the following drugs, when used within indication (see Table 2):

- IFN β-1a;
- Pegylated IFN β-1a;
- IFN β-1b; and
- GA.

We only included drugs when used within marketing authorisation, i.e. when the posology in the trial matched that in the indication, because of the extensive clinical use of these drugs and the corresponding safety and effectiveness profile of these established dosages. A wide variety of alternative dosages has been used across a variety of trials. It was judged that including dosages not matching the indication could present misleading estimates of effectiveness or safety and would introduce unnecessary heterogeneity.

The **comparator** was best supportive care without DMT, or another of the interventions when used within indication. In this review, best supportive care corresponded to arms of RCTs where patients received either placebo added to standard care or no treatment.

The reported **outcomes** included at least one of the following:

- Relapse rate;
- Progression to multiple sclerosis (for patients with CIS);
- Severity of relapse, defined as rate of steroid-treated relapses or rate of relapses graded as moderate or severe;
- Disability, including as measured by the Expanded Disability Status Scale;
- Multiple sclerosis symptoms, such as fatigue, cognition and visual disturbance;
- Freedom from disease activity, defined as composite clinical and MRI outcomes;
- Mortality;
- Health-related quality of life (HRQoL);
- Treatment-related adverse events;
- Discontinuation due to adverse events; and
- Discontinuation due to loss of effectiveness attributed to neutralising antibody formation. We did not consider the rate of neutralising antibody formation alone because of its limited clinical relevance in practice.

The study was reported as a full-text report in English.

8.4 *Exclusion criteria*

We excluded:

- Studies that compared an eligible intervention against an irrelevant comparator;
- Studies that examined an eligible intervention used with a non-recommended dose regimen;
- Studies reporting MRI outcomes alone;
- Studies reporting early versus late treatment only;
- Studies that only examined MS subtypes other than those in the eligible population;
- Studies that only examined patients with highly active or rapidly evolving MS, as best supportive care is not an appropriate comparator for these populations; and
- Studies reported as abstracts or conference proceedings, or reported not in the English language.

8.5 *Study selection process*

First, we examined relevant past systematic reviews (including Tramacere et al. 2015,[155] Filippini et al. 2013[156] and Clerico et al. 2008[154]) for studies meeting the inclusion criteria. We verified inclusion of these studies by examining their full text.

For updated and new searches (including for studies addressing CIS), we collected all retrieved records in a specialised database and duplicate records were identified and removed. The reviewers pilot-tested a screening form based on the predefined study inclusion and exclusion criteria. Subsequently, two reviewers (XA and GJMT) applied the inclusion/exclusion criteria and screened all identified bibliographic records for title/abstract (level I) and then for full text (level II). Any disagreements over eligibility were resolved through consensus or by a third party reviewer (AC). Reasons for exclusion of full text papers were documented. The study flow was documented using a PRISMA diagram.[159]

8.6 *Quality assessment strategy*

Systematic reviews used to locate primary studies were appraised using the AMSTAR checklist.[160] All primary studies were appraised using the Cochrane risk of bias assessment tool.[161] Appraisal was undertaken by two reviewers. Uncertainty and/or any disagreements were crosschecked with a second reviewer and were resolved by discussion.

8.7 *Data extraction strategy*

For all included studies, the relevant data were extracted independently by two reviewers using a data extraction form informed by the NHS Centre for Reviews and Dissemination (CRD).[162] Uncertainty and/or any disagreements were crosschecked with another reviewer and were resolved by discussion. The extracted data were entered into summary evidence tables (see Appendix 2 for a sample data extraction sheet). Where multiple

arms were presented of which only some were relevant to our analysis, we extracted data for only those arms. The extracted information included:

- study characteristics (i.e., author's name, country, design, study setting, sample size in each arm, funding source, duration of follow-up(s), and methodological features corresponding to the Cochrane risk of bias assessment tool);
- patient baseline characteristics (i.e., trial inclusion/exclusion criteria; number of participants enrolled, and number of participants analysed; age, race, and gender; disability (including as measured by EDSS) at baseline; time from diagnosis of MS to study entry; and relapse rate at baseline);
- treatment characteristics (e.g., type of drug, method of administration, dose, and frequency; drug indication as stated; definition of best supportive care as described by trialists); and
- outcome characteristics for each included outcome reported (e.g., definition of outcome measure; timing of measurement; scale of measurement; and effect size as presented, including mean difference, risk ratio, odds ratio, or hazard ratio, or arm-level data necessary to calculate an effect size). Measures of variability and statistical tests used were also be extracted (standard deviation, 95% CI, standard error, p-values).

8.8 ***Data preparation***

Many of the included studies did not present adequate data for key findings to enable inclusion *prima facie* in a meta-analysis model. We used a variety of published methods to derive the necessary data.

Across all studies, we used data for the point of greatest maturity (i.e., last available follow-up) for which effect sizes were estimable. In studies presenting estimates with confirmed relapses and with non-confirmed relapses, we selected estimates with confirmed relapses.

We used rate ratios (abbreviated as RR in the text) to examine relapse outcomes (e.g. the ratio of annualised relapse rates in two study arms). We used summary statistics instead of attempting to approximate individual participant data for each arm, in part due to the use of stratification in estimating study findings. Where necessary, we imputed standard errors by estimating the number of events in each arm (e.g. when relapse rates were analysed using an analysis of variance, or ANOVA, model with Gaussian link, instead of the preferred Poisson distribution for count variables). When arm-level annualised relapse rates (ARRs) were presented without Poisson-based standard errors, we generally assumed that the ARR presented for study arms was a fair approximation and then re-estimated the standard errors for the rate ratio using all available information on person-years of follow-up and number of relapses. Rate ratios were then analysed using a lognormal distribution.

We used hazard ratios (abbreviated as HR in the text) to examine time to event outcomes (e.g. time to first relapse or time to confirmed disability progression). Where hazard ratios were not estimated from a Cox proportional hazards model, we used several methods in order of priority. First, we used methods published by

Tierney et al. (2007)[163] to estimate the HR, in particular using the number of patients analysed, the number of total events and the p-value derived from a log-rank test. When those data were not available to us, we then used the final predicted probabilities of survival in each study arm (generally estimated using Kaplan-Meier curves) and estimated the cumulative hazard using the equation $-\ln(S(t))$, where $S(t)$ is the probability of survival at time t. We then took the ratio of the cumulative hazards and used the log-rank p-value to approximate the standard errors for the HR, under the property that the p-value from the log-rank test for survival asymptotically approaches the p-value from a likelihood ratio test derived from a Cox proportional hazards model.

We used dichotomous outcomes to examine discontinuation due to adverse events.

8.9 *Narrative synthesis and meta-analysis*

Narrative synthesis of studies and meta-analyses were organised hierarchically: first by MS subtype, then by intervention-comparator contrast, and finally by each outcome for which data were available. Within each MS subtype, we examined included studies for similarity. When studies were sufficiently similar, we estimated both pairwise and network meta-analyses. First, we pooled outcomes for each intervention-comparator contrast and by MS subtype using random effects meta-analysis in Stata v14 and examined these pairwise meta-analyses for heterogeneity, measured as Cochran's Q and I^2.

Subsequently, we used the package -network-[164] in Stata v14 to estimate network meta-analyses. Because -network- operates in a frequentist paradigm, there was no need to sensitivity analyse on prior distributions. Where possible, we estimated meta-analyses using random effects; however, some sparse networks, where there were few studies for each contrast between two treatments, required the use of a fixed effects model. We used a common heterogeneity model, where the between-studies variance is assumed equal across comparisons.

After estimating a consistency model (i.e. where direct evidence for a contrast between two treatments is assumed to agree with indirect evidence for that contrast), we checked networks that were not star-shaped in design for inconsistency using two methods. We estimated a design-by-treatment interaction model and examined both the design effects and the overall Wald test for evidence for inconsistency. We also used the side-splitting method to test for differences in the effectiveness estimates between direct and indirect evidence. Where evidence of inconsistency existed, we considered the direction of that inconsistency.

Finally, we used a bootstrapping method to resample from our estimates of intervention effectiveness and develop probabilities of each treatment's relative position to the others. We then used the surface under the cumulative ranking curve (SUCRA) to produce a unified ranking of treatments.

8.9.1 Meta-analyses for CIS

We estimated a network meta-analysis for time to clinically definite MS in patients with CIS. This was the outcome most consistently reported across studies and matched most closely with the decision problem in the NICE scope.

8.9.2 Meta-analyses for RRMS and SPMS

Relapse outcomes and relapse severity

We elected to meta-analyse rate ratio of relapses as an overall measure of relapses in RRMS and SPMS. Though we narratively synthesised analyses for time to relapse and proportion free of relapses, both measures had significant issues; in particular, time to relapse data were inconsistently presented and at times impossible to impute, and proportion relapse-free would have been especially dependent on duration of follow-up and would not have captured the impact of drugs on multiple relapses per person.

We elected to meta-analyse two measures for relapse severity in RRMS: steroid-treated relapses and relapses described as moderate or severe. These were the most commonly reported measures.

Disability progression

We elected to meta-analyse time to disability progression as a measure of disability progression in RRMS and SPMS. We separated estimates for disability progression confirmed at 3 months and confirmed 6 months, as we could not establish whether measures were commensurate. Though we narratively synthesised proportions of patients with disability progression and magnitude of EDSS change, we elected not to meta-analyse these as proportions and magnitude of EDSS change would have been especially dependent on duration of follow-up; in particular, data for magnitude of EDSS change would have required extensive imputation.

Discontinuation due to adverse events

We estimated models for discontinuation due to adverse events (AEs). In order to estimate these models, we examined three outcomes as reported: discontinuation of study drug due to AEs, discontinuation of study due to AEs, and withdrawal from study due to AEs. In the few studies that reported both discontinuation of study drug due to AEs and discontinuation of study due to AEs, we chose discontinuation of study drug due to AEs as we believed it would be a closer match to capturing the relationship between study drugs and discontinuation. We also estimated one model with studies closest to 24 months of follow-up as risk of discontinuation due to AEs is not an annualised measure, like ARR, or an 'instantaneous' measure, like HR, and we could not reliably estimate person-years of follow-up in each arm across all studies to convert study-level estimates to rate ratios.

8.10 *Publication bias*

Were we to have had more than 10 studies for an intervention-comparator contrast, we would have used funnel plots to examine studies for the presence of publication bias in pairwise comparisons.

8.11 ***Industry submissions regarding effectiveness of treatments***

We examined company submissions and present summaries and appraisal of their clinical effectiveness analyses in Section 10 below.

9 RESULTS OF ASSESSMENT OF CLINICAL EFFECTIVENESS

9.1 *Search results*

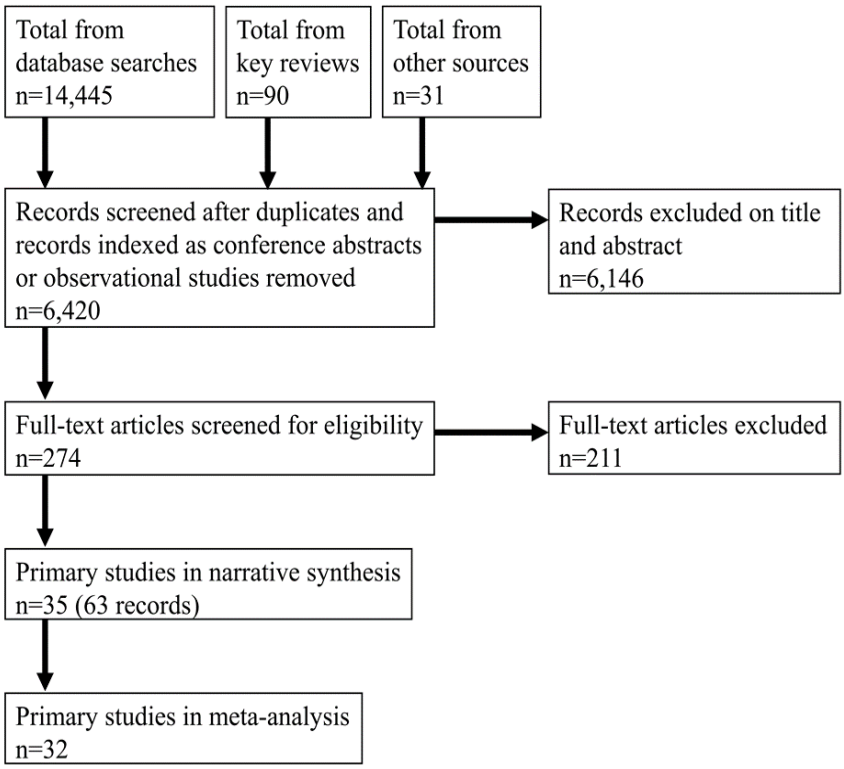
9.1.1 Included studies

The search identified 6,420 potentially relevant records. We removed 6,146 records that did not meet our inclusion criteria at title/abstract stage, leaving 274 records to be examined at full-text. Among these, we excluded 211 leading to 63 publications meeting our inclusion criteria and corresponding to 35 primary studies. Of these primary studies, 32 were included in at least one meta-analysis. The flow diagram describing the process of identifying relevant literature can be found in Figure 1.

9.1.2 Excluded studies

The reasons for exclusion are presented both across records excluded at full text and for each record individually in Appendix 3.

Figure 1: PRISMA flowchart, clinical effectiveness reviews



9.2 *Systematic reviews used to locate primary studies*

Three Cochrane reviews were identified as being of particular relevance to this study, and contributed to the identification of original studies for inclusion. These reviews were Tramacere 2015,[155] Filippini *et al.* 2013[156] and Clerico *et al.* 2008.[154]

9.2.1 Scope and aims

Overview

Filippini et al. aimed to review clinical effectiveness of immunosuppressors and immunomodulators in all MS types [156] and to rank them based on relapse rate, disability progression and acceptability. Tramacere *et al.* aimed to review and rank these agents in RRMS specifically [155]. Clerico and colleagues examined IFN β-1a, IFN β-1b and GA for delaying the conversion of CIS into MS [154], though this analysis was undertaken before revised diagnostic criteria classed many CIS episodes as in fact being RRMS.[62]

Diagnostic criteria used to identify studies

Tramacere et al.[155] used all four sets of diagnostic criteria [62, 64, 66, 165] to identify RCTs of treatment for RRMS with participants over 18 years old.

Filipinni and colleagues[156] included RCTs only, investigating treatment of adults over 18 with MS diagnosed according to Poser,[64] the original McDonald criteria,[165] or the 2005 modified McDonald criteria.[66] Therefore this review included all types of MS. However, it did not incorporate the most recent revision of the McDonald criteria[62], and so excluded CIS studies.

In contrast, Clerico and colleagues[154] used the Poser criteria to identify RCTs and pseudorandomised double-blinded trials of CIS, with reference to specific MRI findings. No exclusion criteria based on study participant age were specified.[166]

Included interventions

Tramacere and colleagues[155] included all immunomodulators and immunosuppressors, even if unlicensed. These included the IFN and GA drugs specified in NICE's scope, as well as 11 other interventions. We noted that the review by Tramacere et al. excluded the Calabrese 2012 study stating that it was non-randomised. To the best of our knowledge, this study is a RCT and it has been included in our review.

The interventions studied by Filippini *et al.* included IFN and GA formulations licenced at the time (i.e. not pegylayed IFN), as well as seven other interventions.[156] Clerico *et al.* would have included licenced IFN and GA interventions (i.e. not pegylated IFN), but only identified three studies comparing IFN to placebo.[155]

All three reviews included studies evaluating DMTs with a dose regimen currently not recommended or authorised (for example, IFN β-1a (Rebif) given once weekly instead of three times weekly). The Cochrane reviews did not account separately for the inclusion of studies with a DMT given under a non-recommended dose regimen in a sensitivity analysis.

9.2.2 Outcomes

Tramacere et al.[155] and Filippini et al.[156] examined risk of relapse over 12 months and 24 months as a dichotomous outcome, as well as presence or absence of disability progression assessed using EDSS. In Filippini et al.,[156] which included progressive forms of multiple sclerosis as well as RRMS, risk of disability progression was reported as the first outcome.

Both reviews assessed adverse events. Filippini et al.[156] also included incidence of relapse over 36 months, and assessments of acceptability of treatment as measured by discontinuation due to adverse events.

Clerico et al.[154] used proportion converting to clinically definite MS as the primary outcome, alongside annualised relapse rate and additional MRI outcomes.

9.2.3 Statistical methods

In Tramacere et al.,[155] network meta-analyses were performed for primary outcomes. Random effects models were used within a frequentist setting. In contrast, Filippini et al.[156] performed network meta-analyses within a Bayesian framework. For both reviews, equal heterogeneity across comparisons was assumed, and any correlations induced by multi-arm studies were accounted for. Both used Surface Under the Cumulative Ranking curve (SUCRA) to describe the ranking of treatments.[167]

9.2.4 Review findings

Tramacere et al.[155] found that in RRMS, the SUCRA for the chance of experiencing relapse over 12 months for GA was 52%, for subcutaneous IFN β-1a (Rebif) 36%, for pegylated IFN β-1a 33%, for IFN β-1b 27% and for intramuscular IFN β-1a (Avonex) it was 25%. The risk ratio of GA vs. placebo for this outcome was 0.80 (95% CI [0.68, 0.93]) whereas all other interventions of interest did not return significant results. The ranking of interventions of interest for prevention of relapse over 24 months in RRMS was GA (most successful), followed by IFN β-1b, subcutaneous IFN β-1a (Rebif), and intramuscular IFN β-1a (Avonex).

SUCRA plots for reducing the worsening of disability over 24 months in RRMS returned results of 58% for GA, 51% for IFN β-1b, 36% for subcutaneous IFN β-1a (Rebif), and 21% for intramuscular IFN β-1a (Avonex). The only interventions of interest with sigificant risk ratios as compared to placebo were GA (0.77, 95% CI [0.64, 0.92]), and IFN β-1b (0.79, [0.65, 0.97]).

Thus, in the Tramacere et al[155] review, GA performed the best of the interventions of interest. Intramuscular IFNb1a (Avonex) was consistently the least effective intervention. However, other interventions included in the Cochrane review (but which are outwith the scope of the current MTA) performed better, such as alemtuzumab (SUCRA: 97%, risk ratio vs. placebo 0.40, 95% CI [0.31, 0.51]).

Filippini et al.[156] returned similar rankings derived from SUCRA values for reducing recurrence of relapses over 12 months. However, for reducing recurrence of relapses at 24 months, the SUCRA values resulted in different rankings: subcutaneous IFNb1a (Rebif), GA, IFN β-1b, and for intramuscular IFN β-1a (Avonex). In terms of reducing disability progression over 24 months, GA ranked best (SUCRA 67%), followed by IFN β-1b (54%),

subcutaneous IFN β-1a (Rebif) (47%), and intramuscular IFN β-1a (Avonex) (18%).

In Clerico et al.,[155] only direct treatment comparisons were performed, using conventional pairwise meta-analyses to compare IFN to placebo. No studies of GA were identified, but IFN was effective against placebo.

9.2.5 Review quality

All three Cochrane Reviews scored 10/11 on the AMSTAR checklist, and were assessed as being of high methodological quality. Tramacere et al.[155] and Filippini et al.[156] inadequately reported grey literature searching, and Clerico et al.[154] did not assess the risk of publication bias.

9.3 *Study characteristics and methodological quality*

9.3.1 Study and participant characteristics

We included 35 primary studies published between 1987 and 2015, which involved 14,623 participants randomly assigned to IFN-β, GA, or placebo added to standard care, or best supportive care alone. The median follow-up was 24 months. Only 4 studies were conducted at single centres. The median number of participating centers was 30.5 (range, 1 to 200). The majority of studies were international (57.1%). Twenty-two (63%) were placebo-controlled, 12 (34%) were head-to-head studies with a comparison between one IFN and GA or between two IFNs, and two (6%) compared an IFN to no treatment (standard care). Of the 22 placebo-controlled studies, 3 aimed to evaluate the effectiveness of DMTs that were excluded in the scope (laquinimod, daclizumab, and dimethyl-fumarate) compared to placebo, with IFN-beta or glatiramer being added as a third descriptive arm. Given the different posology and method of administration between these agents used in the 3 studies (two were oral drugs, one was an IV drug), the comparison of IFN-β or GA to placebo was not blinded.

The key characteristics of included studies are provided in Table 4. A full list of publications is in Appendix 4.

Table 4. Characteristics of included studies.

Study ID MS type (diagnostic criteria) Included in TA32?	Study details	Characteristics of participants at baseline	Intervention	Participants
ADVANCE 2014 RRMS (2005 McDonald criteria)	**Country:** USA, Belgium, Bulgaria, Canada, Chile, Colombia, Croatia, Czech Republic, Estonia, France, Georgia, Germany, Greece, India, Latvia, Mexico, Netherlands, New Zealand, Peru, Poland, Romania, Russian Federation, Serbia, Spain, Ukraine, United Kingdom. **No. of countries:** 26 **Centres**: 183 **Study period**: June 2009 and November 2011. **Sponsor**: Biogen Idec	**Mean age**: 36.5 (9.9) **Mean sex**: 71% female **Race**: 82% white **EDSS Score**: 2.5 **Relapse rate**: 1.6 within the previous 12 months, 2.6 within the previous 36 months **Time from diagnosis of MS**: 3.6 years **Other clinical features of MS**: Time from first MS symptoms: 6.6 years	**Arm 1**: pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy) **Arm 2**: Placebo	**Randomised** 512 arm 1 500 arm 2
AVANTAGE 2014 RRMS/CIS, diagnostic criteria unclear	**Country**: France **No. of countries:** 1 **Centres**: 61 **Study period**: March 2006-April 2008, 3 months follow up **Sponsor**: Bayer	**Mean age**: 38.7 **Mean sex**: 75% female **Race**: NA **EDSS Score**: *1.8 ± 1.3* **Mean number of relapse rate**: 2.1 ± 1.1 **Time from diagnosis of MS**: 3.3 (6.4) years **Other clinical features of MS**: NA	**Arm 1**: IFN β-1b 250 µg SC every other day (Betaferon) via Betaject **Arm 2**: IFN β-1b 250 µg SC every other day (Betaferon) via Betaject light **Arm 3**: IFN β-1a 44 SC three times weekly (Rebif) via Rebiject II	**Included:** 73 arm 1 79 arm 2 68 arm 3
BECOME 2009 RRMS/CIS (likely McDonald 2001 or 2005)	**Country:** USA **No. of countries:** 1 **Centres**: 2 **Study period**: Not specified, follow up over 2 years **Sponsor**: Bayer Schering pharma	**Mean age**: 36 **Mean sex**: 69% females **Race**: 52% white **Median EDSS Score**: *2* **Relapse rate**: 1.8 and 1.9 ARR **Time from diagnosis of MS**: between 0.9 and 1.2 **Other clinical features of MS**: 81% RRMS, 19% CIS; MSFC median 0.13	**Arm 1**: IFN β-1b 250 µg SC every other day (Betaferon) **Arm 2**: GA 20 mg SC daily (Copaxone)	**Randomised** 36 arm 1 39 arm 2
BENEFIT 2006 CIS (Poser, McDonald 2001)	**Country:** Israel, Canada, and 18 European countries including Germany, Spain, United Kingdom, France, Netherlands, Switzerland **No. of countries:** 20 **Centres**: 98	**Median age:** 30 **Mean sex**: 70.7% female **Race**: 98.3% white **EDSS Score (median)**: 1.5	**Arm 1**: IFN β-1b 250 µg SC every other day (Betaferon) **Arm 2**: Injections of	**Randomised** 305 arm 1 182 arm 2

Study ID MS type (diagnostic criteria) Included in TA32?	Study details	Characteristics of participants at baseline	Intervention	Participants
	Study period: February 2002 and June 2003. 24 month follow up **Sponsor**: Schering AG	**Relapse rate**: NA **Time from diagnosis of MS**: Not specified **Other clinical features of MS**: monofocal / plurifocal onset : 52.6%/47.4%	placebo	
BEYOND 2009 RRMS (McDonald 2005)	**Country:** Not specified **No. of countries:** 26 **Centres**: 198 **Study period**: November, 2003, and June, 2005. Follow up between 2-3.5 years **Sponsor**: Bayer	**Mean age** 35.6 **Mean sex**: 69.4% female **Race**: 91.9% white **EDSS Score**: 2.33 **Relapse rate**: 1.6 relapses in last year **Time from diagnosis of MS**: 5.2 years **Other clinical features of MS**: 3.6 relapses previously; 70.6% had two or more relapses in past 2 years	**Arm 1**: IFN β-1b 250 µg SC every other day (Betaferon) **Arm 2:** GA 20 mg SC daily (Copaxone)	**Randomised** 897 arm 1 448 arm 2
Bornstein 1987 RRMS (Poser) Included in TA32	**Country:** USA **No. of countries**: 1 **Centres**: Not specified **Study period**: Not specified, follow up over 2 years **Sponsor**: public (grant from the National Institute of Neurological and Communicative Disorders and Stroke and grant from the National Institutes of Health)	**Mean age**: 30.5 **Mean sex**: 42% male/58% female **Race**: 96% white **EDSS Score**: *3.11* **Relapse rate**: 3.85 over 2 years **Time from diagnosis of MS**: 5.5 years duration of disease **Other clinical features of MS**: NA	**Arm 1**: GA 20 mg SC daily (Copaxone) **Arm 2**: Placebo	**Randomised** 25 arm 1 25 arm 2
BRAVO 2014 RRMS (McDonald 2005)	**Country:** US, Bulgaria, Croatia, Czech Republic, Estonia, Georgia, Germany, Israel, Italy, Lithuania, Macedonia, Poland, Romania, Russia, Slovakia, South Africa, Spain, Ukraine and others not specified **No. of countries:** 18 **Centres**: 140 **Study period**: April 2008 to June 2011. 24 months follow up **Sponsor**: Teva Pharmaceutical Industries	**Mean age:** Median: 37.5 placebo, 38.5 IFN **Mean sex**: 71.3% females in placebo arm, 68.7% females in IFN arm **Race**: N/A **EDSS Score**: Median: 2.5 placebo, 2.5 IFN **Median Relapse rate**: previous year: 1.0 placebo, 1.0 IFN; previous 2 years: 2.0 placebo, 2.0 IFN **Median Time from diagnosis of MS**: 1.2 placebo, 1.4 IFN **Other clinical features of MS**: NA	**Arm 1**: IFN β-1a 30 µg IM once weekly (Avonex) **Arm 2**: Oral placebo once-daily with neurologist monitoring	**Randomised** 447 arm 1 450 arm 2

Study ID **MS type (diagnostic criteria)** **Included in TA32?**	**Study details**	**Characteristics of participants at baseline**	**Intervention**	**Participants**
Calabrese 2012 RRMS (McDonald 2005)	**Country:** Italy **No. of countries:** 1 **Centres**: 1 **Study period**: 1 Jan 2007 – 30 June 2008 Follow up over 2 years **Sponsor**: grant from Merck Serono S.A	**Mean age**: 36.5 (9.9) **Mean sex**: 70.2% of female/20.8 % of male **Race**: NA **EDSS Score**: 2.1 (1.1) **Relapse rate**: 1.2 (0.7) **Time from diagnosis of MS**: 5.6 years (2.4) **Other clinical features of MS**: None	**Arm 1**: IFN β-1a 44 SC three times weekly (Rebif) **Arm 2**: IFN β-1a 30 µg IM once weekly (Avonex) **Arm 3**: GA 20 mg SC daily (Copaxone)	**Randomised** 55 arm 1 55 arm 2 55 arm 3
CHAMPS 2000 CIS (Poser)	**Country:** USA and Canada **No. of countries:** 2 **Centres**: 50 **Study period**: April 1996 until March 2000. Follow up 36 months **Sponsor**: Biogen	**Mean age** 33.0 (0.7) **Mean sex**: 75% female **Race**: 86% white **EDSS Score**: *NA* **Relapse rate**: NA **Time from diagnosis of MS**: NA **Other clinical features of MS**: Type of initial event: optic neuritis (50%), Spinal cord syndrome (22%), Brainstem or cerebellar syndrome (28%) Type of onset (based on new classification): monofocal, 70%; multifocal, 30% Duration of symptoms before initiation of intravenous methylprednisolone: 8 days Duration of symptoms at initiation of study treatment: 19 days	**Arm 1**: IFN β-1a 30 µg IM once weekly (Avonex) **Arm 2**: Placebo	**Randomised** 193 arm 1 190 arm 2
CombiRx 2013 RRMS (McDonald 2001, Poser)	**Country:** United States, Canada **No. of countries:** 2 **Centres**: 68 **Study period**: January 2005-April 2012. Minimally 36 months follow up **Sponsor**: NIH, with materials provided by Biogen and Teva	**Mean age** 38.3 **Mean sex**: 70.3% female **Race**: 87.6% white **EDSS Score**: 2.0 **Relapse rate**: 1.7 relapses in last year, on average **Time from diagnosis of MS**: 1.2 **Other clinical features of MS**:	**Arm 1**: IFN β-1a 30 µg IM once weekly (Avonex) **Arm 2**: GA 20 mg SC daily (Copaxone)	**Randomised** 250 arm 1 259 arm 2

Study ID MS type (diagnostic criteria) Included in TA32?	Study details	Characteristics of participants at baseline	Intervention	Participants
		NA		
CONFIRM 2012 RRMS (McDonald 2005)	**Country:** USA, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Canada, Costa Rica, Croatia, Czech Republic, Estonia, France, Germany, Greece, India, Ireland, Israel, Latvia, Macedonia, Mexico, Republic of Moldova, New Zealand, Poland, Puerto Rico, Romania, Serbia, Slovakia, Spain, Ukraine **No. of countries:** 28 **Centres**: 200 **Study period**: 2 year follow up **Sponsor**: Biogen idec	**Mean age** 36.8 **Mean sex**: 70% female **Race**: 84% white **EDSS Score**: 2.6 **Relapse rate**: 1.4 in prior 12 months **Time from diagnosis of MS**: 4.6 years **Other clinical features of MS**: any prior DMTs (%)=29%	**Arm 1**: GA 20 mg SC daily (Copaxone) **Arm 2**: 2 placebo capsules orally thrice daily	**Randomised** 360 arm 1 363 arm 2
Cop1 MSSG 1995 RRMS (Poser) Included in TA32	**Country:** USA **No. of countries:** 1 **Centres**: 11 **Study period**: October, 1991, and May, 1992. 2 year follow up. **Sponsor**: the FDA orphan drug program, the National multiple sclerosis society, and TEVA pharmaceutical	**Mean age** 34.4. **Mean sex**: 73% female **Race**: 94% white **EDSS Score**: 2.6 **Relapse rate**: 2.9 prior 2-year rate **MS duration**:6.9 years **Other clinical features of MS**: ambulation index= 1.1	**Arm 1**: GA 20 mg SC daily (Copaxone) **Arm 2**: Placebo	**Randomised** 125 arm 1 126 arm 2
ECGASG 2001 RRMS (Poser) Included in TA32 (unpublished at the time)	**Country:** Canada **No. of countries:** 7 **Centres**: 29 **Study period**: Enrollment started in February 1997 and concluded in November 1997. 9 month follow up **Sponsor**: Teva Pharmaceutical Industries	**Mean age** 34 **Mean sex**: NA **Race**: NA **EDSS Score**: 2.4 **Relapse rate**: 2.65 **Disease duration (years):** 8.1 **Other clinical features of MS**: ambulation index=1.15	**Arm 1**: GA 20 mg SC daily (Copaxone) **Arm 2**: Placebo SC injections	**Randomised** 119 arm 1 120 arm 2
ESG 1998 SPMS (Poser, Lublin 1996) Included in TA32	**Country:** European countries **No. of countries:** NA **Centres**: 32 **Study period**: 36 month follow up **Sponsor**: Schering AG	**Mean age** 41.0 **Mean sex**: 61% female **Race**: NA **EDSS Score**: 5.15 **Relapse rate**: NA **Time from diagnosis of MS**: NA **Other clinical features of MS**: Patients without relapses in 2 years before inclusion: 30% Mean disease duration: 13.1 years	**Arm 1**: IFN β-1b 250 µg SC every other day (Betaferon) **Arm 2**: SC injections of placebo	**Randomised** 360 arm 1 358 arm 2

Study ID MS type (diagnostic criteria) Included in TA32?	Study details	Characteristics of participants at baseline	Intervention	Participants
		Time from diagnosis of relapsing risk MS (years): 8.15 Mean time since evidence of deterioration (years): 3.8 Mean time since diagnosis of SP-MS (years): 2.15		
Etemadifar 2006 RRMS (Poser)	**Country:** Iran **No. of countries:** 1 **Centres**: 1 **Study period**: September 2002 and September 2004. 24 month follow up **Sponsor**: Not specified	**Mean age** 28.5 **Mean sex**: 76% female **Race**: NA **EDSS Score**: 2.0 **Relapse rate 1 year prior** : 2.2 **Time from diagnosis of MS**: 3.2 years **Other clinical features of MS**: None	**Arm 1**: IFN β-1b 250 µg SC every other day (Betaferon) **Arm 2**: IFN β-1a 30 µg IM once weekly (Avonex) **Arm 3**: IFN β-1a 44 SC three times weekly (Rebif)	**Randomised** 30 arm 1 30 arm 2 30 arm 3
EVIDENCE 2007 RRMS (Poser)	**Country:** USA, France, UK, Norway, Austria, Germany, France, Finland, Sweden, Canada **No. of countries:** 10 **Centres**: 56 **Study period**: Unclear. Minimally 48 weeks follow up, average 64.2 **Sponsor**: Serono	**Mean age** 37.9 **Mean sex**: 74.8% female **Race**: 91.0% Caucasian **EDSS Score**: 2.3 Median: 2.0 **Relapse rate**: 2.6 Median 2.0 relapses in last 2 years **Duration of MS**: 6.6. Median: 4.0-4.1 years **Other clinical features of MS**: Time since last relapse (months): Median 3.9 to 4.4; mean 5.1	**Arm 1**: IFN β-1a 44 SC three times weekly (Rebif) **Arm 2**: IFN β-1a 30 µg IM once weekly (Avonex)	**Randomised** 339 arm 1 338 arm 2
GALA 2013 RRMS (McDonald 2005)	**Country:** United States, Bulgaria, Croatia, Germany, Poland, Romania, and Ukraine and others **No. of countries:** 17 **Centres**: 142 **Study period**: Not specified. 12 months follow up. **Sponsor**: TEVA pharmaceutical industries	**Mean age** 37.6 **Mean sex**: 68% female **Race**: 98% Caucasian **EDSS Score**: 2.7 **Relapse rate**: 1.3 in the prior 12 months, 1.9 in the prior 24 months **Time from diagnosis of MS**: NA **Other clinical features of MS**: Time from onset of first symptoms of MS=7.7 years	**Arm 1**: GA 40 mg SC three times weekly (Copaxone) **Arm 2**: SC placebo injections	**Randomised** 943 arm 1 461 arm 2
GATE 2015	**Country:** USA, Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Czech	**Mean age** 33.1	**Arm 1**: GA 20 mg SC	**Randomised**

Study ID MS type (diagnostic criteria) Included in TA32?	Study details	Characteristics of participants at baseline	Intervention	Participants
RRMS (McDonald 2010)	Republic, Estonia, Georgia, Germany, Italy, Mexico, Republic of Moldova, Poland, Romania, Russian Federation, Serbia, South Africa, Ukraine, United Kingdom **No. of countries:** 20 **Centres**: 118 **Study period**: Recruited between December 7, 2011, and March 21, 2013; last follow-up December 2, 2013. Follow up 9 months (double-blind follow-up) + additional 15 months (open-label) **Sponsor**: Synthon BV	**Mean sex**: 66.4% female **Race**: NA **EDSS Score**: 2.7 **Relapse rate**: 1.9 in prior 2 years **Time from diagnosis of MS**: NA **Other clinical features of MS**: • Time to onset of first symptoms to randomisation (years): 5.9 • No history of prior disease treatment: 16.1%	daily (Copaxone) **Arm 2**: Placebo	357 arm 1 84 arm 2
IFNB MSSG 1995 RRMS (Poser) Included in TA32	**Country:** USA and Canada **No. of countries:** 2 **Centres**: 11 **Study period**: after 2 years of follow-up, all subjects were given the option of continuing treatment in a double-blind fashion, extending the total treatment period to 5.5 years for some patients **Sponsor**: Triton Biosciences, Berlex Laboratories	**Mean age** 35.6 **Mean sex**: 70% female **Race**: 94% white **EDSS Score**: 2.9 **Relapse rate**: 3.5 in prior 2 years **Time from diagnosis of MS**:4.3 years **Other clinical features of MS**: Baseline Scripps neurological rating scale: 80.8	**Arm 1**: IFN β-1b 250 µg SC every other day (Betaferon) **Arm 2**: SC injections placebo	**Randomised** 124 arm 1 123 arm 2
IMPROVE 2012 RRMS (McDonald 2005)	**Country:** Italy, Germany, Serbia, Canada, Bulgaria, Estonia, Lithuania, Romania, Russia, Spain **No. of countries:** 10 **Centres**: 5 **Study period**: December 2006 to February 2009. Follow up 16 weeks for the double-blind phase, then 24 weeks where all patients received interferon beta 1-a, at last 4 weeks of safety period observation **Sponsor**: Merck Serono S.A.	**Mean age** NA **Mean sex**: NA **Race**: NA **EDSS Score**: NA **Relapse rate**: NA **Time from diagnosis of MS**: NA **Other clinical features of MS**: NA	**Arm 1**: IFN β-1a 44 SC three times weekly (Rebif) **Arm 2**: SC injections of placebo	**Randomised** 120 arm 1 60 arm 2
INCOMIN 2002 RRMS (Poser)	**Country:** Italy **No. of countries:** 1 **Centres**: 15 **Study period**: October, 1997, and June, 1999. 2 year follow up **Sponsor**: Istituto Superiore di Sanita' of the Italian Ministry of Health and the Italian MS Society	**Mean age** 36.9 **Mean sex**: 65% female **Race**: NA **EDSS Score**: 1.97 **Relapse rate 2 years prior**: 1.45 **Time from diagnosis of MS**: 6.3 years **Other clinical features of MS**: None	**Arm 1**: IFN β-1b 250 µg SC every other day (Betaferon) **Arm 2**: IFN β-1a 30 µg IM once weekly (Avonex)	**Randomised** 92 arm 1 96 arm 2

Study ID **MS type (diagnostic criteria)** **Included in TA32?**	**Study details**	**Characteristics of participants at baseline**	**Intervention**	**Participants**
Kappos 2011 RRMS (McDonald 2001)	**Country:** Belgium, Bulgaria, Canada, Czech Republic, Denmark, France, Germany, Italy, Mexico, Romania, Russian Federation, Serbia, Slovakia, Spain, Switzerland, Ukraine, United Kingdom, USA and others **No. of countries:** 20 **Centres**: 79 **Study period**: Not specified. Up to 96 weeks follow up. **Sponsor**: F Hoffmann-La Roche Ltd, Biogen Idec Inc	**Mean age** 37.5 **Mean sex**: 65% female **Race**: 96% white **EDSS Score**: 3.3 **Relapse rate**: NA **Time from diagnosis of MS**: median only **Other clinical features of MS**: NA	**Arm 1**: IFN β-1a 30 µg IM once weekly (Avonex) **Arm 2**: placebo injection every other week	**Randomised** 55 arm 1 54 arm 2
Knobler 1993 RRMS (Poser)	**Country:** USA **No. of countries:** 1 **Centres**: 3 **Study period**: June and October 1986. Follow up 3 years (24 weeks of initial follow-up for the 5 groups then all the patients that had received 0.8mU, 4MU and 16MU for 24 weeks received a dose of 8MU from week 24 to 3 years) **Sponsor**: Triton Biosciences, Inc and Berlex Laboratories, Inc	**Mean age** 35.6 **Mean sex**: 48% female **Race**: NA **EDSS Score**: 3.1 **Mean exacerbation in prior 2 years**: 2.84 **Time from diagnosis of MS**: 6.6 years **Other clinical features of MS**: mean Scripps Neurological Rating Scale (NRS): 76.6	**Arm 1**: IFN β-1b 250 µg SC every other day (Betaferon) **Arm 2**: Subcutaneous injection of placebo (1mL like Betaseron 8 MU)	**Randomised** 6 arm 1 7 arm 2
MSCRG 1996 RRMS (Poser) Included in TA32	**Country:** USA **No. of countries:** 1 **Centres**: 4 **Study period**: November, 1990 to early 1993 2 years follow up for all-patients + 2 additional years for patients completing dosing before the end of the first period of follow-up. **Sponsor**: National Institutes of Health, National Institute of Neurological Disorders and Stroke (NINDS) grant R01-26321 and Biogen, Inc.	**Mean age** 36.8 **Mean sex**: 73.7% female **Race**: 93% white **EDSS Score**: *2.4* **Relapse rate**: 1.2 **MS duration (years):** 6.5 **Other clinical features of MS**: None	**Arm 1**: IFN β-1a 30 µg IM once weekly (Avonex) **Arm 2**: Placebo	**Randomised** 158 arm 1 143 arm 2
NASG 2004 SPMS (Poser, Lublin 1996)	**Country:** US/Canada **No. of countries:** 2 **Centres**: 35 **Study period**: Unclear. 3 year follow up **Sponsor**: Biogen	**Mean age** 46.8 **Mean sex**: 63.2% female **Race**: NA **EDSS Score**: 5.1 **Relapse rate**: Relapses in two years prior to study: 0.8 **Time from diagnosis of MS**: 14.7 years **Other clinical features of MS**: Time from SPMS diagnosis: 4.0 years	**Arm 1**: IFN β-1b 250 µg SC every other day (Betaferon) **Arm 2**: Injectable placebo (note two types, one calibrated to body surface area)	**Randomised** 317 arm 1 308 arm 2

Study ID MS type (diagnostic criteria) Included in TA32?	Study details	Characteristics of participants at baseline	Intervention	Participants
		Those relapse-free in two years prior to study: 55%		
Pakdaman 2007 CIS (Poser)	**Country:** Iran **No. of countries:** 1 **Centres**: 4 **Study period**: February 2002 to August 2005. 36 months follow up **Sponsor**:Unclear	**Mean age** 28.0 **Mean sex**: 67.8% female **Race**: NA **EDSS Score**: NA **Relapse rate**: NA **Time from diagnosis of MS**: NA **Other clinical features of MS**: Type of initial event: optic neuritis 48.0%, spinal cord syndrome 23.8%, brain/cerebellar syndrome 21.8%	**Arm 1**: IFN β-1a 30 µg IM once weekly (Avonex) **Arm 2**: Injectable placebo	**Randomised** 104 arm 1 98 arm 2
PreCISe 2009 CIS (McDonald 2005, Poser)	**Country:** Italy, Romania, Argentina, Finland, Austria, Germany, Sweden, Australia, Hungary, France, Norway, Spain, Denmark, Canada, USA, United Kingdom, **No. of countries:** 16 **Centres**: 80 **Study period**: Enrolled from January, 2004, to January, 2006. 36 months follow up **Sponsor**: Teva Pharmaceutical Industries	**Mean age** 31.2 (6.9) **Mean sex**: 67% FEMALE **Race**: 96% white **EDSS Score**: 1.0 (1.0) **Relapse rate**: NA **Time from diagnosis of MS**:NA **Other clinical features of MS**: Time from first symptom (days): mean=74.0 (14.1); median=78.8 (33–104)	**Arm 1**: GA 20 mg SC daily (Copaxone) **Arm 2**: Daily placebo injections	**Randomised** 243 arm 1 238 arm 2
PRISMS 1998 RRMS (Poser) Included in TA32	**Country:** Australia, Belgium, Canada, Finland, Germany, Netherlands, Sweden, Switzerland, UK **No. of countries:** 9 **Centres**: 22 **Study period**: May 1994 to February 1995 with 2 years follow up. **Sponsor**: Ares- Serono	**Mean age** Median: 34.9 **Mean sex**: 69% female **Race**: NA **EDSS Score**: 2.5 (SD 1.2) **Relapse rate**: 3.0 (SD 1.2) **Time from diagnosis of MS**: Median: 5.3 years) **Other clinical features of MS**: NA	**Arm 1**: IFN β-1a 22 µg SC three times weekly (Rebif) **Arm 2**: IFN β-1a 44 SC three times weekly (Rebif) **Arm 3**: Placebo	**Randomised** 189 arm 1 184 arm 2 187 arm 3
REFLEX 2012 CIS (McDonald 2005)	**Country:** Argentina, Austria, Belgium, Bulgaria, Canada, Croatia, Czech Republic, Estonia, Finland, France, Germany, Greece, Israel, Italy, Latvia, Lebanon, Morocco, Poland, Portugal, Romania, Russian Federation, Saudi Arabia, Serbia, Slovakia, Spain, Turkey **No. of countries:** 26 **Centres**: 80	**Mean age** 30.7 **Mean sex**: 66% female **Race**: NA **EDSS Score**: median 1.5 **Relapse rate**: NA **Time from diagnosis of MS**:NA	**Arm 1**: IFN β-1a 44 SC three times weekly (Rebif) **Arm 2**: Thrice weekly injections	**Randomised** 146 arm 1 146 arm 2

Study ID MS type (diagnostic criteria) Included in TA32?	Study details	Characteristics of participants at baseline	Intervention	Participants
	Study period: November, 2006 to August, 2010. 24 month double-blind follow up, plus 12 months for optional open label extension **Sponsor**: Merck Serono SA	**Other clinical features of MS**: Time since first demyelinating event (days)= 57.6) Fulfilling McDonald 2010 MS criteria: 37.7% (from Freedman 2014)		
REFORMS 2012 RRMS (McDonald 2005, Poser)	**Country:** USA **No. of countries:** 1 **Centres**: 27 **Study period**: December 2006-November 2007. 12 weeks follow up **Sponsor**: EMD Serono, Pfizer	**Mean age** 40.52 (SD 9.65) **Mean sex**: 70% female **Race**: 87.6% white **EDSS Score**: NA **Relapse rate**: 1.33 (SD 0.49) (of those with relapses) **Time from diagnosis of MS**: 1.47 yrs (3.31) **Other clinical features of MS**: Percentage with no relapse in last 12 months: 24 (18.6%) Time since onset: 5.12 yrs (6.68) Percentage diagnosed with Poser criteria: 36 (27.9%) Time since last relapse, of those with last-year relapses: 3.76 mos (2.93) Steroid treatment episodes: 0.50 (0.55) Percentage needing more than one course of steroids: 49 (38.0%)	**Arm 1**: IFN β-1a 44 SC three times weekly (Rebif) **Arm 2**: IFN β-1b 250 µg SC every other day (Betaferon)	**Randomised** 65 arm 1 64 arm 2
REGARD 2008 RRMS (McDonald 2001)	**Country:** Argentina, Austria, Brazil, Canada, France, Germany, Ireland, Italy, Netherlands, Russia, Spain, Switzerland, UK, and USA **No. of countries:** 14 **Centres**: 80 **Study period**: February and December 2004, with 96 weeks follow up **Sponsor**: EMD Serono, Pfizer	**Mean age** 36.8 **Mean sex**: 29.5% male **Race**: 93.6% white **EDSS Score**: 2.34 **Relapse rate**: Presented as distribution of relapses; months since last relapse about 5 on average **Time from diagnosis of MS**: Years since first relapse: 6.2 **Other clinical features of MS**: Receiving steroid treatment in last 6 months: 43.7%	**Arm 1**: IFN β-1a 44 SC three times weekly (Rebif) **Arm 2**: GA 20 mg SC daily (Copaxone)	**Randomised** 386 arm 1 378 arm 2

Study ID MS type (diagnostic criteria) Included in TA32?	Study details	Characteristics of participants at baseline	Intervention	Participants
REMAIN 2012 RRMS/SPMS (diagnostic criteria unclear)	**Country:** Germany **No. of countries:** 1 **Centres**: 9 **Study period**: October 2005-November 2009. 96 weeks follow up **Sponsor**: Merck-Serono	**Mean age** 44.3 (SD 6.7) **Mean sex**: 70% female **Race**: NA **EDSS Score**: Not provided overall; median between 4.0 and 4.3 **Relapse rate**: 26 had no relapses in prior year, 3 had 1 relapse, and 1 had 2 relapses **Time from diagnosis of MS**: NA **Other clinical features of MS**: Time since onset: 12.3 years (7.2) RRMS: 13 (43.3%); SPMS 17 (56.7%)	**Arm 1**: IFN β-1a 44 SC three times weekly (Rebif) **Arm 2**: No treatment; presumably BSC	**Randomised** 15 arm 1 15 arm 2
Schwartz 1997 RRMS (Poser)	**Country:** USA **No. of countries:** 1 **Centres**: Unclear **Study period**: Unclear but 12 months follow up **Sponsor**: Colorado Neurological Institute, Rocky Mountain MS Center, Agency for Health Care Policy and Research	**Mean age** 43.6 **Mean sex**: 77.7% female **Race**: NA **EDSS Score**: NA **Relapse rate**: NA **Time from diagnosis of MS**: 9.2 years **Other clinical features of MS**: NA	**Arm 1**: IFN β-1b 250 µg SC every other day (Betaferon) **Arm 2**: No placebo indicated; likely ongoing BSC	**Randomised** 34 arm 1 45 arm 2
SPECTRIMS 2001 SPMS (Lublin 1996) Included in TA32	**Country:** Canada, Australia, Denmark, France, Netherlands, Sweden, Switzerland, UK **No. of countries:** 8 **Centres**: 22 **Study period**: Not specified. 3 years follow up **Sponsor**: Serono Pharmaceuticals	**Mean age** 42.8 (SD 7.1) **Mean sex**:63% female **Race**: NA **EDSS Score**: mean, SD 5.4 **Relapse rate**: mean, SD 0.9 (1.3) exacerbation in 2 years before study **Time from diagnosis of MS**: 13.3 yrs (SD 7.1) **Other clinical features of MS**: 53% exacerbation-free in last 2 years, average change in EDSS score over last two years 1.6 (0.9), duration of SPMS 4.0 yrs (3.0), SNRS score 63.5 (11.8), ambulation index 3.6 (1.4)	**Arm 1**: IFN β-1a 44 SC three times weekly (Rebif) **Arm 2**: IFN β-1a 22 µg SC three times weekly (Rebif) **Arm 3**: Placebo	**Randomised** 204 arm 1 209 arm 2 205 arm 3

9.3.2 Risk of bias and methodological quality

The risk of bias graphs for all MS types and for each MS type across all included studies are presented in Figure 2. Figure 3 also provides the assessment of risk of bias for each of the included studies.

Risk in randomization or allocation methods

All studies that adequately detailed their method of randomization (21/35) used a method that was judged to be at low risk of bias. Studies that reported methods of allocation concealment (the concealment of study allocation before the beginning of assigned treatment) were also judged to be at low risk of bias (22/35), with the exception of one study that used open allocation (Bornstein 1987[168]). All studies citing central allocation were judged as having a low risk of bias.

Risk in methods of blinding

In the studies examined, 83% (30/35) were at high risk of bias from either complete or partial participant unblinding. In 14 studies, most of which were comparisons between different active drugs, specifically did not blind participants or practitioners, and in another 16 studies, participants were initially blinded, but at high risk of unblinding from increased rates of side effects. In particular, the lack of blinding in comparisons between different drugs meant that risk of bias was imbalanced across different comparisons for the same outcome. We designated all studies in which the rates of side effects (in particular, injection site reactions) in one study group were double that of another to be at high risk of bias from participant unblinding. In the two studies designated as low risk of bias in participant blinding, side effect rates were not increased by a factor of two (one study tested active versus active treatments).

Blinding of outcome assessment was made similarly difficult by injection site reactions. Blinding of outcome assessment was only designated as low risk if injection sites reaction rates were increased by less than a factor of 2 in the treatment group (two studies), or if participants were specifically instructed to cover their injection sites (eight studies). In nine cases, outcome assessors were otherwise blinded but injection sites were not covered, and these studies were designated to be at high risk of bias. Additionally, studies in which participants were unblinded were designated at high risk of bias in outcome assessment, if studies did not report that participants were given specific instructions against sharing treatment information with assessors. All studies that reported MRI outcomes and detailed methods for blinding of MRI assessment were found to be at low risk of bias (13/15).

Risk in data analysis and reporting

29% (10/35) of studies were found to be at high risk of bias from missing data, based on large amounts of missing data, difference in rates of loss to follow-up between arms, or lack of reporting of imputation methods. In 17% (6/35) of studies outcomes were not reported as stated, and these were designated to be at high risk of bias from selective reporting. Finally, all studies funded by drug manufacturers were designated as high risk of bias under the ‘other’ category, as this was not covered by other questions in the risk of bias tool.

Figure 2: Risk of bias by MS type

Figure 3: Risk of bias by study

MS type	Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment (except MRI)	Blinding of MRI outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
CIS	BENEFIT 2006	?	+	-	+	+	+	?	-
CIS	CHAMPS 2000	?	?	-	+	+	?	+	-
CIS	Pakdaman 2007	?	?	?	?	N/A	-	-	-
CIS	PreCISe 2009	+	+	-	-	?	+	+	+
CIS	REFLEX 2012	+	+	-	+	?	+	?	-
RRMS	ADVANCE 2014	+	+	-	-	+	-	+	-
RRMS	AVANTAGE 2014	?	?	-	-	N/A	?	+	+
RRMS	BECOME 2009	?	?	-	-	+	+	+	-
RRMS	BEYOND 2009	+	+	-	-	N/A	?	+	-
RRMS	Bornstein 1987	?	-	-	-	N/A	+	+	+
RRMS	BRAVO 2014	+	+	-	+	N/A	+	-	-
RRMS	Calabrese 2012	+	+	-	-	+	+	-	+
RRMS	CombiRx 2013	+	+	+	+	N/A	-	+	+
RRMS	CONFIRM 2012	+	+	-	-	+	-	+	-
RRMS	Cop1 MSSG 1995	?	+	-	-	N/A	+	+	+
RRMS	ECGASG 2001	+	+	-	-	+	+	?	-
RRMS	Etemadifar 2006	?	?	-	-	N/A	+	?	?
RRMS	EVIDENCE 2007	+	+	-	-	N/A	+	+	-
RRMS	GALA 2013	?	+	-	-	+	?	+	-
RRMS	GATE 2015	+	+	-	-	+	+	+	-
RRMS	IFNB MSSG 1995	?	?	-	-	+	-	+	-

MS type	Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment (except MRI)	Blinding of MRI outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
RRMS	IMPROVE 2012					N/A			
RRMS	INCOMIN 2002								
RRMS	Kappos 2011								
RRMS	Knobler 1993					N/A			
RRMS	Mokhber 2014					N/A			
RRMS	MSCRG 1996								
RRMS	PRISMS 1998					N/A			
RRMS	REFORMS 2012					N/A			
RRMS	REGARD 2008					N/A			
RRMS	REMAIN 2012					N/A			
RRMS	Schwartz 1997					N/A			
SPMS	ESG 1998					N/A			
SPMS	NASG 2004					N/A			
SPMS	SPECTRIMS 2001					N/A			

9.3.3 Summary: study characteristics and risk of bias

We located 35 primary studies from a variety of settings and covering all the drugs listed in the NICE scope. These studies were of variable quality, with particular issues posed by risk of unblinding of patients and outcome assessors due to injection site reactions, as well as imbalanced risk of bias from open-label comparisons. Many studies were sponsored by manufacturers, and most studies were at high risk of bias due to missing data.

9.4 *Clinical effectiveness: clinically isolated syndrome*

Our analysis was informed by five included trials: BENEFIT 2006,[169] CHAMPS 2000,[170] Pakdaman 2007,[171] PreCISe 2009[172] and REFLEX 2012.[173] It should be noted that trialists generally examined time to 'clinically definite MS', defined using Poser criteria and involving a second relapse or neurological deterioration, though some also presented analyses examining time to 'McDonald MS', in which MRI findings could be used with clinical findings to arrive at a diagnosis.

9.4.1 IFN β-1a 30 µg IM once a week (Avonex) vs. placebo

Two trials evaluated IFN β-1a 30 µg IM once a week, both against placebo: CHAMPS 2000[170] and Pakdaman 2007.[171]

Time to diagnosis of MS

Both studies reported significant differences in favour of IFN β-1a in delaying time to confirmation of clinically definite MS, diagnosed generally by a second relapse, but in some cases by progressive neurological deterioration. CHAMPS 2000,[170] which followed up 393 patients up to three years, found a reduction in hazard of more than half (HR=0.49, 95% CI [0.33, 0.73]). Pakdaman 2007,[171] which followed up 202 patients up to three years, found a reduction in conversion to clinically definite MS (incidence 36.6% vs. 58.2%). We converted this to a hazard ratio of 0.54 (0.36, 0.81).

In separate publications, CHAMPS 2000 also presented analyses stratified by risk levels, site of first lesion[174] and type of first attack.[175] In analyses comparing patients with monofocal and multifocal disease at first demyelinating event,[175] patients with monofocal disease had a similar reduction in hazard to the whole trial population (HR=0.45, 95% CI [0.27, 0.74]) while patients with multifocal disease had a decreased reduction in hazard (0.64, [0.32, 1.28]).

Freedom from disease activity

CHAMPS 2000[174] evaluated freedom from disease activity via several composite outcomes, each of which showed a reduction in hazard associated with IFN β-1a. Patients receiving IFN β-1a were less likely to have a composite outcome of clinically definite MS or more than one new or enlarging T2 lesion, though this outcome may be closer to McDonald MS (adjusted HR 0.47, 95% CI [0.36, 0.62]); of clinically definite MS or at least one new or enlarging T2 lesion (0.55, [0.42, 0.71]); or of either clinically definite MS, at least one new or enlarging T2 lesion, or at least one gadolinium-enhancing lesion (0.60, [0.47, 0.78]).

Adverse events and mortality

Full results are available on request. Mortality was not reported in these studies.

9.4.2 IFN β-1a 44 µg SC three times a week (Rebif) vs. placebo

One trial evaluated IFN β-1a 44 µg SC three times a week against placebo: REFLEX 2012. [173] (This trial also included an arm testing IFN β-1a 44 µg SC once a week which we will not consider further here as it is not covered by the recommended posology).

Time to diagnosis of MS

In REFLEX 2012,[173] 340 patients in the relevant trial arms were followed for up to two years, and a significant reduction in hazard for conversion to clinically definite MS was found (HR 0.48, 95% CI [0.31, 0.73]). An additional analysis examined time to conversion to McDonald MS (i.e. using MRI criteria as well) and found a similar reduction in hazard (0.49, [0.38, 0.64]), corresponding to a difference in median days to diagnosis of 310 vs. 97.

Several subgroup analyses were undertaken on the study sample by risk level, and key findings from Freedman and colleagues[176] are summarised here. In examining time to clinically definite MS, patients with monofocal presentation (HR 0.58, 95% CI [0.40, 0.84]) and with multifocal presentation (0.45, [0.31, 0.64]) both experienced decreased hazard of conversion to clinically definite MS, but type of presentation did not appear to be a significant moderator. Similarly, an analysis that 're-diagnosed' patients as having McDonald MS or not based on the revised 2010 criteria found that patients who were McDonald 2010 MS negative had a significantly decreased hazard of conversion to McDonald 2005 MS (HR 0.49, $p<0.001$), as did those who were McDonald 2010 MS positive at baseline (0.54, $p=0.01$).

Adverse events and mortality

Full results are available on request. Mortality was not significantly different between the groups, though no events occurred in the study drug arm and two deaths occurred in the placebo arm.

9.4.3 IFN β-1b 250 µg SC every other day (Betaferon/Extavia) vs. placebo

One trial evaluated IFN β-1b 250 µg SC every other day against placebo: BENEFIT 2006.[169]

Time to diagnosis of MS

In BENEFIT 2006,[169] 468 patients were followed for up to two years. The study drug delayed time to clinically definite MS (HR=0.50, 95% CI [0.36, 0.70]). This reduction in hazard corresponded to a difference in days to diagnosis of 618 vs. 255 at the 25th percentile. Trialists also considered time to McDonald MS, an effect that was similar in magnitude (0.54, [0.43, 0.67]).

BENEFIT 2006 also presented analyses stratified by risk levels, site of first lesion and type of first attack.[177] In analyses comparing patients with monofocal and multifocal disease at first demyelinating event, patients with monofocal disease had a similar reduction in hazard to the whole trial population (HR=0.45, 95% CI [0.29, 0.71]) while patients with multifocal disease had a decreased reduction in hazard (0.63, [0.40, 0.99]).

MS symptoms and health-related quality of life

Patients in BENEFIT 2006 were assessed for cognitive performance using the paced auditory serial addition test (PASAT-3").[178] At year 2, patients receiving the study drug had greater increases in score on this test than patients receiving placebo, including under conservative assumptions (2.0 vs 0.6, *p*=0.021). Additionally, patient-reported physical health and health-related quality of life data were collected in this trial.[169] Scores were not different between groups and were stable over the trial.

Adverse events and mortality

Full results are available on request. No deaths were reported in BENEFIT 2006.[169]

9.4.4 GA 20 mg SC once daily (Copaxone) vs. placebo

One trial evaluated GA 20 mg SC once daily against placebo: PreCISe 2009.[172]

Time to diagnosis of MS

PreCISe 2009[172] followed up 481 patients for up to three years, though the trial was stopped early for benefit. Participants receiving GA 20 mg SC once daily had reduced hazard of conversion to clinically definite MS (HR=0.55, 95% CI [0.4, 0.77]), though clinically definite MS was defined here as the occurrence of a second exacerbation. The corresponding difference in days to diagnosis was 722 vs. 336 at the 25th percentile.

Adverse events and mortality

Full results are available on request. Mortality was not significantly different between groups, although PreCISe 2009[172] reported only one death, in the study drug arm.

9.4.5 Meta-analyses: time to clinically definite MS

Pairwise meta-analyses

Direct evidence from comparisons is shown in Figure 4. All comparisons were against placebo. Only one comparison, IFN β-1a 30 μg IM once a week vs. placebo, included more than one study. The pooled effect size suggested that IFN β-1a 30 μg IM once a week reduces time to clinically definite MS (HR=0.52, 95% CI [0.39, 0.68]), with low heterogeneity (I2=0%, p=0.718).

Network meta-analysis

The set of studies reporting hazard ratios for time to clinically definite MS formed a connected network (see Figure 12). This network was star-shaped, meaning it contained no comparisons between active drugs. We estimated this model using random effects as per the protocol.

Rankings from the network meta-analysis suggested that IFN β-1a 44 μg SC thrice weekly was ranked best, followed by IFN β-1b 250 μg SC every other day, IFN β-1a 30 μg IM once a week and GA 20 mg SC once daily (see Table 5). Placebo was ranked last.

Figure 4: Pairwise meta-analyses, time to clinically definite MS

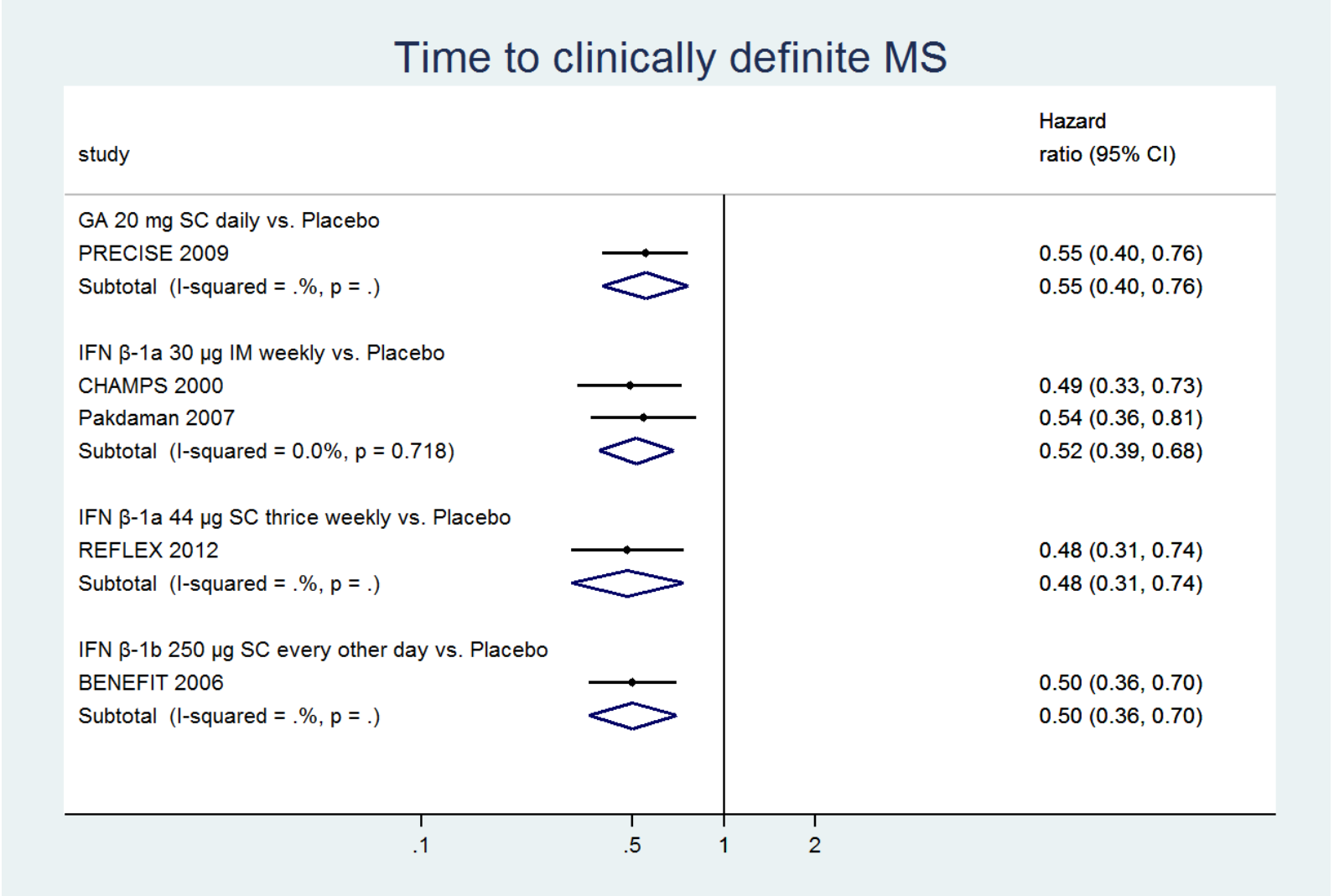
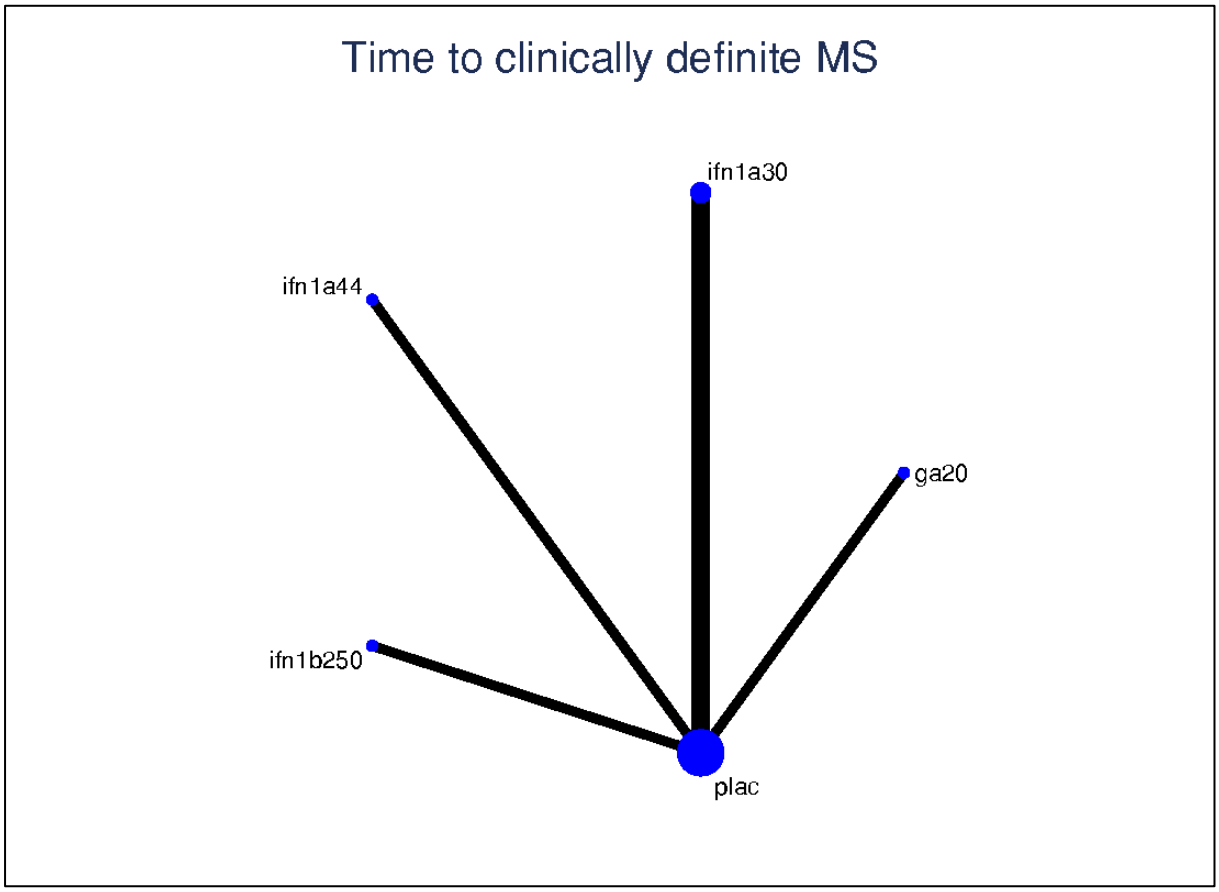


Figure 5: Network of studies, time to clinically definite MS

ifn1a30: IFN β-1a 30 µg IM once a week; ifn1a44: IFN β-1a 44 µg SC three times weekly; ifn1b250: IFN β-1b 250 µg SC every other day; ga20: GA 20 mg SC once daily; plac: placebo



Findings for comparisons between active drugs against placebo were identical, as expected, to those in the pairwise meta-analyses. Findings for indirect comparisons between drugs did not suggest superiority of any one drug over another.

Because the network was star-shaped, we could not test for inconsistency.

Sensitivity analysis

We also re-estimated the network with effect sizes for time to conversion to McDonald MS for those studies reporting it. Effectiveness estimates were robust to this change.

9.4.6 Meta-analyses: not possible for adverse events in CIS

Of the four studies (PreCISe 2009,[172] REFLEX 2012,[173] CHAMPS 2000,[170] BENEFIT 2006[169]) reporting discontinuations due to adverse events, two studies reported discontinuations over 36 months (PreCISe 2009, CHAMPS 2000) and two reported discontinuations over 24 months (REFLEX 2012 and BENEFIT 2006). As a result, we did not estimate a network meta-analysis for discontinuations in CIS. Estimates can be found in Table 6.

Table 5: Network meta-analysis: time to clinically definite MS

Findings are expressed as HR (95% CI).

Drug	SUCRA	IFN β-1a 44 µg SC thrice weekly	IFN β-1b 250 µg SC every other day	IFN β-1a 30 µg IM weekly	Glatiramer 20 mg daily	Placebo
IFN β-1a 44 µg SC thrice weekly	0.70		0.96 (0.56, 1.65)	0.93 (0.56, 1.55)	0.87 (0.51, 1.50)	0.48 (0.31, 0.74)
IFN β-1b 250 µg SC every other day	0.68			0.97 (0.63, 1.50)	0.91 (0.57, 1.45)	0.50 (0.36, 0.70)
IFN β-1a 30 µg IM weekly	0.62				0.94 (0.61, 1.45)	0.52 (0.39, 0.68)
Glatiramer 20 mg daily	0.5					0.55 (0.40, 0.76)
Placebo	0					

Table 6: Discontinuation due to AEs in CIS studies

Study	Comparison	Follow-up (months)	Treatment arm events	Treatment group	Treatment events proportion	Placebo arm events	Placebo group	Placebo events proportion
PreCISe 2009	GA 20 mg daily vs. Placebo	36	14	243	5.8%	4	238	1.7%
REFLEX 2012	IFN β-1a 44 µg SC thrice weekly vs. Placebo	24	5	171	2.9%	6	171	3.5%
CHAMPS 2000	IFN β-1a 30 µg IM weekly vs. Placebo	36	1	193	0.5%	7	190	3.7%
BENEFIT 2006	IFN β-1b 250 µg SC every other day vs. Placebo	24	24	292	8.2%	1	176	0.6%

9.4.7 Summary: clinically isolated syndrome

Comparisons for included drugs all relied on one or two trials, but each comparison suggested that that IFN or GA delayed time to clinically definite MS over a two to three year follow-up. This finding appeared to be robust to the diagnostic criteria used to establish a definitive MS diagnosis. The network meta-analysis did not suggest the superiority of one drug over another. Adverse events tended to be higher in trial arms receiving the active drugs, though where mortality was reported, it was not significantly higher in patients receiving the study drug. Findings on additional outcomes (MS symptoms, health-related quality of life) were infrequently reported.

9.5 *Clinical effectiveness: relapsing remitting MS*

Our analysis was informed by 27 trials. Of these 27 trials, one evaluated health-related quality of life measures alone (Schwartz 1997[179]) and one evaluated adverse effects alone (AVANTAGE 2014[180]). In addition, two trials reported on mixed populations: REMAIN 2012[181] and BECOME 2009.[182] REMAIN 2012,[181] which followed up 30 participants over 96 weeks, included a mixed RRMS (n=13) and SPMS (n=17) population. Because of the size of this open-label trial, because data were not stratified by type of MS and because treatment switching was allowed, we decided to include this trial in narrative synthesis but not in meta-analyses. In contrast, BECOME 2009,[182] which followed up 75 participants over two years, included 14 patients diagnosed with CIS before the revision of the McDonald criteria. Because we judged it likely that many of the 14 patients originally diagnosed as having CIS would have been classed as having RRMS under the most recent criteria, we analysed this trial alongside other RRMS-only trials. Thus, 24 relevant trials reported key clinical outcomes.

Several characteristics of the 'epidemiology' of the trial network bear discussing first: design of included multiarm trials, two-arm trials comparing active drugs against each other and trials with mixed populations. Of the 25 trials reporting clinical outcomes, four trials had three relevant treatment arms:

- both Etemadifar 2006[183] and Mokhber 2014[184, 185] evaluated a) IFN β-1a 44 µg SC three times a week against b) IFN β-1a 30 µg IM once a week against c) IFN β-1b 250 µg SC every other day;
- Calabrese 2012[186] evaluated a) IFN β-1a 44 µg SC three times a week against b) IFN β-1a 30 µg IM once a week against c) GA 20 mg SC once daily; and
- PRISMS 1998[187] compared IFN β-1a 44 µg SC three times a week against b) IFN β-1a 22 µg SC three times a week against c) placebo.

An additional seven two-arm trials compared active drugs against each other:

- two trials, BECOME 2009[182] and BEYOND 2009,[188] compared IFN β-1b 250 µg SC every other day against GA 20 mg SC once daily;
- CombiRx 2013[189] compared IFN β-1a 30 µg IM once a week against GA 20 mg SC once daily; and
- REGARD 2008[190] compared IFN β-1a 44 µg SC three times a week against GA 20 mg SC once daily.
- EVIDENCE 2007[191-193] compared IFN β-1a 44 µg SC three times a week against IFN β-1a 30 µg I M once a week;
- INCOMIN 2002[194] compared IFN β-1b 250 µg SC every other day against IFN β-1a 30 µg IM once a week; and

- REFORMS 2012[195] compared IFN β-1a 44 µg SC three times a week against IFN β-1b 250 µg SC every other day.

9.5.1 IFN β-1a 30 µg IM once a week (Avonex) vs. placebo

Our analysis was informed by three trials comparing IFN β-1a 30 µg IM once a week against placebo: BRAVO 2014,[196] Kappos 2011[197] and Multiple Sclerosis Collaborative Research Group 1996 (referred to as MSCRG 1996[198]). BRAVO 2014[196] was designed as a trial to compare oral laquinimod against IFN β-1a 30 µg IM once a week and oral placebo, while Kappos 2011[197] compared intravenous ocrelizumab against IFN β-1a 30 µg IM once a week and intravenous placebo. MSCRG 1996[198] compared IFN β-1a 30 µg IM once a week against an IM placebo.

An additional six trials compared IFN β-1a 30 µg IM once a week against other drugs: three multi-arm trials (Calabrese 2012,[186] Etemadifar 2006,[183] Mokhber 2014[184, 185]) and three two-arm trials (CombiRx 2013,[189] EVIDENCE 2007[191-193] and INCOMIN 2002[194]).

Relapse outcomes

Findings on relapse outcomes relied on three trials with different follow-up, including two of the largest trials in this review. All three studies suggested a beneficial effect of IFN β-1a 30 µg IM once a week in reducing the rate of relapses. BRAVO 2014,[196] which followed 887 patients in the relevant trial arms for 24 months, found that patients receiving IFN β-1a 30 µg IM once a week had a 26% reduction in the ARR (RR=0.74, 95% CI [0.60, 0.92]). In Kappos 2011,[197] 108 patients were followed up over 24 weeks, and while ARR was lower in patients receiving I FN β-1a 30 µg IM once a week (ARR=0.36, 95% CI [0.22, 0.60]) than in patients receiving placebo (ARR=0.64, 95% CI [0.43, 0.94]), this difference was only marginally significant (p=0.07). Finally, in MSCRG 1996,[198] 301 patients were followed up for up to three years, though the study was stopped early for efficacy and thus patients had variable time to follow-up. In analyses including all patients, the ARR for patients receiving the study drug was significantly less than the ARR for patients receiving placebo (0.67 vs. 0.82, p=0.04).

Only MSCRG 1996[198] reported time to first relapse. This was not presented with an estimate of a hazard ratio, but a log rank test suggested that IFN β-1a 30 µg IM once a week did not significantly delay time to first exacerbation as compared to placebo (median weeks 47.3 vs. 36.1, p=0.34).

Finally, the three studies reported findings for proportion relapse-free, though findings were somewhat heterogeneous and comparability is limited by differential follow-up. BRAVO 2014[196] found that 69% of patients receiving IFN β-1a 30 µg IM once a week were relapse free, as compared to 61% of patients receiving placebo (p=0.023). This difference was narrower in Kappos 2011[197] (IFN β-1a 30 µg IM once a week 78% vs. placebo 76%), with risk ratio for experiencing any relapses of 0.92 (95% CI [0.46, 1.84]). MSCRG 1996[198] only reported proportions for those patients with the intended 104 weeks on study, excluding those enrolled but who did not complete the 104 weeks before the study was stopped. For the 85 patients included who received

IFN β-1a 30 µg IM once a week, 38% were free of relapses, as opposed to 26% of the 87 patients receiving placebo. A significance test was not presented.

Relapse severity

We could not locate any relevant comparisons between IFN β-1a 30 µg IM once a week and placebo on outcomes relating to moderate or severe relapses or steroid-treated relapses.

Disability progression

Only BRAVO 2014[196] estimated time to disability progression confirmed at 3 months. Patients receiving IFN β-1a 30 µg IM once a week and placebo were delayed, but not significantly so, in time to progression (HR=0.74, 95% CI [0.51, 1.09]). Results for disability progression confirmed at 6 months were similar (0.73, [0.47, 1.14]). MSCRG 1996[198] also reported time to progression confirmed at 6 months. Based on a Kaplan-Meier analysis, predicted probability of progression at 2 years was 21.9% in patients receiving IFN β-1a 30 µg IM once a week as compared to 34.9% in patients receiving placebo (log rank p=0.02), indicating a slowing of time to progression[198, 199]. In a separate publication, the reduction in hazard was reported as 43.0% (i.e. HR=0.570, p=0.03)[200].

Empirical proportions of patients with progression confirmed at 3 months were also reported by BRAVO 2014[196] (IFN β-1a 30 µg IM once a week 11% vs. placebo 13%). Proportion progression at 6 months was similarly low (IFN β-1a 30 µg IM once a week 8% vs. placebo 10%). In MSCRG 1996, empirical proportions for patients with progression confirmed at 6 months were reported for the full sample in a publication separate to the main study report[200]. Patients receiving IFN β-1a 30 µg IM once a week had a lower probability of progression than patients receiving placebo (15% vs. 25%), though follow-up was variable. Significance tests were not presented for these proportions *per se* (i.e. not as part of survival analysis, discussed above) by any of the three trials.

Magnitude of change from baseline in EDSS score was only presented by MSCRG 1996.[198] In patients completing 104 weeks on study, patients receiving IFN β-1a 30 µg IM once a week had lesser increase in EDSS as compared to patients receiving placebo (0.25 vs. 0.74, p=0.02). This finding was similar in patients examined to week 130, in which the lower of the scores at week 104 or week 130 were taken as a measure of 'sustained' change (0.02 vs. 0.61, p=0.02). In BRAVO 2014,[196] patients receiving IFN β-1a 30 µg IM once a week had a lesser decrease in the Multiple Sclerosis Functional Composite at 24 months, but this difference was not significant (z-scores -0.045 vs. -0.14, p=0.21).

Freedom from disease activity

We could not locate any relevant comparisons between IFN β-1a 30 µg IM once a week and placebo on combined clinical-MRI outcomes for freedom from disease activity.

MS symptoms and health-related quality of life

MSCRG 1996[201] reported performance on both the Comprehensive and Brief Neuropsychological Batteries by examining change from baseline to two years, and estimated models with both no covariates and with baseline performance as a covariate. While exact effect sizes were not provided, the study found that in patients completing 104 weeks on study and as compared to placebo, IFN β-1a 30 µg IM once a week improved information processing and memory (p=0.036 unadjusted, p=0.011 adjusted) and visuospatial abilities and executive functions (p=0.005 unadjusted, p=0.085 adjusted), but not verbal abilities and attention span (p=0.603 unadjusted, p=0.917 adjusted). Findings were similar for the Brief Neuropsychological Battery (p=0.020 for both unadjusted and adjusted), though IFN β-1a 30 µg IM once a week did not significantly delay time to onset of deterioration confirmed at 6 months (log rank p=0.094). Analyses of the PASAT indicated that while the difference in magnitude of change did not rise to significance (p=0.119 unadjusted, p=0.090 adjusted), patients receiving IFN β-1a 30 µg IM once a week did delay time to sustained deterioration (log rank p=0.023).

Additionally, patients receiving IFN β-1a 30 µg IM once a week had decreased hazard of sustained worsening in the timed 25-foot walk (HR=0.401, p=0.04). However this decreased hazard was not evidenced in the nine-hole peg test with dominant hand (HR=0.514, p=0.07) or non-dominant hand (HR=0.494, p=0.10), or the box and block test in the dominant hand (HR=0.581, p=0.45) or non-dominant hand (HR=0.835, p=0.75).[200] Investigators also tested a variety of combinations of these endpoints. In a separate publication, use of an instrument to examine functional independence showed that change over 104 weeks in cognitive aspects of functional independence was not significant. This was the case both when considered as difference in means (p=0.08) and in time to sustained worsening (log rank p=0.188), with similar findings for difference in means in motor aspects of functional independence (p=0.10, log rank p=0.368).[202] Total changes in functional independence were significant at 104 weeks (p=0.03).

Finally, MSCRG 1996 reported on effects on the Sickness Impact Profile as a measure of quality of life.[203] In the study population as a whole, there were no differences between placebo and the study drug on the overall measure, nor on its physical or psychosocial components. However, when considering patients with low health-related quality of life at baseline (defined as a score greater than or equal to 10 on the measure), patients receiving the study drug had a greater improvement on physical aspects of the measure (-3.78 vs. 3.57, p<0.05).

Adverse events and mortality

We stratified comparison of AEs by type of placebo, as local AEs (e.g. injection site reactions) would not apply in studies with oral or intravenous placebos. Full results are available on request.

Mortality was not different between groups for either type of placebo. However, only one death occurred in MSCRG 1996[198] (in the study drug arm), no deaths occurred in Kappos 2011,[197] and only one death occurred in BRAVO 2014[196] (in the study drug arm).

Summary of the narrative synthesis: IFN β-1a 30 µg IM once a week (Avonex) vs. placebo

Findings from three trials suggested that relative to placebo, IFN β-1a 30 µg IM once a week reduces relapse rate, though findings were less clear for other relapse-related outcomes. Findings from two trials suggested that IFN β-1a 30 µg IM once a week also has a beneficial effect in delaying disability progression, though only MSRCG 1996[198] presented significant results. Findings from MSCRG 1996[198-202] on MS symptoms were inconsistent across tests. We were unable to find any relevant comparisons for relapse severity, defined as moderate/severe or steroid-treated relapses, or combined clinical-MRI measures of freedom from disease activity. Mortality was rare and not significantly different between groups.

9.5.2 IFN β-1a 30 µg IM once a week (Avonex) vs. IFN β-1a 44 µg SC three times a week (Rebif)

Four trials compared IFN β-1a 30 µg IM once a week against IFN β-1a 44 µg SC three times a week: Calabrese 2012,[186] Etemadifar 2006,[183] EVIDENCE 2007[191-193] and Mokhber 2014.[184, 185]

Relapse outcomes

Findings for relapse outcomes relied on three trials, of which EVIDENCE 2007[191-193] was the largest by far. Calabrese 2012[186] analysed 141 patients randomised to either IFN β-1a 30 µg IM once a week (n=47), IFN β-1a 44 µg SC three times a week (n=46) or GA 20 mg SC once daily (n=48) over two years with complete follow-up for analysed patients. Relapses were apparently analysed using a normal distribution, though formal significance tests were not presented. At two years, patients receiving IFN β-1a 30 µg IM once a week had an average ARR of 0.5 (SD=0.6) while patients receiving IFN β-1a 44 µg SC three times a week had an average ARR of 0.4 (SD=0.6). We estimated a rate ratio of 1.25 (95% CI [0.81, 1.92]). Etemadifar 2006[183] analysed 90 patients randomised 1:1:1 to either IFN β-1a 30 µg IM once a week, IFN β-1a 44 µg SC three times a week or IFN β-1b 250 µg SC every other day. Because relapses were analysed using a repeated measures ANOVA method with normal distributions, we re-estimated rate ratios based on number of relapses in each arm. Based on a total of 57 relapses in patients receiving IFN β-1a 30 µg IM once a week and 66 relapses in patients receiving IFN β-1a 44 µg SC three times a week, we estimated a rate ratio of 0.86 (95% 0.61, 1.23). Finally, EVIDENCE 2007[192, 193] randomised 677 patients and followed them up for an intended period of at least 48 weeks, with median follow-up of 64 weeks. Patients receiving IFN β-1a 30 µg IM once a week had a higher ARR (0.65) than patients receiving IFN β-1a 44 µg SC three times a week (0.54), which was a statistically significant difference (RR=1.20, p=0.033).

Only EVIDENCE 2007[192, 193] presented data for time to first relapse. The 40th percentile of patients receiving IFN β-1a 30 µg IM once a week had their first relapse at 6.7 months, as opposed to the 40th percentile of patients receiving IFN β-1a 44 µg SC three times a week, who had their first relapse at 13.5 months. Relative to patients receiving IFN β-1a 30 µg IM once a week, patients receiving IFN β-1a 44 µg SC three times a week had decreased hazard of first relapse (HR=0.70, 95% CI [0.56, 0.88]).

Both studies presenting data on proportions of patients free of relapse were in agreement on the direction of effect. In Etemadifar 2006,[183] patients receiving IFN β-1a 30 µg IM once a week were less likely to be free of

relapses than patients receiving IFN β-1a 44 µg SC three times a week (20.0% vs. 56.7%), but a pairwise significance test was not presented. In EVIDENCE 2007,[192, 193] patients receiving IFN β-1a 30 µg IM once a week were less likely to be relapse-free (48%) than patients receiving IFN β-1a 44 µg SC three times a week (56%). That is, the OR for being relapse free at the study's end favoured patients receiving IFN β-1a 44 µg SC three times a week (OR=1.5, 95% CI [1.1, 2.0]).

Relapse severity

Only EVIDENCE 2007[192, 193] reported outcomes related to relapse severity; in this case, ARR for steroid-treated relapses. Patients receiving IFN β-1a 30 µg IM once a week had an ARR for steroid-treated relapses of 0.28, as compared to 0.19 in patients receiving IFN β-1a 44 µg SC three times a week. Thus, the rate ratio for steroid-treated relapses is 1.47 (p=0.009).

Disability progression

Only EVIDENCE 2007[191] reported time to disability progression and proportion of patients progressing. Drawing from interim data on all patients at 48 weeks of follow-up, patients receiving IFN β-1a 30 µg IM once a week appeared to progress faster than patients receiving IFN β-1a 44 µg SC three times a week. However this finding was not significant for either progression confirmed at 3 months (44 µg SC vs. 30 µg IM: HR=0.87, 95% CI [0.58, 1.31]) or progression confirmed at 6 months (HR=0.70, 95% CI [0.39, 1.25]). At end of study, there was no statistical difference in the proportion of patients with disability progression confirmed at three months between those receiving IFN β-1a 30 µg IM once a week and those receiving IFN β-1a 44 µg SC three times a week (17% vs. 16%, p=0.710).

In Calabrese 2012,[186] magnitude of EDSS change did not appear to be numerically different in IFN β-1a 30 µg IM once a week (0.2, SD=0.4) as compared to IFN β-1a 44 µg SC three times a week (0.2, SD=0.5) but formal significance testing was not reported. However, in Etemadifar 2006,[183] patients receiving IFN β-1a 30 µg IM once a week reduced EDSS score by 0.1 (95% CI [-0.2, 0.5]), a numerically smaller decrease than patients receiving IFN β-1a 44 µg SC three times a week (0.3, [0.03, 0.5]). Again, formal significance testing was not reported. Finally, Mokhber 2014[184, 185] found no difference between baseline and 12-month follow-up on EDSS score for IFN β-1a 30 µg IM once a week (0.0, n=20, p=0.548), though a test for change was significant for IFN β-1a 44 µg SC three times a week (-1.0, n=21, p=0.001). Pairwise testing was not performed but an overall test was not significant.

Freedom from disease activity

We could not locate any relevant comparisons between IFN β-1a 30 µg IM once a week and IFN β-1a 44 µg SC three times a week on combined clinical-MRI outcomes for freedom from disease activity.

MS symptoms and health-related quality of life

Mokhber 2014[184] presented tests of cognitive function, though without pairwise comparisons. On all tests presented (selective reminding test, spatial recall test, symbol digit modalities test, PASAT and word list

generation), comparisons across all three treatment groups were not statistically significant except for the symbol digit modalities test. Post hoc tests found evidence that patients receiving IFN β-1a 30 µg IM once a week did not improve as much as patients receiving IFN β-1a 44 µg SC three times a week on the word list generation and PASAT-easy tests.

Additionally, Mokhber 2014[185] disaggregated the MS Quality of Life-54 scale into its subcomponents, including mental health (five components) and physical health (eight components). There were few significant within-groups differences in this small trial, and pairwise significance tests, as well as estimates of change from baseline, were not presented in a standard format, permitting only discussion of direction and significance of differences. Patients receiving IFN β-1a 30 µg IM once a week significantly worsened in energy and fatigue as compared to patients receiving IFN β-1a 44 µg SC three times a week, who improved. However, patients receiving IFN β-1a 30 µg IM once a week significantly improved in experience of physical role limitations as compared to patients receiving IFN β-1a 44 µg SC three times a week, who also improved. Patients receiving IFN β-1a 30 µg IM once a week also significantly improved in both experience of emotional role limitations and cognitive function as compared to patients receiving IFN β-1a 44 µg SC three times a week. Differences were not significant for physical function, health perceptions, pain, sexual function, social function, health distress, overall quality of life or emotional wellbeing.

Adverse events and mortality

Only EVIDENCE 2007[204] reported AEs. No studies reported mortality. Full results are available on request.

Summary of the narrative synthesis: IFN β-1a 30 µg IM once a week (Avonex) vs. IFN β-1a 44 µg SC three times a week (Rebif)

Findings from three trials, of which one was considerably larger than the others, suggested that IFN β-1a 30 µg IM once a week was less effective than IFN β-1a 44 µg SC three times a week on reducing and delaying relapses. Findings from EVIDENCE 2007[192, 193] suggested that IFN β-1a 30 µg IM once a week was also less effective than IFN β-1a 44 µg SC three times a week in reducing steroid-treated relapses. Across disability progression outcomes, findings did not show a clear pattern, and the largest trial, EVIDENCE 2007,[191] did not find a significant difference on disability progression outcomes. Findings on MS symptoms and health-related quality of life were poorly reported and inconsistent, and relied on one small trial. We were unable to locate any comparisons on combined clinical-MRI measures of freedom from disease activity, and included studies did not report mortality.

9.5.3 IFN β-1a 30 µg IM once a week (Avonex) vs. IFN β-1b 250 µg SC every other day (Betaferon/Extavia)

Three trials compared IFN β-1a 30 µg IM once a week against IFN β-1b 250 µg SC every other day: Etemadifar 2006,[183] INCOMIN 2002[194] and Mokhber 2014.[184, 185]

Relapse outcomes

Findings for relapse outcomes relied on two trials, both with 24 months of follow-up. In Etemadifar 2006,[183] patients receiving IFN β-1a 30 µg IM once a week had fewer relapses over two years of follow-up than patients receiving IFN β-1b 250 µg SC every other day (57 vs. 65; n=30 in both groups). We estimated this as a rate ratio of 0.88 (95% CI [0.61, 1.25]). However, in INCOMIN 2002,[194] which followed up 188 patients over 24 months, patients receiving IFN β-1a 30 µg IM once a week had a higher ARR (0.7) than patients receiving IFN β-1b 250 µg SC every other day (0.5). Because authors presented the effect size estimate as a standardised mean difference, we re-estimated the rate ratio as 1.4 (95% CI [1.07, 1.83]).

Both trials suggested that the proportion of patients relapse free was comparatively higher in IFN β-1a 44 µg SC three times a week. Proportions of patients experiencing relapses were significantly different between the relevant arms in Etemadifar 2006,[183] with patients receiving IFN β-1a 30 µg IM once a week less likely to be free of relapse (20% vs. 43.3%, p=0.049). In INCOMIN 2002,[194] patients receiving IFN β-1a 30 µg IM once a week were also less likely to be free of relapse than patients receiving IFN β-1b 250 µg SC every other day (36% vs. 51%, risk ratio=0.76, 95% CI [0.59, 0.99]).

Relapse severity

Only INCOMIN 2002[194] presented findings for relapse severity; specifically, ARR for steroid-treated relapses. While patients receiving IFN β-1a 30 µg IM once a week were more likely to have steroid-treated relapses than those receiving IFN β-1b 250 µg SC every other day (0.5 vs. 0.38), this difference was not significant (estimated RR=1.32, 95% CI [0.96, 1.80]).

Disability progression

Only INCOMIN 2002[194] presented differences in time to disability progression confirmed at 6 months and for proportions with disability progression. More patients receiving IFN β-1a 30 µg IM once a week progressed as compared to patients receiving IFN β-1b 250 µg SC every other day (30% vs. 13%), with patients in the IFN β-1b 250 µg SC every other day group having a reduction in risk of progression of 56% (p=0.005). In combination with a log rank test reported as p<0.01, this gives an estimated hazard ratio of 2.24 (95% CI [1.21, 4.13]).

Findings from all three trials suggested that IFN β-1a 30 µg IM once a week did not have as beneficial an effect on magnitude of EDSS change as IFN β-1a 250 µg SC every other day. In Etemadifar 2006,[183] patients receiving IFN β-1a 30 µg IM once a week reduced EDSS score by 0.1 (95% CI [-0.2, 0.5]), a numerically smaller decrease than patients receiving IFN β-1a 250 µg SC every other day (0.7, [0.5, 0.9]). Again, formal pairwise significance testing was not reported. Moreover, in a comparatively small trial, Mokhber 2014[184, 185] found no evidence for a significant difference between baseline and 12-month follow-up on EDSS score for IFN β-1a 30 µg IM once a week (0.0, n=20, p=0.548), though a test for change was significant for IFN β-1b 250 µg SC every other day (-0.6, n=19, p=0.028). Pairwise testing was not performed but an overall test was not significant. Finally, in an ANCOVA-adjusted estimate, INCOMIN 2002[194] found that patients receiving IFN β-

1a 30 µg IM once a week had a higher EDSS score at end of trial than patients receiving IFN β-1a 250 µg SC every other day (2.5 vs. 2.1, *p*=0.004).

MS symptoms and health-related quality of life

Mokhber 2014[184] presented tests of cognitive function, though without pairwise comparisons. It should be reiterated that this was a small trial with 39 patients analysed in total in the relevant contrasts. On all tests presented (selective reminding test, spatial recall test, symbol digit modalities test, PASAT and word list generation), comparisons across all three treatment groups were not statistically significant except for the symbol digit modalities test. Post hoc tests found evidence that patients receiving IFN β-1a 30 µg IM once a week did not improve as much as patients receiving IFN β-1b 250 µg SC every other day on the symbol digit modalities and PASAT-easy tests.

Additionally, Mokhber 2014[185] disaggregated the MS Quality of Life-54 scale into its subcomponents, including mental health (five components) and physical health (eight components). There were few significant within-groups differences in this small trial, and pairwise significance tests, as well as estimates of change from baseline, were not presented in a standard format, permitting only discussion of direction and significance of differences. Patients receiving IFN β-1a 30 µg IM once a week significantly improved in health perceptions and pain as compared to patients receiving IFN β-1b 250 µg SC every other day, who declined on both measures. However, patients receiving IFN β-1b 250 µg SC every other day improved more on overall quality of life, overall mental health aspects of quality of life and emotional wellbeing as compared to patients receiving IFN β-1a 44 µg SC three times a week. Differences were not significant for overall physical health aspects of quality of life, physical function, energy/fatigue, physical role limitations, sexual function, social function, health distress, emotional role limitations or cognitive function.

Adverse events and mortality

Only INCOMIN 2002[194] reported adverse events. No studies reported mortality. Full results are available on request.

Summary of the narrative synthesis: IFN β-1a 30 µg IM once a week (Avonex) vs. IFN β-1b 250 µg SC every other day (Betaferon/Extavia)

Though trials were in conflict on the relative effect of the drugs on relapse rate, INCOMIN 2002[194] suggested that IFN β-1a 30 µg IM once a week was less effective than IFN β-1b 250 µg SC every other day in reducing relapse rate, and both studies found that the proportion of patients free of relapses was lower in IFN β-1a 30 µg IM once a week. INCOMIN 2002 did not find a difference on relapse severity, measured as steroid-treated relapses, but both studies agreed that IFN β-1a 30 µg IM once a week was less effective than IFN β-1b 250 µg SC every other day on disability progression. Findings on MS symptoms and health-related quality of life relied on one small trial with inconsistent effects and poor reporting. No studies reported mortality.

9.5.4 IFN β-1a 30 µg IM once a week (Avonex) vs. GA 20 mg SC once daily (Copaxone)

Two trials compared IFN β-1a 30 µg IM once a week against GA 20 mg SC once daily: Calabrese 2012[186] and CombiRx 2013.[189]

Relapse outcomes

Findings for relapse outcomes relied on two trials with substantial follow-up; one trial (CombiRx 2013[189]) was considerably larger than the other. In Calabrese 2012,[186] patients receiving IFN β-1a 30 µg IM once a week (n=47), when compared to patients receiving GA 20 mg SC once daily (n=48), did not appear to have a numerically different ARR (0.5 [SD=0.6]) vs. 0.5 [SD=0.4]) after two-year follow-up. A formal significance test was not reported, but we re-estimated the rate ratio as 1.00 (95% CI [0.67, 1.50]). However, in the larger CombiRx 2013[189] trial with 36-month follow-up, patients receiving IFN β-1a 30 µg IM once a week (n=250) had a higher ARR than patients receiving GA 20 mg SC once daily (0.16 vs. 0.11). This difference was tested using a Cox proportional hazards model with correction for repeated events, which found statistically significant evidence of a shorter time between relapses as compared to GA 20 mg SC once daily (HR=1.43, 95% CI [1.04, 1.95]). This finding was robust to a sensitivity analysis including non-protocol defined relapses.

However, CombiRx 2013[189] did not find a significant difference in time to first relapse between groups (p=0.19). Additional information was not reported. CombiRx 2013 also did not find a significant difference between groups in proportions with protocol defined relapses at 36 months (74.0% vs. 79.5%, p=0.14).

Relapse severity

We were unable to locate any relevant comparisons between IFN β-1a 30 µg IM once a week and GA 20 mg SC once daily on outcomes relating to moderate or severe relapses or steroid-treated relapses.

Disability progression

CombiRx 2013[189] reported proportions of patients with EDSS progression at 6 months. Fewer patients receiving IFN β-1a 30 µg IM once a week progressed as compared to patients receiving GA 20 mg SC once daily (21.6% vs. 24.8%) but this difference was reported as not statistically significant.

In Calabrese 2012,[186] patients receiving IFN β-1a 30 µg IM once a week had a numerically lower increase in EDSS scores at two years (0.2, SD=0.4) as compared to patients receiving GA 20 mg SC once daily (0.3, SD=0.5) but formal significance testing was not reported.

Freedom from disease activity

Only CombiRx 2013[189] reported freedom from disease activity outcomes in this comparison. In CombiRx 2013, proportions with freedom from disease activity (defined as absence of exacerbation, EDSS progression or combined unique lesion activity—i.e. no new of enhanced lesions, unenhanced T2 lesions or enlarged unenhanced T2 lesions) was not different (p=0.62) between patients receiving IFN β-1a 30 µg IM once a week

(21.2%) and patients receiving GA 20 mg SC once daily (19.4%). This finding was robust to the inclusion of non-protocol defined exacerbations (17.1% vs. 16.1%, *p*=0.762).

MS symptoms and health-related quality of life

In CombiRx 2013,[189] change from baseline to 36 months was measured for the Multiple Sclerosis Functional Composite and several of its components, but no differences between groups were significantly different. Overall MSFC improved slightly in both IFN β-1a 30 µg IM once a week (mean 0.1, SD=0.5) and in GA 20 mg SC once daily (mean 0.2, SD=0.5). Time in seconds complete the timed 25-foot walk increased slightly in both groups (0.2 [1.1] vs. 0.2 [1.7]) but time in seconds to complete the nine-hole peg test decreased slightly (-0.4 [3.8] vs. -0.1 [4.1]), and both groups improved in the number of questions correct in the PASAT (3.5 [8.1] vs. 4.3 [7.4]).

Adverse events and mortality

Only CombiRx 2013[189] reported AEs or mortality. Full results are available on request. One death occurred in each of the relevant arms of CombiRx 2013, and thus differences were not significant.

Summary of the narrative synthesis: IFN β-1a 30 µg IM once a week (Avonex) vs. GA 20 mg SC once daily (Copaxone)

Findings from two studies were mixed on relapse outcomes, but the larger of the two trials suggested that IFN β-1a 30 µg IM once a week was less effective than GA 20 mg SC once daily at reducing relapses. Findings for disability progression, combined clinical-MRI measures on freedom from disease activity or MS symptoms did not suggest a difference between the two drugs. We were unable to locate any evidence on relapse severity, defined as moderate or severe relapses or steroid-treated relapses. Mortality was rare and not different between drugs in CombiRx 2013.[189]

9.5.5 IFN β-1a 44 µg and 22 µg SC three times a week (Rebif) vs. placebo

Our analysis was informed by three trials comparing IFN β-1a 44 µg SC three times a week against no treatment: IMPROVE 2012,[205] PRISMS 1998[187] and REMAIN 2012.[181] REMAIN 2012[181] used best supportive care alone as a comparator, whereas the other two trials used placebo. As noted above, REMAIN 2012 is of limited interest but is included here for completeness. One trial, PRISMS 1998,[187] also compared IFN β-1a 22 µg SC three times a week against no treatment.

An additional six trials compared IFN β-1a 44 µg SC three times a week against other drugs: three multi-arm trials (Calabrese 2012,[186] Etemadifar 2006[183] and Mokhber 2014[184, 185]) and three two-arm trials (EVIDENCE 2007,[191-193] REFORMS 2012[195] and REGARD 2008[190]). Comparisons in EVIDENCE 2007[191-193] were discussed in the prior section.

Relapse outcomes

Both key studies reported relapse outcomes. PRISMS 1998,[187] which tested both doses of IFN β-1a SC three times a week, followed up 560 patients (n=184 in the 44 µg arm, n=189 in the 22 µg arm, n=187 in the placebo

arm) over two years. Relative to placebo, both the 44 µg dose (RR=0.73, 95% CI [0.61, 0.86]) and the 22 µg dose (0.67, [0.56, 0.79]) reduced the rate of relapses. IMPROVE 2012,[205] a comparatively short trial which followed up 180 patients over 16 weeks (n=120 in the 44 µg arm, n=60 in the placebo arm), showed a substantial decrease in rate of relapses for those receiving the study drug as well (0.43, [0.23, 0.82]). Time to first relapse outcomes were cursorily presented by PRISMS 1998.[187] Both the 44 µg and 22 µg doses delayed time to first relapse by 5 months and 3 months respectively, though a significance test was not presented. However, [redacted].

Finally, PRISMS 1998[187] reported proportions free of relapse. In both doses, proportions relapse-free were greater than placebo at two years of follow-up. As compared to a placebo arm with 16% free of relapses, patients receiving 44 µg had a 32% chance of being free of relapses (OR=2.57, 95% CI [1.56, 4.25]) and patients receiving 22 µg had a 27% chance of being free of relapses (2.01, [1.21, 3.35]).

REMAIN 2012,[181] which followed up 30 patients with either RRMS or SPMS for 96 weeks, did not find a significant difference between arms on time to first relapse or proportion relapse-free.

Relapse severity

PRISMS 1998[187] presented data for both moderate or severe relapses and steroid-treated relapses. Patients receiving placebo had, on average, more moderate or severe relapses over the course of the study (0.99) than patients receiving 44 µg of the study drug (0.62) or patients receiving 22 µg (0.71). We re-estimated these as rate ratios of 0.64 (95% CI [0.53, 0.74]) and 0.72 (0.61, 0.84) respectively. Correspondingly, patients receiving 44 µg were more likely to be free of any moderate or severe relapses (OR=2.32, 95% CI [1.47, 3.37]). Findings were similar for the 22 µg dose as compared to placebo (2.13, [1.41, 3.21]).

The pattern of findings in PRISMS 1998[187] for steroid treatments was similar. Patients receiving placebo had, on average, more courses of steroids for MS relapses over the course of the study (1.39) than patients receiving 44 µg (0.75) or patients receiving 22 µg (0.97). We re-estimated the corresponding rate ratios for 44 µg compared to placebo as 0.54 (95% CI [0.46, 0.63]) and for 22 µg compared to placebo as 0.70 (0.61, 0.80]). Correspondingly, patients receiving 44 µg were more likely to be free of any steroid-treated relapses (OR=1.99, 95% CI [1.32, 3.02]), as were patients receiving 22 µg (1.71, [1.14, 2.57]).

Disability progression

In PRISMS 1998,[187] time to disability progression confirmed at 3 months was slowed by both doses of the study drug as compared to placebo. The 25th percentile of the distribution of time to progression was 21.3 months for patients receiving 44 µg and 18.5 months for patients receiving 22 µg, as compared to 11.9 for patients receiving placebo. Corresponding hazard ratios showed evidence of statistically significant delay of progression (44 µg: HR=0.62, 95% CI [0.43, 0.91]; 22 µg: 0.68, [0.48, 0.98]).

Both PRISMS 1998[187] and IMPROVE 2012[205] reported the magnitude of EDSS change. As compared to placebo in PRISMS 1998,[187] both 44 µg and 22 µg had a smaller increase in EDSS score. The difference was 0.25 EDSS points (both $p<0.05$). IMPROVE 2012[205] did not report a standard significance test, though median EDSS changes in both the 44 µg and the placebo arm were 0.

In REMAIN 2012,[181] magnitude of EDSS change, time to progression and proportions with progressing were not significantly different between arms.

Freedom from disease activity

We were unable to locate any relevant comparisons between IFN β-1a 44 µg or 22 µg SC three times a week and placebo on combined clinical-MRI outcomes for freedom from disease activity.

MS symptoms and health-related quality of life

PRISMS 1998 reported effects of IFN β-1a 44 µg and 22 µg SC three times a week on various MS symptoms across two publications.[187, 206] As noted in the original trial report,[187] patients receiving the 44 µg dose were less likely to have a sustained worsening in ambulation as compared to placebo (7% vs. 13%, $p<0.05$), but the proportion in patients receiving the 22 µg dose (12%) was not significantly different from placebo. Subsequently, Gold and colleagues[206] reported that though patients in all three groups increased from baseline on the Center for Epidemiological Studies Depression Rating Scale, these changes were not different between groups (44 µg: 0.2, 22 µg: 1.8, placebo: 0.9; $p=0.60$). Similarly, risk of exceeding the cutoff score for depression on this scale was not different in 44 µg (risk ratio=0.7, 95% CI [0.3, 1.6]) or 22 µg (0.8, [0.3, 1.8]) as compared to placebo, and proportions of patients exceeding the cutoff on the Beck Hopelessness Scale were not different between placebo (6.9%) and either 44 µg (6.9%, $p=1.0$) or 22 µg (10.5%, $p=0.55$). Finally, data were not presented numerically, but groups were reported as having no difference in scores on the General Health Questionnaire, nor on its subscales.

Adverse events and mortality

All studies presented AEs. Full results are available on request. None of the studies reported deaths related to the study drugs.

Summary of the narrative synthesis: IFN β-1a 44 µg and 22 µg SC three times a week (Rebif) vs. placebo

Findings from two trials suggested a beneficial effect of IFN β-1a 44 µg SC three times a week against placebo on relapse outcomes. Additionally, findings from PRISMS 1998[187] suggested a beneficial effect of IFN β-1a 44 µg SC three times a week on relapse severity (both moderate/severe relapses and steroid-treated relapses) and on delaying disability progression. Findings from PRISMS 1998[187, 206] also suggested a beneficial effect of the IFN

β-1a 44 µg SC three times a week on ambulation, but not mental health. Findings for the 22 µg dose in PRISMS 1998[187, 206] were similar except for ambulation. Mortality was not reported.

9.5.6 IFN β-1a 44 µg SC three times a week (Rebif) vs. IFN β-1b 250 µg SC every other day (Betaferon/Extavia)

Three trials compared IFN β-1a 44 µg SC three times a week against IFN β-1b 250 µg SC every other day: Etemadifar 2006,[183] Mokhber 2014[184, 185] and REFORMS 2012.[195] An additional trial, AVANTAGE 2014,[180] compared these drugs on adverse events.

Relapse outcomes

Assessment of relapse outcomes in this comparison relied on two small studies with very different follow-up. In Etemadifar 2006,[183] patients receiving IFN β-1a 44 µg SC three times a week had 66 relapses, as compared to 65 relapses in patients receiving IFN β-1b 250 µg SC every other day, all over two years of follow-up (n=30 in both groups). We estimated this as a rate ratio of 1.02 (95% CI [0.72, 1.43]). In REFORMS 2012,[195] patients receiving IFN β-1a 44 µg SC three times a week had an ARR of 0.15 as compared to patients receiving IFN β-1b 250 µg SC every other day, who had an ARR of 0.11. This difference was statistically significant (p<0.001), though this was a relatively small trial (n=129), patients were only followed up for 12 weeks and patient relapses were self-reported rather than assessed by a neurologist.

In Etemadifar 2006,[183] the proportion of patients without relapses at two years was numerically higher in IFN β-1a 44 µg SC three times a week against IFN β-1b 250 µg SC every other day (56.7% vs. 43.3%), but no pairwise significance testing was performed.

Relapse severity

We were unable to find any comparisons between IFN β-1a 44 µg SC three times a week and IFN β-1b 250 µg SC every other day on outcomes relating to moderate or severe relapses or steroid-treated relapses.

Disability progression

Analysis of disability progression in both trials was by magnitude of EDSS change, though both trials inadequately reported analysis details. In Etemadifar 2006,[183] patients receiving IFN β-1a 44 µg SC three times a week had a decrease in EDSS score of 0.3 (95% CI [0.03, 0.5]), as compared to a decrease of 0.7 (0.5, 0.9) in patients receiving IFN β-1b 250 µg SC every other day. A pairwise significance test was not performed. Patients in Mokhber 2014[184, 185] also decreased in EDSS score across both comparisons, but in the opposite direction (-1.0, p=0.001 vs. -0.6, p=0.028). Again, a pairwise significance test was not performed.

Freedom from disease activity

We were unable to find any comparisons between IFN β-1a 44 µg SC three times a week and IFN β-1b 250 µg SC every other day on outcomes relating to combined clinical-MRI outcomes for freedom from disease activity.

MS symptoms and health-related quality of life

As noted previously, analyses in Mokhber 2014[184] for cognitive function were not significant across groups but for the symbol digit modalities test. Post hoc analyses indicated that patients receiving IFN β-1a 44 µg SC three times a week improved more than IFN β-1b 250 µg SC every other day on tests of the symbol digit modalities test and the PASAT-easy.

Across the quality of life domains tested in Mokhber 2014[185], IFN β-1a 44 µg SC three times a week was not significantly different from IFN β-1b 250 µg SC every other day but for overall mental health aspects of health-related quality of life, where patients receiving IFN β-1b 250 µg SC every other day improved significantly more.

Adverse events and mortality

AEs were only reported by AVANTAGE 2014[180] and REFORMS 2012.[195] Only AVANTAGE 2014 reported death, but no events occurred in either study arm. Full results are available on request.

Summary of the narrative synthesis: IFN β-1a 44 µg SC three times a week (Rebif) vs. IFN β-1b 250 µg SC every other day (Betaferon/Extavia)

Findings were derived from three small trials and should thus be treated with caution. Two trials reporting relapse outcomes disagreed, though there was some evidence from REFORMS 2012[195] that patients receiving IFN β-1a 44 µg SC three times a week had a higher ARR. Findings for disability progression, MS symptoms and health-related quality of life were inconsistent and poorly reported. We were unable to find comparisons for relapse severity or combined clinical-MRI measures of freedom from disease activity. No deaths were reported.

9.5.7 IFN β-1a 44 µg SC three times a week (Rebif) vs. GA 20 mg SC once daily (Copaxone)

Two trials compared IFN β-1a 44 µg SC three times a week against GA 20 mg SC once daily: Calabrese 2012[186] and REGARD 2008.[190]

Relapse outcomes

In Calabrese 2012,[186] patients receiving IFN β-1a 44 µg SC three times a week had a numerically lower ARR than patients receiving GA 20 mg SC once daily after two years of follow up (0.4 [SD=0.6] vs. 0.5 [SD=0.4]), but formal significance testing was not reported and relapses were analysed using a normal distribution. We re-estimated this rate ratio as 0.80 (95% CI [0.52, 1.23]). In the larger REGARD 2008[190] trial, 764 patients were followed up for 96 weeks. ARRs were not significantly different between patients receiving IFN β-1a 44 µg SC three times a week and patients receiving GA 20 mg SC once daily (0.30 vs. 0.29, p=0.828).

REGARD 2008[190] did not find a significant difference in time to first relapse between patients receiving IFN β-1a 44 µg SC three times a week and those receiving GA 20 mg SC once daily (HR=0.94, 95% CI [0.74, 1.21]), nor did the trial find a difference in patients free of relapses at 96 weeks (62% vs. 62%, p=0.96).

Relapse severity

In REGARD 2008,[190] the ARR for steroid-treated relapses was not significantly different between patients receiving IFN β-1a 44 µg SC three times a week and those receiving GA 20 mg SC once daily (0.19 vs. 0.17, *p*=0.386).

Disability progression

REGARD 2008[190] reported proportions of patients with disability progression confirmed at 6 months. Proportions were not significantly different (*p*=0.117) between patients receiving IFN β-1a 44 µg SC three times a week (11.7%) and those receiving GA 20 mg SC once daily (8.7%).

In Calabrese 2012,[186] patients receiving IFN β-1a 44 µg SC three times a week had a numerically lower increase in EDSS scores at two years (0.2, SD=0.5) as compared to patients receiving GA 20 mg SC once daily (0.3, SD=0.5) but formal significance testing was not reported.

Freedom from disease activity

We were unable to locate any comparisons between IFN β-1a 44 µg SC three times a week and GA 20 mg SC once daily on combined clinical-MRI outcomes for freedom from disease activity.

MS symptoms and health-related quality of life

We were unable to locate any comparisons between IFN β-1a 44 µg SC three times a week and GA 20 mg SC once daily on MS symptoms or health-related quality of life.

Adverse events and mortality

AEs and mortality were reported by REGARD 2008.[190] Only one death occurred, in the IFN arm, and thus mortality was not significantly different between groups. Full results are available on request.

Summary of the narrative synthesis: IFN β-1a 44 µg SC three times a week (Rebif) vs. GA 20 mg SC once daily (Copaxone)

Findings from two trials did not suggest the presence of a difference between the two drugs on relapse outcomes, relapse severity or disability progression. We could not locate comparisons relating to combined clinical-MRI measures of freedom from disease activity or to MS symptoms or health-related quality of life. Mortality was not different between groups.

9.5.8 IFN β-1b 250 µg SC every other day (Betaferon/Extavia) vs. placebo

We included two trials comparing IFN β-1b 250 µg SC every other day against placebo: IFNB Multiple Sclerosis Study Group 1995 (referred to as IFNB MSSG 1995[207, 208]) and Knobler 1993.[209] Schwartz 1997[179] examined quality of life outcomes only, and used best supportive care instead of placebo.

An additional 6 trials compared IFN β-1b 250 µg SC every other day against other drugs: two multi-arm trials (Etemadifar 2006,[183] Mokhber 2014[184, 185]) and four two-arm trials (BECOME 2009,[182] BEYOND 2009,[188] INCOMIN 2002,[194] REFORMS 2012[195]). Comparisons for Etemadifar 2006,[183] Mokhber 2014[184, 185], INCOMIN 2002[194] and REFORMS 2012[195] have been discussed in previous sections.

Relapse outcomes

Both studies reporting ARRs suggested a beneficial effect of IFN β-1b 250 µg SC every other day, though only IFNB MSSG 1995[207, 208] may have been powered to detect a difference. In IFNB MSSG 1995,[207, 208] 247 patients in the relevant arms were followed up for variable amounts of time, with the initial two-year study phase continuing into a blinded extension; thus, some patients were followed for up to 5.5 years, with median follow up 46.0 months for the placebo arm and 48.0 months for the relevant study drug arm. At the end of the study, patients receiving IFN β-1b 250 µg SC every other day had a lower ARR than patients receiving placebo (0.78, 95% CI [0.70, 0.88] vs. 1.12, 95% CI [1.02, 1.23]; p=0.0006). In a comparatively small trial, Knobler 1993[209] followed up 30 patients over three years, including a six-month dose-finding period at the start of the study. The 24 patients receiving IFN β-1b 250 µg SC every other day had an ARR of 0.7 as compared to the 6 patients receiving placebo, who had an ARR of 0.9. This difference was not significant (p=0.33).

Both studies also reported information on time to first relapse. Knobler 1993[209] reported that median time to first relapse was delayed, but not significantly so, in patients receiving IFN β-1b 250 µg SC every other day as compared to patients receiving placebo (14 months vs. 2 months, log rank p=0.07). The comparatively larger IFNB MSSG 1995 reported a similar finding at the three-year follow-up,[207] albeit at smaller magnitude and rising to statistical significance. Median time to first exacerbation was delayed in patients receiving IFN β-1b 250 µg SC every other day as compared to placebo (264 days vs. 147 days, log rank p=0.028).

Proportions free of relapse were also only available at the three-year follow-up for IFNB MSSG 1995.[207] Proportions free of relapse were not significantly different between groups (IFN β-1b 250 µg SC every other day 21.8% vs. placebo 13.8%, p=0.097). Three-year results from Knobler 1993[209] showed a similar trend (42% vs. 17%), though these findings were not significant either (p=0.37).

Relapse severity

Relapse severity was reported based on both two-year and final data from IFNB MSSG 1995,[207, 208] but only results from the two-year data were usable. At two years of follow-up, patients receiving IFN β-1b 250 µg SC every other day had a lower ARR for moderate or severe relapses as compared to placebo (0.23 vs. 0.45, p=0.002). Similar findings based on final data reported only a p-value (p=0.012) for a relationship in the same direction. Knobler 1993[209] did not find a significant relationship for 'attack severity', though findings were only reported as a non-significant p-value (p=0.67) and relapse severity was not defined.

Disability progression

IFNB MSSG 1995 reported that IFN β-1b 250 µg SC every other day delayed disability progression confirmed at 3 months, but not significantly so, with median time to progression of 4.79 years as compared to 4.18 years in

placebo (log rank p=0.096).[208] Proportions with confirmed progression showed a similar trend (35% vs. 46%). We re-estimated this as a hazard ratio of 0.71 (95% CI [0.48, 1.06]). Knobler 1993[209] examined change from baseline EDSS between groups, but only noted that the difference was not statistically significant (p=0.42).

Freedom from disease activity

We were unable to locate any relevant comparisons between IFN β-1b 250 µg SC every other day and placebo for combined clinical-MRI outcomes relating to freedom from disease activity.

MS symptoms and health-related quality of life

In Schwartz 1997,[179] 34 patients receiving IFN β-1b 250 µg SC every other day were compared against 45 patients receiving best supportive care. Over the course of a year, patients were not different on quality-adjusted time without symptoms and toxicity, measured in months (106 vs. 10.4, p=0.50).

Adverse events and mortality

AEs were reported by IFNB MSSG 1995[208] and Knobler 1993.[209] None of the studies reported mortality. Full results are available on request.

Summary of the narrative synthesis: IFN β-1b 250 µg SC every other day (Betaferon/Extavia) vs. placebo

Findings from two studies suggested a beneficial effect of IFN β-1b 250 µg SC every other day on relapse outcomes as compared to placebo (though not for proportions relapse-free). Findings from IFNB MSSG 1995[207, 208] suggested a reduction in rate of moderate or severe relapses, but findings from Knobler 1993[209] were uninterpretable. Neither study found evidence of delaying time to disability progression. One small study comparing IFN β-1b 250 µg SC every other day against best supportive care did not find differences in health-related quality of life over a year. We were unable to find comparisons for combined clinical-MRI freedom from disease activity. None of the studies reported mortality.

9.5.9 IFN β-1b 250 µg SC every other day (Betaferon/Extavia) vs. GA 20 mg SC once daily (Copaxone)

Two trials compared IFN β-1b 250 µg SC every other day against GA 20 mg SC once daily: BECOME 2009[182] and BEYOND 2009.[188]

Relapse outcomes

Both BECOME 2009[182] and the larger BEYOND 2009[188] trial reported ARRs. In BECOME 2009,[182] 75 patients were followed up for up to two years. Patients receiving IFN β-1b 250 µg SC every other day did not have a significantly different ARR than patients receiving GA 20 mg SC once daily (0.37 vs. 0.33, p=0.68).

Findings from BEYOND 2009,[188] in which 1345 patients from the relevant trial arms were followed up for at least two and up to 3.5 years, suggested a similar trend (0.36 vs. 0.34, one-tailed p=0.79). This was expressed using a Cox proportional hazards model with modification for repeated events (HR=1.06, 95% CI [0.89, 1.26]).

Time to first relapse was also not significantly different between arms in either study. In BECOME 2009,[182] of patients who had relapses, median time for those receiving IFN β-1b 250 µg SC every other day (123 days) was not very different from those receiving GA 20 mg SC once daily (121 days), with a non-significant log rank test on the whole sample (p=0.12). In BEYOND 2009,[188] patients at the 25th percentile did not have substantially different days to first relapse (IFN β-1b 250 µg SC every other day 283 vs. GA 20 mg SC once daily 271; one-sided log rank p=0.75). This was supported by proportions relapse-free at two years estimated from a Kaplan-Meier model, which were very similar (59% vs. 58%).

Finally, only BECOME 2009[182] reported empirical proportions of patients relapsing. Fewer patients receiving IFN β-1b 250 µg SC every other day were relapse free as compared to patients receiving GA 20 mg SC once daily, but this difference was not significant (53% vs. 72%, p=0.10).

Relapse severity

Only BEYOND 2009[188] reported ARRs for severity of relapse. ARRs for major relapse were not significantly different between patients receiving IFN β-1b 250 µg SC every other day and those receiving GA 20 mg SC once daily (0.19 vs. 0.18, one-sided p=0.36). Time to first major relapse was not significantly different, with both arms having proportions at two years of 27%as predicted by a Kaplan-Meier model (log rank p=0.56).

Both studies reported empirical proportions for patients receiving steroid treatment for MS. In BECOME 2009,[182] more patients receiving IFN β-1b 250 µg SC every other day (44%) required steroid treatment for relapses than patients receiving GA 20 mg SC once daily (23%), but this difference was only of marginal significance (p=0.09). In contrast, proportions of patients requiring steroid treatment for relapses were not meaningfully different in BEYOND 2009[188] (34% vs. 32%, p=0.43).

Disability progression

BEYOND 2009[188] reported time to disability progression confirmed at 3 months. Because median time to progression was not reached, the time to progression at the 10th percentile was reported. The 10th percentile of patients receiving IFN β-1b 250 µg SC every other day progressed after 274 days, whereas patients receiving GA 20 mg SC once daily progressed after 268 days (log rank p=0.35). Alternative estimates were provided based on Kaplan-Meier models, in which the probability of progression at the end of two years was 21% in those receiving IFN β-1b 250 µg SC every other day and 20% in those receiving GA 20 mg SC once daily (log rank p=0.68). We estimated a hazard ratio of 1.06 (95% CI [0.81, 1.37]) from these statistics.

In a separate publication to the main trial report, BECOME 2009[210] reported time to disability progression confirmed at 6 months. Empirical proportions of patients progressing in each arm were dissimilar (IFN β-1b 250 µg SC every other day 12.1% vs. GA 20 mg SC once daily 17.6%), but with a non-significant log rank test

(p=0.51). Based on these statistics, we estimated a hazard ratio of 0.66 (95% CI [0.19, 2.28]). BECOME 2009[210] also reported progression based on the MS Functional Composite, in which an increase of 0.2 SD confirmed at 6 months constitutes evidence of progression. The same trend was apparent (5.7% vs. 10.3%, log rank p=0.39).

Freedom from disease activity

We were unable to locate any relevant comparisons between IFN β-1b 250 µg SC every other day and GA 20 mg SC once daily on combined clinical-MRI measures of freedom from disease activity.

MS symptoms and health-related quality of life

We were unable to locate any relevant comparisons between IFN β-1b 250 µg SC every other day and GA 20 mg SC once daily on MS symptoms or health-related quality of life. However, BECOME 2009[182] did present results for the MS Functional Composite, discussed above.

Adverse events and mortality

Both studies reported AEs, but only BEYOND 2009[188] reported mortality. Differences were not significant for mortality, though only one death occurred, in the GA arm of BEYOND 2009. Full results are available on request.

Summary of the narrative synthesis: IFN β-1b 250 µg SC every other day (Betaferon/Extavia) vs. GA 20 mg SC once daily (Copaxone)

Findings from two trials—one small and one large—did not suggest a difference between the two drugs on relapse outcomes, relapse severity, or disability progression. We were unable to locate any comparisons for combined clinical-MRI measures on freedom from disease activity. Differences between groups were not significant for mortality.

9.5.10 Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy) vs. placebo

We included one trial comparing pegylated IFN β-1a 125 µg SC every two weeks against placebo: ADVANCE 2014.[211] We were unable to locate any trials including comparisons between pegylated IFN β-1a 125 µg SC every two weeks and other drugs. In its placebo-controlled phase, ADVANCE 2014 compared pegylated IFN β-1a 125 µg SC every two weeks and every four weeks against placebo for 48 weeks. The relevant arms included a total of 1012 patients analysed.

Relapse outcomes

Participants receiving pegylated IFN β-1a 125 µg SC every two weeks had a decrease in ARR (RR=0.644, 95% CI [0.500-0.831]).[211] Time to first relapse was also delayed in patients receiving the active drug (HR=0.61, 95% CI [0.47, 0.80]).

Relapse severity

Publications arising from this study did not report relapse severity.

Disability progression

Participants receiving pegylated IFN β-1a 125 µg SC every two weeks experienced a delay in time to disability progression confirmed at three months (HR=0.62, 95% CI [0.40, 0.97]).[211] As reported in the summary of product characteristics filed by the European Medicines Agency, the time to disability progression confirmed at six months was longer in patients receiving the study drug than in patients receiving placebo (0.46, [0.26, 0.81]).

Freedom from disease activity

In ADVANCE 2014, measures of freedom from disease activity included mixed clinical and MRI, clinical only, and MRI only definitions, and were reported in a publication separate to the main study report.[212] As stated in the methods, we report here the mixed clinical and MRI definition, which included both absence of relapses and of onset of disability progression confirmed at three months as well as no gadolinium-enhancing lesions and no new or newly enlarging T2 hyperintense lesions. Between baseline and week 48 of the trial, 33.9% of patients (n=466 in this analysis) receiving the study drug had no evidence of disease activity, whereas 15.1% of patients (n=484 in this analysis) receiving placebo did (OR=2.89, 95% CI [2.11, 3.95]). This finding was robust to sensitivity analysis on data missingness.

MS symptoms and health-related quality of life

In ADVANCE 2014, patients receiving pegylated IFN β-1a 125 µg SC every two weeks did not significantly worsen over 48 weeks on the MSIS-29 physical subscale (MD=0.08, 95% CI [-1.10, 1.27]) although placebo patients did (1.24, [0.05, 2.44]).[213] Both groups improved on the MSIS-29 psychological subscale, though differences were not significant between groups (pegylated IFN β-1a: -2.06 [-3.58, -0.53]; placebo: -2.17, [-3.63, -0.70]). Participants also completed the SF-12 (both the Physical Component Summary and the Mental Component Summary), EQ-5D, and EQ-5D visual analogue scale. None of the differences between groups or within groups were statistically significant (authors did not present specific data) but patients receiving pegylated IFN β-1a every two weeks did have a significant improvement on the visual analogue scale (2.06, [0.58, 3.54]).

Adverse events and mortality

ADVANCE 2014[211] reported AEs and mortality. Full results are available on request. Differences between groups for mortality were not significant, but one event occurred in the study drug arm and two events occurred in the placebo arm.

Summary of the narrative synthesis: pegylated IFN β-1a 125 µg SC every two weeks (Plegridy) vs. placebo

Findings from the one study included in this comparison suggested a beneficial effect of pegylated IFN β-1a 125 µg SC every two weeks against placebo on relapse outcomes, disability progression, and freedom from disease activity. Pegylated IFN β-1a 125 µg SC every two weeks were not different from placebo on health-related quality of life measures. Relapse severity outcomes were not reported. Groups were not significantly different on mortality.

9.5.11 GA 20 mg SC once daily and 40 mg SC three times a week (Copaxone) vs. placebo

We included five trials comparing GA 20 mg SC once daily against placebo: Bornstein 1987,[168] CONFIRM 2012,[214] Copolymer 1 Multiple Sclerosis Study Group 1995 (referred to as Cop1 MSSG 1995[215, 216]), European/Canadian Glatiramer Acetate Study Group 2001 (referred to as ECGASC 2001[217]), and GATE 2015.[218] One trial, GALA 2013,[219] tested GA 40 mg SC three times a week against placebo.

Additionally, one multi-arm trial (Calabrese 2012[186]) and four two-arm trials (BECOME 2009,[182] BEYOND 2009,[188] CombiRx 2013[189] and REGARD 2008[190]) compared GA 20 mg SC once daily against other drugs. These comparisons have been discussed above in the relevant sections.

Relapse outcomes

All five studies comparing GA 20 mg SC once daily against placebo reported relapse rate, as did the one study comparing GA 40 mg SC three times a week against placebo. Bornstein 1987[168] followed up 48 patients over two years. With a total of 16 relapses over two years in the 25 patients receiving GA 20 mg SC once daily and 62 relapses in the 23 patients receiving placebo, we estimated this as a rate ratio of 0.25 (95% CI [0.14, 0.43]). In another early study, Cop1 MSSG 1995[215, 216] followed up 251 patients over at least two years, with an extension of up to 11 months. At two years, the ARR in patients receiving GA 20 mg SC once daily was 0.59, as compared to patients receiving placebo, who had an ARR of 0.84.[215] This difference was statistically significant (p=0.007). Subsequent studies found similar reductions in ARR. In ECASG 2001,[217] which followed up 239 patients over nine months, ARR in the study drug group was 0.81 as compared to 1.21 in placebo (RR=0.67, p=0.012). CONFIRM 2012[214] followed up 713 patients in relevant study arms for two years and found a significant difference in ARRs as well (GA 20 mg SC once daily 0.29 vs. placebo 0.40, RR=0.71, 95% CI [0.55, 0.93]). However, in a trial following up 357 patients receiving branded GA against 84 patients receiving placebo for nine months (GATE 2015),[218] ARRs were not substantially different between groups (GA 20 mg SC once daily 0.40, 95% CI [0.26, 0.62] vs. placebo 0.38, 95% CI [0.22, 0.66]), though a standard significance test was not presented. GALA 2013[219] compared GA 40 mg three times a week against placebo in 1404 patients (n=943 GA 40 mg three times a week vs. n=461 placebo) over 12 months. Patients receiving the study drug had a significantly lower ARR than patients receiving placebo (GA 40 mg SC three times a week 0.33, 95% CI [0.28, 0.39] vs. placebo 0.51, 95% CI [0.42, 0.61]) with an associated significant rate ratio (0.66, 95% CI [0.54, 0.80]).

Two studies reported time to relapse. Including the extension phase, patients receiving GA 20 mg SC once daily in Cop1 MSSG 1995[216] had a delayed time to first relapse as compared to patients receiving placebo, but this difference was not significant (median days to first relapse 287 vs. 198, p=0.057). However, in the larger CONFIRM 2012[214] trial, patients receiving GA 20 mg SC once daily did have a significant delay in time to relapse (HR=0.71, 95% CI [0.55, 0.92]). Patients receiving GA 40 mg three times a week in GALA 2013[219] also had longer median time to first relapse (393 days vs. 377 days), with a hazard ratio of 0.61 (95% CI [0.49, 0.74]).

Finally, empirical proportions free of relapse tended to be greater in patients receiving GA 20 mg SC once daily as compared to patients receiving placebo, but this trend was not completely consistent. In Bornstein 1987,[168] 56% of patients receiving the study drug were relapse-free at two years as opposed to 26% of patients receiving placebo (adjusted OR=4.6, p=0.036). Similarly, Cop1 MSSG 1995[216] found that over the whole trial, patients receiving the study drug were more likely to be free of relapses (33.6% vs. 24.6%, p=0.002). In ECGASC 2001,[217] this trend did not rise to significance (55.5% vs. 49.2%, OR=1.47, 95% CI [0.84, 2.56]), and in GATE 2015,[218] proportions were not substantially different (73.9% vs. 73.8%), though a significance test was not provided. In GALA 2013,[219] patients receiving GA 40 mg three times a week were more likely to be free of relapses than patients receiving placebo (77.0% vs. 65.5%, OR=1.93, 95% CI [1.49, 2.49]).

Relapse severity

In ECGASC 2001,[217] patients receiving GA 20 mg SC once daily had fewer steroid treated relapses (54 vs. 84). We estimated this as a rate ratio for steroid-treated relapses of 0.65 (95% CI [0.46, 0.91]). The proportion of patients with steroid-treated relapses was correspondingly lower (33.6% vs. 39.2%) but this was not tested for significance. In GALA 2013,[219] patients receiving GA 40 mg SC three times weekly had a lower ARR (0.30, 95% CI [0.25, 0.36]) for 'severe' relapses, defined as steroid-treated or hospitalised relapses, than patients receiving placebo (0.47, [0.38, 0.57]). This translated into a rate ratio of 0.64 (95% CI [0.53, 0.79]).

Disability progression

Three studies presented data on time to disability progression confirmed at 3 months, whereas only CONFIRM 2012[214] presented data time to progression confirmed at 6 months. Studies suggested a beneficial, but generally not significant, impact of GA 20 mg SC once daily on confirmed disability progression. In Bornstein 1987,[168] the median time to progression confirmed at 3 months was not reached for patients receiving GA 20 mg SC once daily, but was 18 months for patients receiving placebo. This difference was significant (log rank p=0.05). Together with proportions of patients with progression of 20% in the study drug arm and 48% in the placebo arm, we estimated the hazard ratio of progression as 0.37 (95% CI [0.14, 1.00]). In Cop1 MSSG 1995,[216] probabilities of non-progression were 76.8% in the GA 20 mg SC once daily arm as compared to 70.6% in the placebo arm. Using the value from a related significance test (p=0.199), we estimated the hazard ratio as 0.76 (95% CI [0.50, 1.16]). Finally, CONFIRM 2012[214] did not find that GA 20 mg SC once daily slowed time to progression confirmed at 3 months (HR=0.93, 95% CI [0.63, 1.37]). This finding was not different when disability progression was confirmed at 6 months (0.87, [0.55, 1.38]).

Only two studies presented data on proportions of patients with confirmed disability progression in comparisons of GA 20 mg SC once daily against placebo. As noted above, in Bornstein 1987,[168] 20% of patients receiving GA 20 mg SC once daily progressed over two years, while 48% of patients receiving placebo progressed. In univariate analyses, this finding was not significant (p=0.064), but multivariate analyses found a significant effect on probability of progression (p=0.033). In Cop1 MSSG 1995,[216] proportions with progression confirmed at 3 months were 23.2% in patients receiving GA 20 mg SC once daily as opposed to 29.4% in patients receiving placebo over the whole trial. In GALA 2013,[219] which compared GA 40 mg SC three times weekly against placebo, 95.5% of patients receiving the study drug were free of confirmed progression as compared to 96.3% of patients receiving placebo, but a formal significance test was not presented.

Finally, magnitude of EDSS change was reported by most studies, but changes were small across studies. In Bornstein 1987,[168] findings were presented as proportions improving or worsening by magnitude of improvement. We estimated that patients receiving GA 20 mg SC once daily improved by 0.12 EDSS points and patients receiving placebo worsened by 0.74 EDSS points, with a significant difference between groups (p<0.05). In Cop1 MSSG 1995,[216] patients receiving GA 20 mg SC once daily did not have a significant improvement in EDSS score (-0.11, 95% CI [-0.31, 0.10]) while patients receiving placebo had significant worsening (0.34, [0.13, 0.54]). This difference was statistically significant (p=0.006). In ECGASC 2001,[217] mean EDSS change from baseline was not significantly different between groups (GA 20 mg SC once daily 0.02 vs. placebo 0.05) but a p-value or confidence intervals were not presented. In GATE 2015,[218] neither patients receiving the study drug (-0.08, [-0.19, 0.03]) nor patients receiving placebo (-0.02, [-0.17, 0.14]) had significant improvements in EDSS score. Change in GALA 2013[219] was negligible as well (GA 40 mg SC three times weekly 0.0, SD=0.6 vs. placebo 0.1, SD=0.6).

Freedom from disease activity

GATE 2015[218] was the only study that reported combined clinical-MRI findings for freedom from disease activity. Proportions were slightly greater in patients receiving GA 20 mg SC once daily (9.2% vs. 7.1%), with similar findings once proportions were adjusted for stratification variables (8.5% vs. 6.6%). A formal significance test was not presented.

MS symptoms and health-related quality of life

CONFIRM 2012[214] presented data for health-related quality of life disaggregated by subscale of the SF-36. Compared to placebo, which showed a negative trend, change from baseline in the GA 20 mg SC once daily group was positive and the two groups were significantly different on the physical component summary (p=0.0259). However, the groups were not significantly different on the mental component summary. GA 20 mg SC once daily significantly improved (p<0.05) over placebo in physical functioning (0.3 vs. -2.2), bodily pain (2.3 vs. -1.3), and general health (1.9 vs. -0.6), but not physical (0.3 vs. -2.2) or emotional (1.4 vs. -3.3) aspects of role limitation, vitality (1.1 vs. 0.4), social functioning (-0.6 vs. -0.1), or mental health (0.3 vs. 0.6). Changes in EQ-5D scores were not presented, but were stated to be stable in all groups over the course of the study. As compared to placebo, patients receiving GA 20 mg SC once daily were not more likely to have been

stable or improved in either the physical component (OR=1.24, 95% CI [0.83, 1.85]) or the mental component (1.22, [0.82, 1.83]) of the SF-36.

At two years in Cop1 MSSG 1995,[215] the mean ambulation index scores were not different between patients receiving GA 20 mg SC once daily (0.27) and patients receiving placebo (0.28).

Adverse events and mortality

We stratified comparisons by type of placebo. All studies reported AEs, but only GALA 2013,[219] GATE 2015[218] and CONFIRM 2012[214] reported deaths. Only one death occurred, in the placebo arm of GALA 2013,[219] in studies with matched placebos; in CONFIRM 2012,[214] one death occurred in each arm. Full results are available on request.

Summary of the narrative synthesis: GA 20 mg SC once daily and 40 mg SC three times a week (Copaxone) vs. placebo

Taken together, findings from the five trials testing GA 20 mg SC once daily and the one trial testing GA 40 mg SC three times a week suggested a beneficial effect on relapse outcomes. Both studies (GA 20 mg: EGCASG 2001;[217] GA 40 mg: GALA 2013[219]) reporting relapse severity outcomes also found an effect of the study drug on decreasing the rate of steroid-treated relapses. Findings for disability progression were less convincing, and studies generally did not present significant results. Only one study presented combined clinical-MRI measures of freedom from disease activity, and this study did not show a large difference between groups, though significance testing was not undertaken. One study showed some effects of GA 20 mg SC once daily on health-related quality of life measures. Groups were not significantly different on mortality.

9.5.12 Meta-analyses: relapse rate

Pairwise meta-analyses

Direct evidence from comparisons against placebo is shown in Figure 6. All drugs had a statistically significant beneficial effect on relapse rate as compared to placebo. Findings for IFN β-1a pegylated SC 125 µg every two weeks, for GA 40 mg SC thrice weekly and for IFN β-1a 22 µg SC thrice weekly all relied on one study. Comparisons that relied on multiple studies were diverse in heterogeneity. Heterogeneity ranged from I^2 of 0% (IFN β-1b 250 µg SC every other day, IFN β-1a 30 µg IM once a week) to I^2 of 43% (IFN β-1a 44 µg SC thrice weekly) and 73% (GA 20 mg SC once daily). However, there were too few studies in each comparison to enable exploration of heterogeneity.

Direct evidence from comparisons between active drugs is shown in Figure 7. None of the pooled comparisons showed evidence of a statistically significant effect favouring one drug over another. Though several analyses had high I^2, each comparison had too few studies to permit exploration of heterogeneity.

Network meta-analyses

The set of studies reporting ratios of relapse rates formed a connected network (Figure 8). In the network, all drugs were compared against placebo, but GA 40 mg thrice weekly and IFN β-1a pegylated SC 125 µg every

two weeks were not compared against other active drugs in the network. IFN β-1a 22 μg SC thrice weekly was connected to the network because of its inclusion in PRISMS 1998,[187] which also the 44 μg dose.

Random effects network meta-analysis generated estimates of each drug against placebo and against every other drug (see Table 7). Ranking of the drugs suggested that the drug with the highest cumulative probability SUCRA (surface under the cumulative ranking curve) of being the best was GA 20 mg SC once daily, followed by IFN β-1a pegylated SC 125 μg every two weeks and GA 40 mg thrice weekly, with IFN β-1a 30 μg IM once a week ranked second to last and placebo ranked last.

Findings derived from the network meta-analysis for comparisons between each drug and placebo substantially mirrored those of the pairwise comparisons, and reflected statistically significant reductions in relapse rates in patients receiving active drugs. Pairwise comparisons between drugs mostly revealed little evidence of superiority of one drug over another, though GA 20 mg SC once daily (RR=0.82, 95% CI [0.73, 0.93]), IFN β-1a 44 μg SC thrice weekly (0.85, [0.76, 0.95]) and IFN β-1b 250 μg SC every other day (0.86, [0.76, 0.97]) all produced significant reductions in relapse rate as compared to IFN β-1a 30 μg IM once a week. These pairwise comparisons from the network meta-analysis, which all included direct (i.e., head-to-head) evidence, were similar in magnitude of effect to findings from the pairwise meta-analyses, but may have benefited from a 'stabilised' heterogeneity parameter due to the assumption of equal between-studies variance.

Tests of inconsistency in the network did not suggest that direct and indirect evidence were in disagreement. A Wald test for overall inconsistency derived from a design-by-treatment interaction model was not statistically significant (p=0.38), and comparisons between the direct and indirect evidence derived from the side-splitting model did not show any statistically significant differences.

Figure 6: Pairwise meta-analyses: ARR for active vs. placebo trials in RRMS

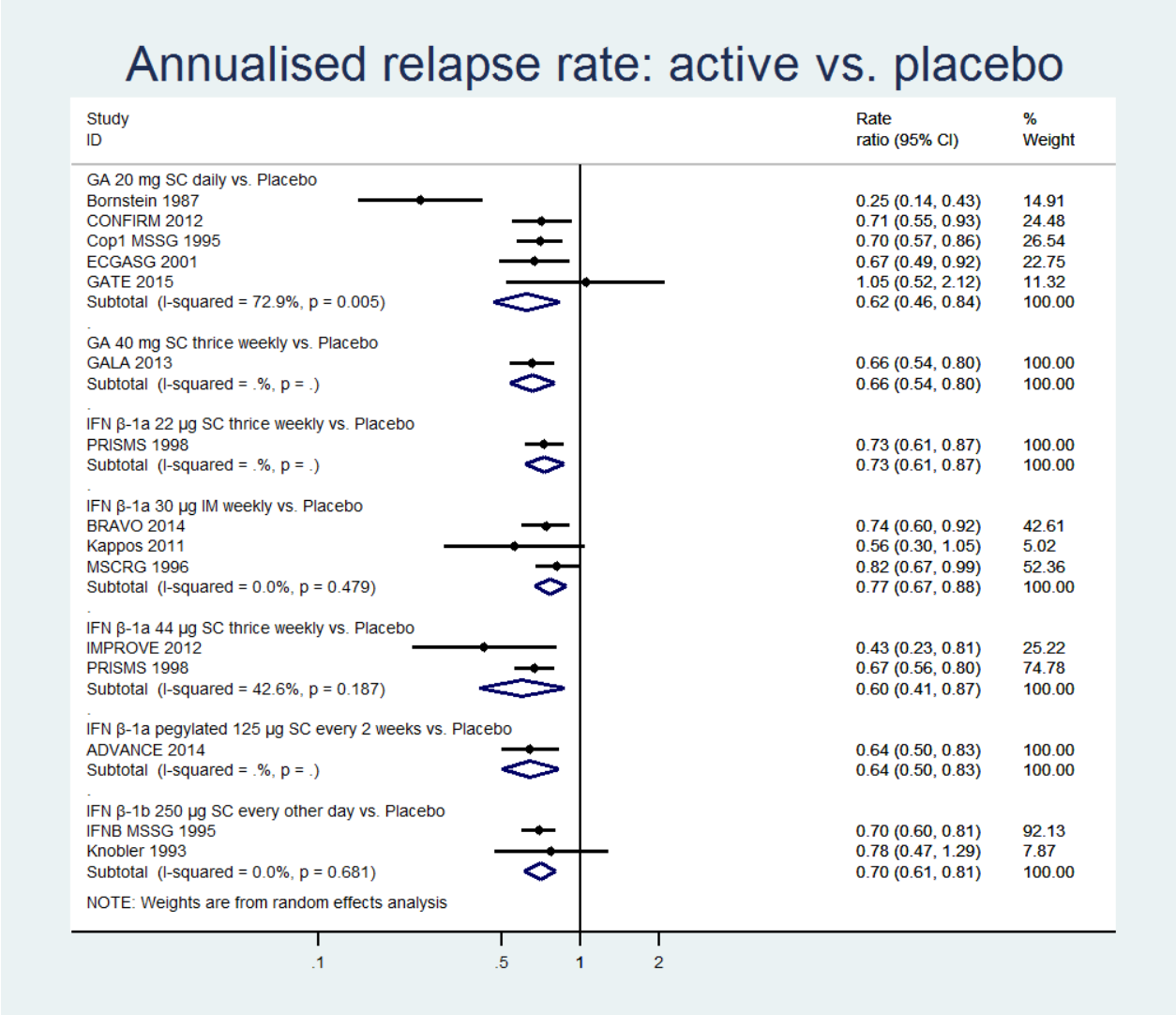


Figure 7: Pairwise meta-analyses: ARR for active vs. placebo trials in RRMS

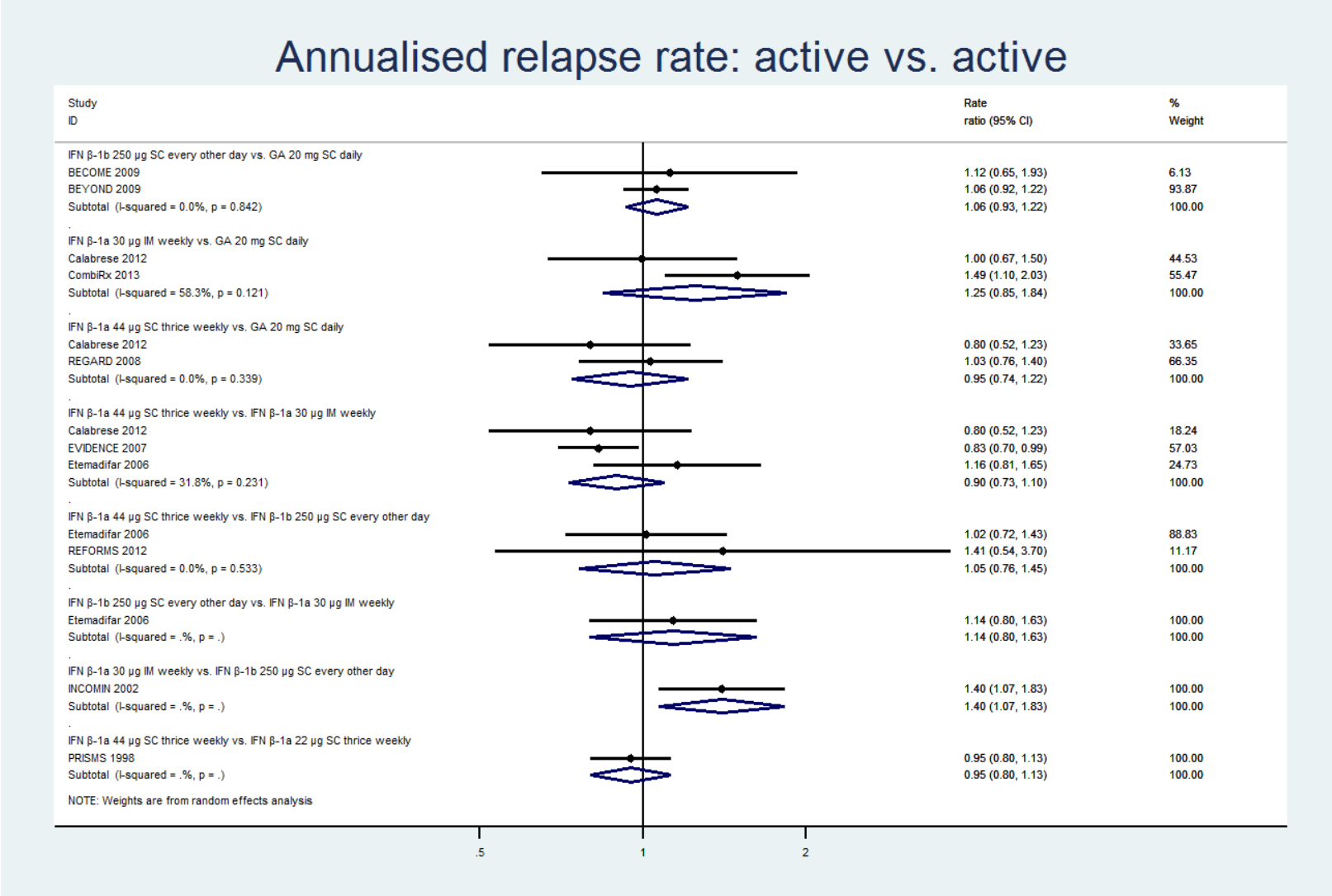


Figure 8: Network of studies, ARR in RRMS

ifn1a30: IFN β-1a 30 µg IM once a week; ifn1a44: IFN β-1a 44 µg SC three times weekly; ifn1a22: IFN β-1a 22 µg SC three times weekly; ifn1b250: IFN β-1b 250 µg SC every other day; peg: IFN β-1a pegylated 125 µg SC every two weeks; ga20: GA 20 mg SC once daily; ga40: GA 40 mg SC thrice weekly; plac: placebo

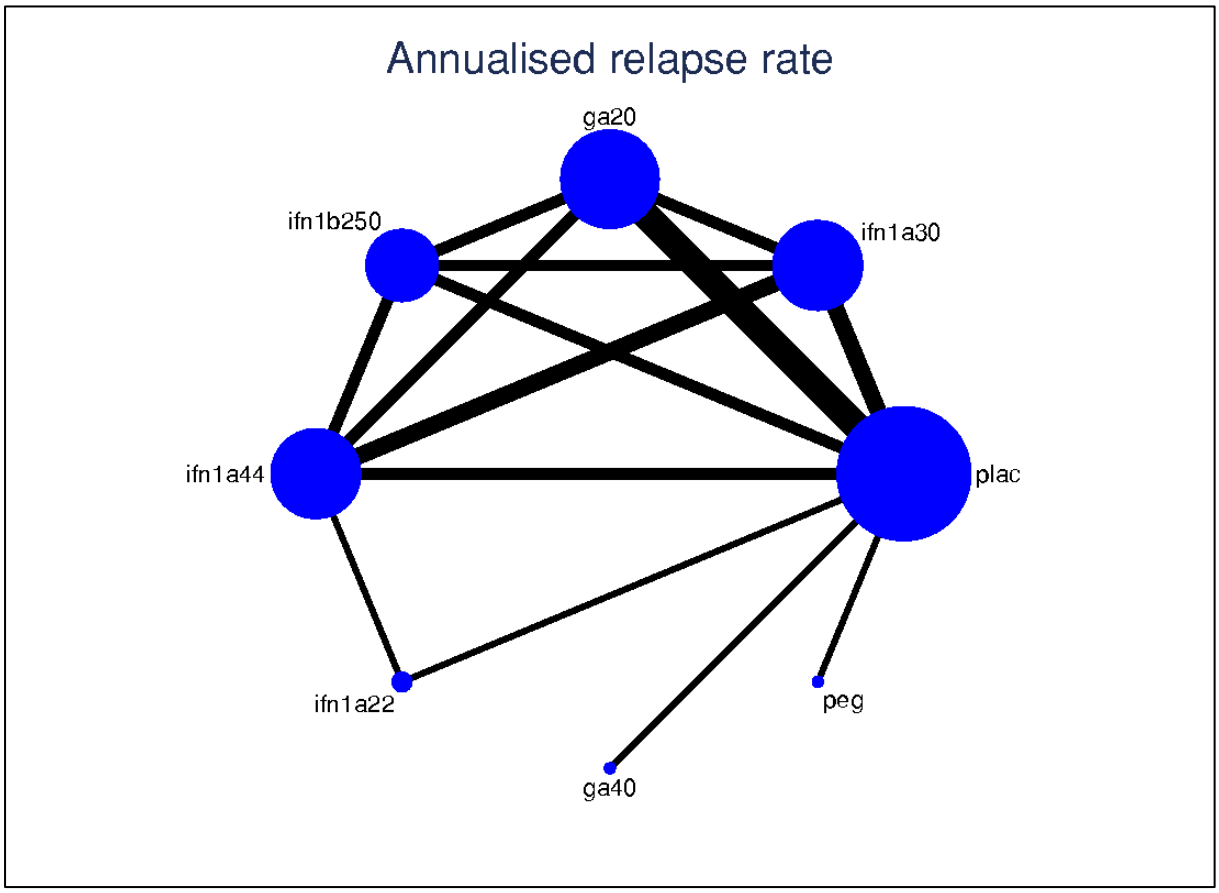


Table 7: Network meta-analysis: annualised relapse rates in RRMS

Findings are expressed as rate ratio (RR) with 95% CI.

Drug	SUCRA	GA 20 mg daily	IFN β-1a pegylated 125 µg every 2 weeks	GA 40 mg thrice weekly	IFN β-1a 44 µg SC thrice weekly	IFN β-1b 250 µg SC every other day	IFN β-1a 22 µg SC thrice weekly	IFN β-1a 30 µg IM weekly	Placebo
GA 20 mg daily	0.77		1.01 (0.77, 1.33)	1.00 (0.80, 1.24)	0.97 (0.85, 1.10)	0.95 (0.86, 1.05)	0.91 (0.76, 1.08)	0.82 (0.73, 0.92)	0.65 (0.59, 0.72)
IFN β-1a pegylated 125 µg every 2 weeks	0.73			0.98 (0.71, 1.35)	0.95 (0.72, 1.26)	0.94 (0.71, 1.23)	0.89 (0.66, 1.21)	0.81 (0.62, 1.06)	0.64 (0.50, 0.83)
GA 40 mg thrice weekly	0.70				0.97 (0.77, 1.22)	0.96 (0.77, 1.19)	0.91 (0.71, 1.17)	0.82 (0.66, 1.03)	0.66 (0.54, 0.80)
IFN β-1a 44 µg SC thrice weekly	0.64					0.99 (0.86, 1.13)	0.94 (0.80, 1.10)	0.85 (0.76, 0.95)	0.68 (0.60, 0.76)
IFN β-1b 250 µg SC every other day	0.56						0.95 (0.79, 1.14)	0.86 (0.76, 0.97)	0.69 (0.62, 0.76)
IFN β-1a 22 µg SC thrice weekly	0.43							0.91 (0.76, 1.08)	0.72 (0.61, 0.85)
IFN β-1a 30 µg IM weekly	0.18								0.80 (0.72, 0.88)
Placebo	0								
Wald test for inconsistency (χ^2, df, p)	11.71, 11, 0.38								

Table 8: Network meta-analysis: annualised relapse rates in RRMS, excluding Bornstein 1987[168]

Findings are expressed as rate ratio (RR) with 95% CI.

Drug	SUCRA	IFN β-1a pegylated 125 µg every 2 weeks	Glatiramer 40 mg thrice weekly	Glatiramer 20 mg daily	IFN β-1a 44 µg SC thrice weekly	IFN β-1b 250 µg SC every other day	IFN β-1a 22 µg SC thrice weekly	IFN β-1a 30 µg IM weekly	Placebo
IFN β-1a pegylated 125 µg every 2 weeks	0.76		0.98 (0.71, 1.35)	0.95 (0.73, 1.25)	0.94 (0.71, 1.24)	0.92 (0.70, 1.21)	0.89 (0.66, 1.20)	0.80 (0.61, 1.05)	0.64 (0.50, 0.83)
Glatiramer 40 mg thrice weekly	0.73			0.97 (0.78, 1.21)	0.96 (0.77, 1.20)	0.94 (0.75, 1.17)	0.91 (0.70, 1.17)	0.82 (0.65, 1.02)	0.66 (0.54, 0.80)
Glatiramer 20 mg daily	0.69				0.99 (0.87, 1.12)	0.98 (0.86, 1.12)	0.93 (0.78, 1.12)	0.84 (0.74, 0.95)	0.68 (0.61, 0.75)
IFN β-1a 44 µg SC thrice weekly	0.65					0.98 (0.86, 1.12)	0.94 (0.80, 1.11)	0.85 (0.76, 0.95)	0.68 (0.61, 0.76)
IFN β-1b 250 µg SC every other day	0.55						0.96 (0.80, 1.15)	0.87 (0.77, 0.98)	0.70 (0.63, 0.77)
IFN β-1a 22 µg SC thrice weekly	0.45							0.90 (0.76, 1.07)	0.72 (0.62, 0.85)
IFN β-1a 30 µg IM weekly	0.17								0.80 (0.73, 0.89)
Placebo	0.00								
Wald test for inconsistency (χ2, df, p)	12.59, 11, 0.32								

Sensitivity analyses

Several characteristics of the trials included in this network suggested that additional analyses would confirm the robustness of our findings. All of these analyses were post hoc. First, we excluded REFORMS 2012[195] from the analysis, as it was the only study were relapses were self-reported by subjects instead of documented by an examining neurologist. Effect estimates remained essentially unchanged for all pairwise comparisons.

Second, we compared findings for studies with 'true', blinded placebos against studies that did not have blinded placebos. That is, several studies did not deliver placebos via the same route of administration. Specifically, BRAVO 2014,[196] CONFIRM 2012[214] and Kappos 2011[197] did not administer placebo via the same route as the relevant IFN or GA arm in each trial. We found that effects for these drugs against placebo were robust to inclusion of a covariate in the model for trials without a blinded placebo.

Third, we noticed that Bornstein 1987[168] was an outlier in the comparison between GA 20 mg SC once daily and placebo. When we excluded this trial from the pairwise meta-analysis, the pooled rate ratio for relapses still suggested a reduction in ARR as compared to placebo (RR=0.71, 95% CI [0.62, 0.82]), with I^2 of 0%. Re-estimation of the network meta-analysis yielded a change in the SUCRA-based rankings, with GA 20 mg SC once daily now ranked third, but point estimates and confidence intervals were not substantially different in the new model (see Table 8).

9.5.13 Meta-analyses: relapse severity, moderate and severe relapses

Pairwise meta-analyses

Direct evidence from pairwise comparisons is shown in Figure 9. Each comparison was informed by one study. All drugs compared against placebo had a statistically significant beneficial effect in reducing the rate of moderate or severe relapses. In comparisons based on active drugs, there was no evidence that one dose of IFN β-1a SC thrice weekly was statistically better than the other (44 μg vs 22 μg), nor that IFN β-1b 250 μg SC every other day was different from GA 20 mg SC once daily. GA 40 mg thrice weekly, IFN β-1a 30 μg IM once a week and IFN β-1a pegylated SC 125 μg every two weeks were not represented in this analysis.

Network meta-analyses

The set of studies reporting ratios of relapse rates for moderate and severe relapses formed a connected network (Figure 10). In the network, direct evidence for GA 20 mg SC once daily was only against another active drug, IFN β-1b 250 μg SC every other day.

Because of the shape of the network, in which there was no opportunity for inconsistency and in which no direct comparison was informed by more than one trial, the model was estimated using fixed effects instead of random effects as in the protocol. Ranking of drugs suggested that GA 20 mg SC once daily was best, followed by IFN β-1b 250 μg SC every other day, IFN β-1a SC thrice weekly (44 μg and 22 μg), and placebo ranked last (see Table 9).

Figure 9: Pairwise estimates: ARR for moderate or severe relapses in RRMS

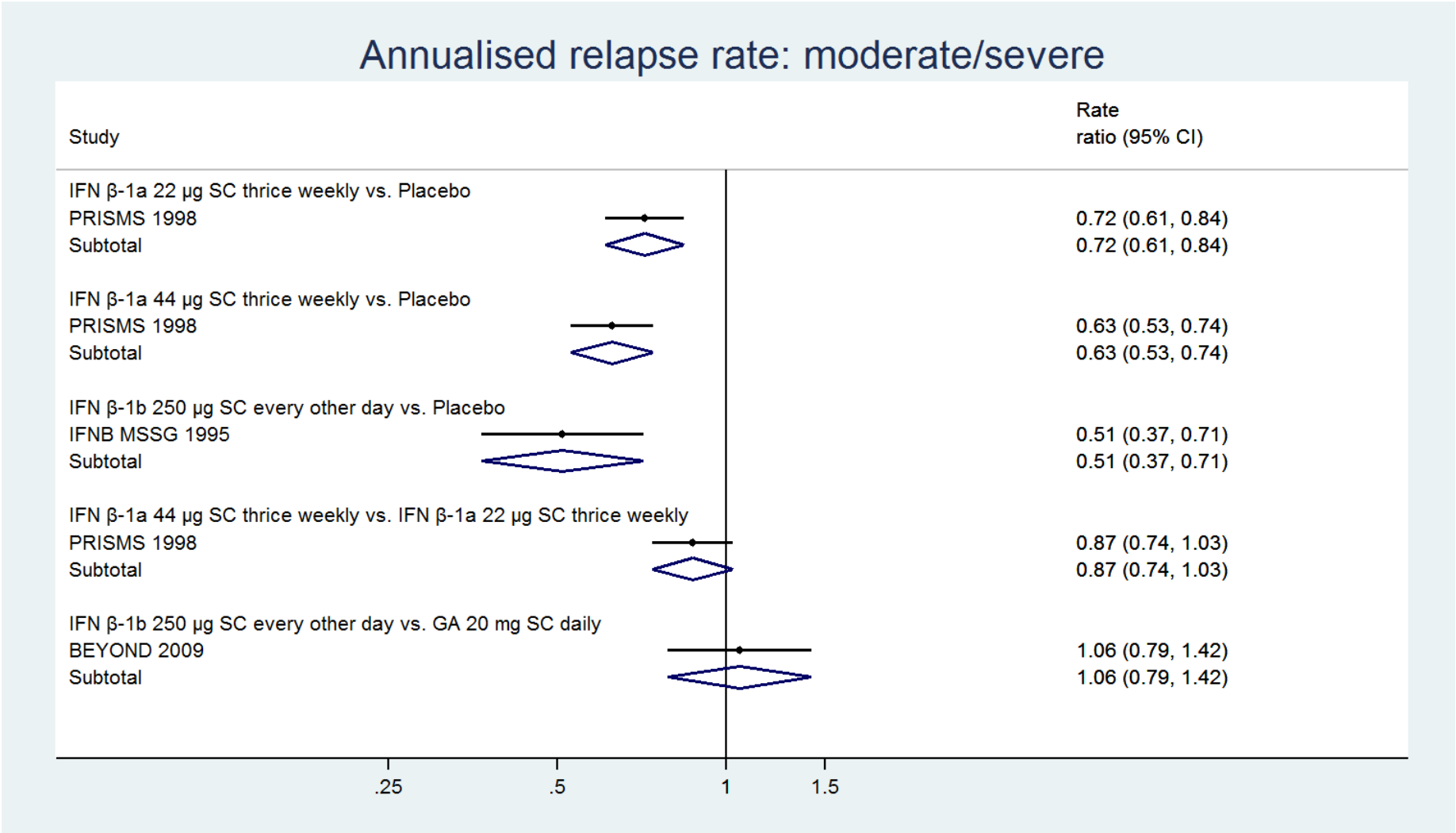


Figure 10: Network of studies, ARR for moderate or severe relapses in RRMS

ifn1a44: IFN β-1a 44 µg SC three times weekly; ifn1a22: IFN β-1a 22 µg SC three times weekly; ifn1b250: IFN β-1b 250 µg SC every other day; ga20: GA 20 mg SC once daily; plac: placebo

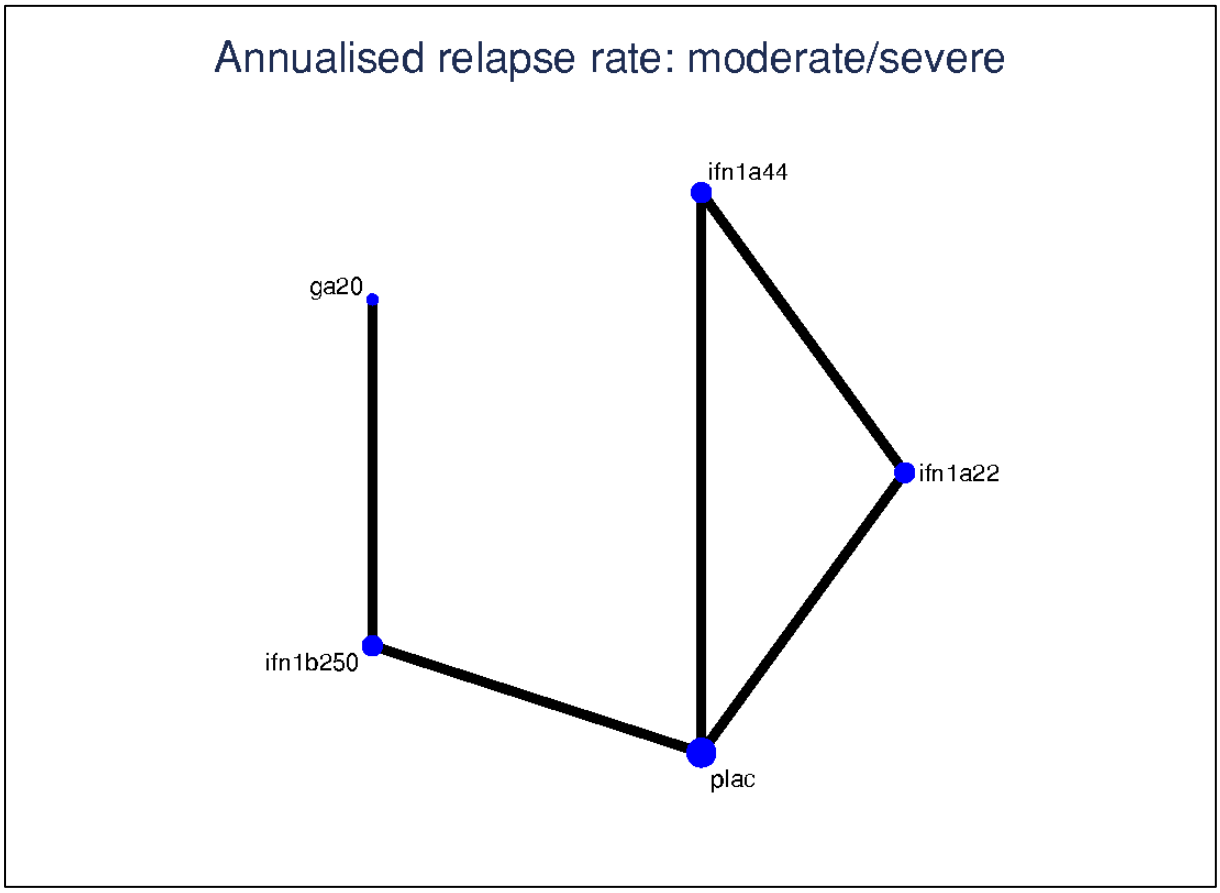


Table 9: Network meta-analysis: annualised relapse rate, moderate/severe relapses in RRMS

Findings are expressed as RR (95% CI)

Drug	SUCRA	GA 20 mg daily	IFN β-1b 250 µg SC every other day	IFN β-1a 44 µg SC thrice weekly	IFN β-1a 22 µg SC thrice weekly	Placebo
GA 20 mg daily	0.85		0.95 (0.70, 1.27)	0.77 (0.48, 1.24)	0.68 (0.42, 1.08)	0.48 (0.31, 0.76)
IFN β-1b 250 µg SC every other day	0.80			0.82 (0.56, 1.19)	0.71 (0.49, 1.03)	0.51 (0.37, 0.71)
IFN β-1a 44 µg SC thrice weekly	0.57				0.87 (0.74, 1.03)	0.63 (0.53, 0.74)
IFN β-1a 22 µg SC thrice weekly	0.28					0.72 (0.61, 0.84)
Placebo	0.00					

Findings derived from the network meta-analysis for comparisons between each drug and placebo were similar to comparisons against placebo from the direct evidence, as would be expected. In an indirect comparison, GA 20 mg SC once daily reduced the rate of moderate and severe relapses as compared to placebo (RR=0.48, 95% CI [0.31, 0.76]). Pairwise comparisons between active drugs did not yield evidence of superiority of any one drug over another.

Because there was not the possibility for inconsistency in the network, we did not test for it.

9.5.14 Meta-analyses: relapse severity, steroid-treated relapses

Pairwise meta-analysis

Direct evidence from comparisons against placebo is shown in Figure 11. Each comparison was informed by one study. All drugs that were compared against placebo showed a significant effect in reducing the rate of steroid-treated relapses. In head-to-head comparisons between active drugs, IFN β-1a 44 µg SC thrice weekly produced a greater reduction in steroid-treated relapses than the 22 µg dose of the same drug (RR=0.77, 95% CI [0.67, 0.89]) and as compared to IFN β-1a 30 µg IM once a week (0.68, [0.51, 0.91]). Pairwise comparisons between IFN β-1a 30 µg IM once a week and IFN β-1b 250 µg SC every other day, and between IFN β-1a 44 µg SC thrice weekly and GA 20 mg SC once daily, did not show statistical evidence of superiority. IFN β-1a pegylated SC 125 µg every two weeks was not included in this analysis.

Network meta-analyses

The set of studies reporting ratios of steroid-treated relapse rates formed a connected network (Figure 12). In the network, each comparison was informed by one study, but there were closed loops between studies, suggesting the possibility of inconsistency. Because in this parametrisation of the model inconsistency is regarded as a source of heterogeneity—even though there is no potential for heterogeneity in any of the comparisons informed by direct evidence—we estimated the model as both a fixed effects and a random effects model.

Numerical estimates of intervention effectiveness were not meaningfully different between the random and fixed effects models (see Table 10). However, the random effects model did not support that IFN β-1b 250 µg SC every other day significantly reduces the rate of steroid-treated relapses (fixed effects RR=0.62, 95% CI [0.40, 0.98]; random effects 0.64, [0.36, 1.14]). The random effects model also did not support the superiority

of any one drug against another, except for IFN β-1a 44 μg SC thrice weekly over IFN β-1a 30 μg IM once a week (0.68, [0.48, 0.97]). However, in the fixed effects model, IFN β-1a 44 μg SC thrice weekly improved over both IFN β-1a 30 μg IM once a week (0.68, [0.51, 0.91]) and IFN β-1a 22 μg SC thrice weekly (0.79, [0.68, 0.91]), both of which were comparisons informed by direct evidence. GA 20 mg SC once daily also improved over both IFN β-1a 30 μg IM once a week (0.67, [0.47, 0.95]) and IFN β-1a 22 μg SC thrice weekly (0.77, [0.61, 0.98]), though neither comparison was informed by direct evidence.

Because the overall Wald test of inconsistency did not provide evidence of a difference between direct and indirect evidence (p=0.20), the fixed effects model may be preferable.

Figure 11: Pairwise estimates: ARR for steroid-treated relapses in RRMS

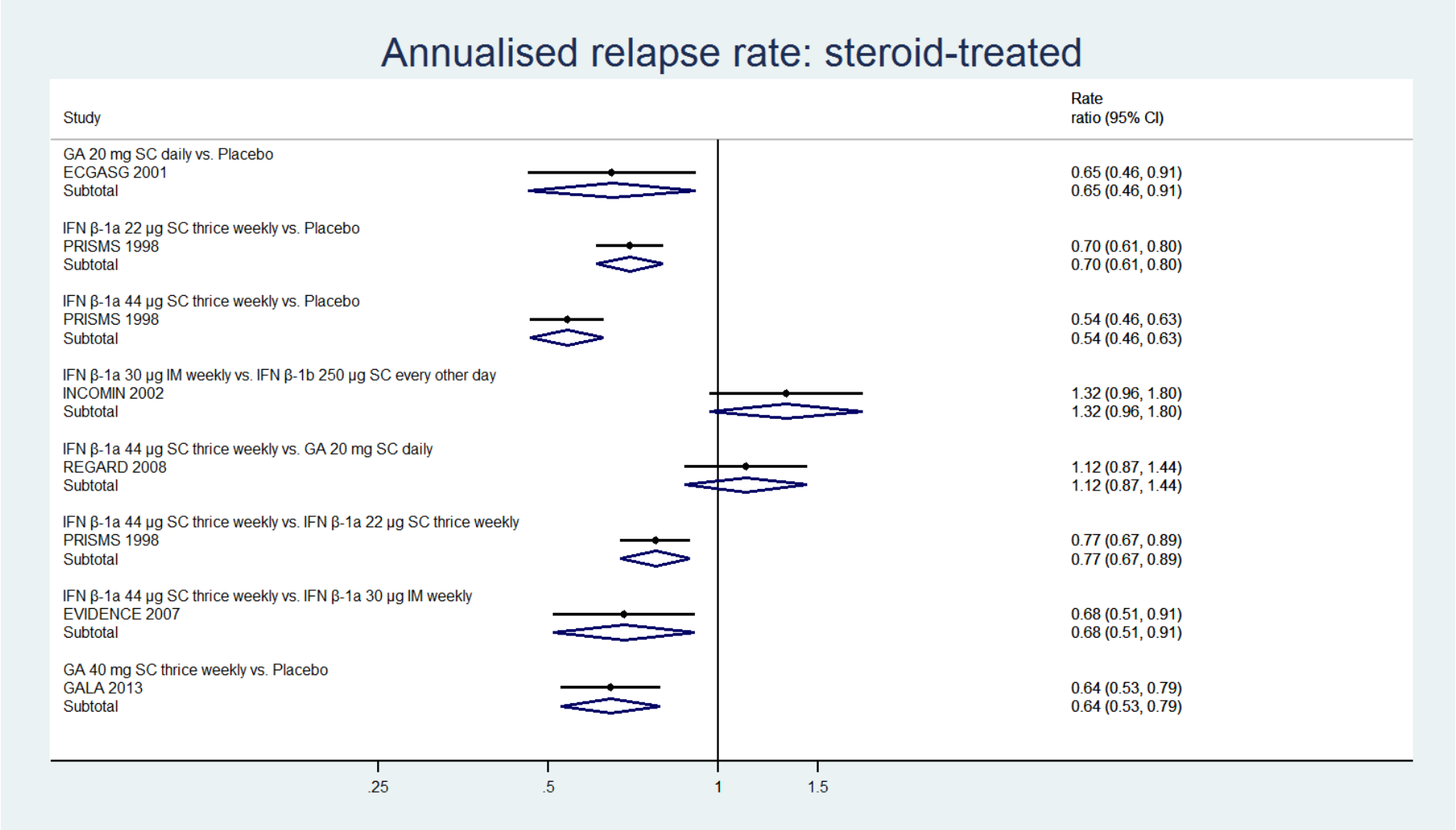


Figure 12: Network of studies, ARR for steroid-treated relapses in RRMS

ifn1a30: IFN β-1a 30 µg IM once a week; ifn1a44: IFN β-1a 44 µg SC three times weekly; ifn1a22: IFN β-1a 22 µg SC three times weekly; ifn1b250: IFN β-1b 250 µg SC every other day; ga20: GA 20 mg SC once daily; ga40: GA 40 mg SC thrice weekly; plac: placebo

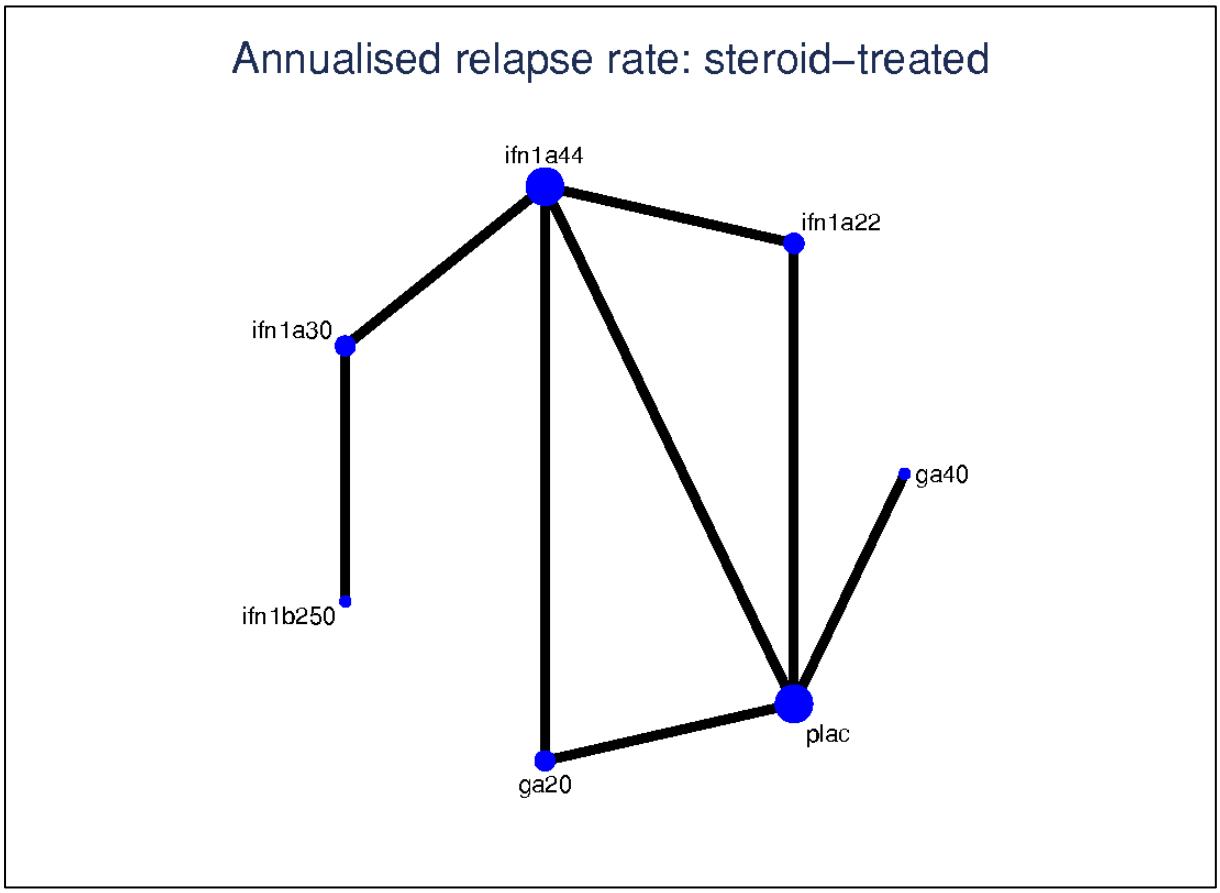


Table 10: Network meta-analysis: annualised relapse rate, steroid-treated relapses in RRMS

Findings are expressed as RR (95% CI)

Drug	**Fixed effects model**							
	SUCRA	**Glatiramer 20 mg daily**	**IFN β-1a 44 µg SC thrice weekly**	**IFN β-1b 250 µg SC every other day**	**Glatiramer 40 mg thrice weekly**	**IFN β-1a 22 µg SC thrice weekly**	**IFN β-1a 30 µg IM weekly**	**Placebo**
GA 20 mg daily	0.85		0.98 (0.80, 1.21)	0.88 (0.55, 1.41)	0.85 (0.63, 1.15)	0.77 (0.61, 0.98)	0.67 (0.47, 0.95)	0.55 (0.44, 0.68)
IFN β-1a 44 µg SC thrice weekly	0.83			0.89 (0.58, 1.37)	0.87 (0.68, 1.11)	0.79 (0.68, 0.91)	0.68 (0.51, 0.91)	0.56 (0.48, 0.64)
IFN β-1b 250 µg SC every other day	0.64				0.97 (0.59, 1.58)	0.88 (0.56, 1.38)	0.76 (0.56, 1.04)	0.62 (0.40, 0.98)
GA 40 mg thrice weekly	0.56					0.91 (0.71, 1.16)	0.79 (0.54, 1.15)	0.64 (0.53, 0.79)
IFN β-1a 22 µg SC thrice weekly	0.40						0.86 (0.63, 1.19)	0.71 (0.62, 0.81)
IFN β-1a 30 µg IM weekly	0.20							0.82 (0.59, 1.13)
Placebo	0.02							
Wald test for inconsistency (χ^2, df, p)	1.65, 1, 0.20							
Drug	**Random effects model**							
	SUCRA	**GA 20 mg daily**	**IFN β-1a 44 µg SC thrice weekly**	**IFN β-1b 250 µg SC every other day**	**GA 40 mg thrice weekly**	**IFN β-1a 22 µg SC thrice weekly**	**IFN β-1a 30 µg IM weekly**	**Placebo**
GA 20 mg daily	0.82		0.98 (0.75, 1.29)	0.88 (0.49, 1.58)	0.87 (0.57, 1.34)	0.78 (0.56, 1.10)	0.67 (0.43, 1.05)	0.56 (0.41, 0.77)
IFN β-1a 44 µg SC thrice weekly	0.81			0.89 (0.53, 1.50)	0.89 (0.60, 1.31)	0.80 (0.62, 1.03)	0.68 (0.48, 0.97)	0.57 (0.44, 0.74)
IFN β-1b 250 µg SC every other day	0.64				0.99 (0.52, 1.90)	0.89 (0.50, 1.58)	0.76 (0.52, 1.11)	0.64 (0.36, 1.14)
GA 40 mg thrice weekly	0.59					0.90 (0.61, 1.32)	0.67 (0.43, 1.05)	0.64 (0.48, 0.86)
IFN β-1a 22 µg SC thrice weekly	0.44						0.85 (0.55, 1.32)	0.72 (0.56, 0.92)
IFN β-1a 30 µg IM weekly	0.23							0.84 (0.54, 1.30)
Placebo	0.06							
Wald test for inconsistency (χ2, df, p)	1.63, 1, 0.20							

9.5.15 Meta-analyses: time to disability progression confirmed at three months

Pairwise meta-analyses

Direct evidence from comparisons is shown in Figure 13. Only one comparison, IFN β-1a 44 μg SC thrice weekly vs. placebo, included more than one study. GA 40 mg thrice weekly was not represented in this analysis.

Comparison of drugs against placebo showed a mixed pattern of results. GA 20 mg SC once daily (HR=0.79, 95% CI [0.60, 1.05]), IFN β-1a 30 μg IM once a week (0.74, [0.51, 1.08]), and IFN β-1b 250 μg SC every other day (0.71, [0.48, 1.06]) did not show evidence of delaying disability progression. However, IFN β-1a in both doses—44 μg SC thrice weekly (0.62, [0.43, 0.90]) and 22 μg SC thrice weekly (0.68, [0.48, 0.97])—and IFN β-1a pegylated SC 125 μg every two weeks (0.62, [0.40, 0.97]) did show evidence of delaying disability progression. None of the three direct comparisons between active drugs suggested a benefit of one over another.

Network meta-analyses

The set of studies reporting hazard ratios for time to disability progression confirmed at three months formed a connected network (see Figure 14). In the network, all active drugs were compared against placebo, and three comparisons between active drugs were present as well.

The network meta-analysis, which was estimated with random effects per the protocol, generated estimates of each drug against placebo and against every other drug (see Table 11). Ranking of the drugs suggested that the drug with the highest cumulative probability of being the best was IFN β-1a 44 μg SC thrice weekly, followed by IFN β-1a pegylated SC 125 μg every two weeks and IFN β-1a 22 μg SC thrice weekly, with IFN β-1b 250 μg SC every other day ranked second to last and placebo ranked last.

Comparisons for active drugs vs. placebo were similar between the network meta-analysis and the pairwise meta-analyses. Notably, additional information from indirect comparisons yielded a more precise estimate of effectiveness for both IFN β-1a 30 μg IM once a week vs placebo (HR=0.73, 95% CI [0.53, 1.00], p=0.0499) and GA 20 mg SC once daily (0.76, [0.60, 0.97]). Comparisons between active drugs estimated from the network meta-analysis did not indicate than any one drug was statistically better than the others, as all pairwise comparisons were not statistically significant.

Tests of inconsistency in the network did not suggest that direct and indirect evidence were in disagreement. An overall Wald test derived from a design-by-treatment interaction model returned a non-significant results (p=0.84), and comparisons between the direct and indirect evidence derived from the side-splitting model did not show any statistically significant differences.

Figure 13: Pairwise meta-analyses: time to disability progression confirmed at 3 months in RRMS

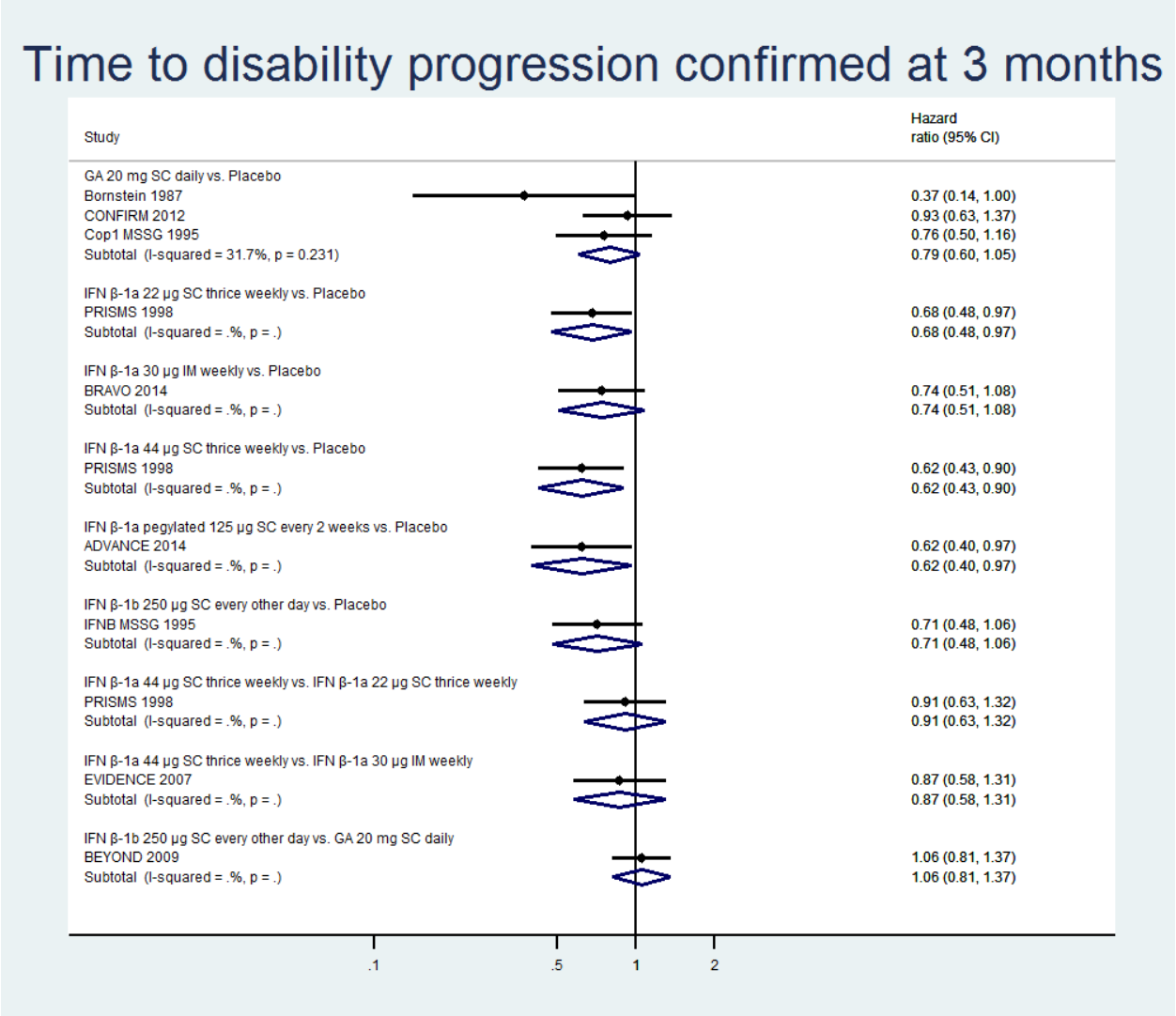


Figure 14: Network of studies, time to disability progression confirmed at 3 months in RRMS

ifn1a30: IFN β-1a 30 µg IM once a week; ifn1a44: IFN β-1a 44 µg SC three times weekly; ifn1a22: IFN β-1a 22 µg SC three times weekly; ifn1b250: IFN β-1b 250 µg SC every other day; peg: IFN β-1a pegylated 125 µg SC every two weeks; ga20: GA 20 mg SC once daily; plac: placebo

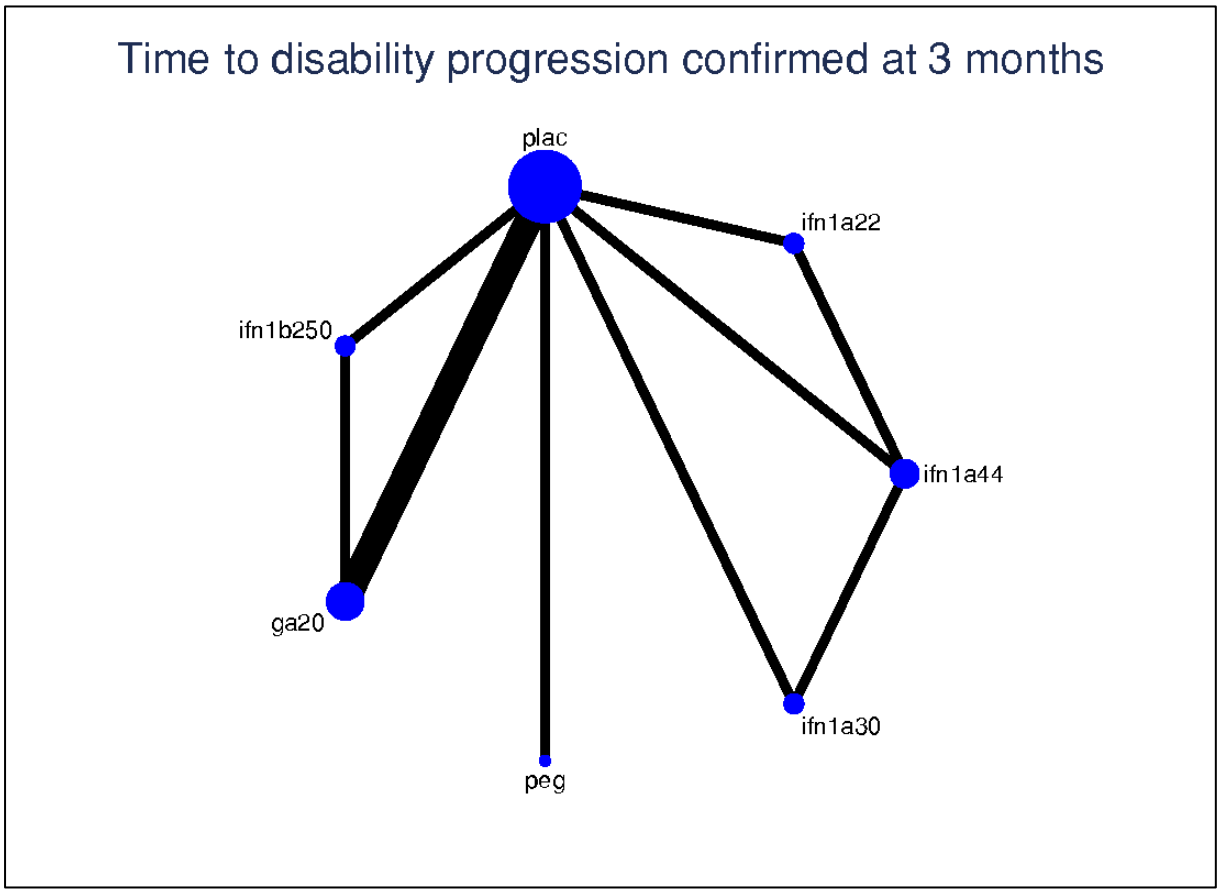


Table 11: Network meta-analysis: time to disability progression confirmed at 3 months in RRMS

Findings are labelled as HR (95% CI).

Drug	**SUCRA**	**IFN β-1a 44 µg SC thrice weekly**	**IFN β-1a pegylated 125 µg every 2 weeks**	**IFN β-1a 22 µg SC thrice weekly**	**IFN β-1a 30 µg IM weekly**	**GA 20 mg daily**	**IFN β-1b 250 µg SC every other day**	**Placebo**
IFN β-1a 44 µg SC thrice weekly	0.77		1.01 (0.59, 1.74)	0.92 (0.65, 1.30)	0.86 (0.62, 1.19)	0.82 (0.56, 1.22)	0.81 (0.53, 1.22)	0.63 (0.46, 0.86)
IFN β-1a pegylated 125 µg every 2 weeks	0.75			0.91 (0.52, 1.59)	0.85 (0.49, 1.46)	0.81 (0.49, 1.34)	0.80 (0.47, 1.34)	0.62 (0.40, 0.97)
IFN β-1a 22 µg SC thrice weekly	0.62				0.94 (0.62, 1.42)	0.90 (0.59, 1.36)	0.88 (0.57, 1.36)	0.68 (0.49, 0.96)
IFN β-1a 30 µg IM weekly	0.50					0.96 (0.65, 1.42)	0.94 (0.62, 1.43)	0.73 (0.53, 1.00)*
GA 20 mg daily	0.44						0.98 (0.78, 1.24)	0.76 (0.60, 0.97)
IFN β-1b 250 µg SC every other day	0.39							0.78 (0.59, 1.02)
Placebo	0.02							
Wald test for inconsistency (χ2, df, p)	0.35, 2, 0.84							

9.5.16 Meta-analyses: time to disability progression confirmed at six months

Pairwise meta-analyses

Direct evidence from comparisons is shown in Figure 15. All comparisons were based on a single study, except for IFN β-1a 30 μg IM once a week as compared to placebo. GA 40 mg thrice weekly was not represented in this analysis.

Three drugs were compared against placebo. GA 20 mg SC once daily did not delay confirmed disability progression as compared to placebo, but IFN β-1a 30 μg SC once weekly (HR=0.66, 95% CI [0.47, 0.92]) and IFN β-1a pegylated 125 μg every two weeks (0.46, [0.26, 0.81]) did. Of the three comparisons between active drugs, only IFN β-1a 30 μg IM once a week yielded a significant improvement, when compared to IFN β-1b 250 μg SC every other day.

Network meta-analysis

The set of studies reporting hazard ratios for time to disability progression confirmed at six months formed a connected network (see Figure 16). In the network, IFN β-1b 250 μg SC every other day and IFN β-1a 44 μg SC thrice weekly are not compared to placebo, but only to other active drugs.

The network meta-analysis, which was estimated with random effects per the protocol, generated estimates of each drug against placebo and against every other drug (see Table 12). Ranking of the drugs suggested that the drug with the highest cumulative probability of being the best was IFN β-1b 250 μg SC every other day, followed by IFN β-1a pegylated 125 μg every two weeks, IFN β-1a 44 μg SC thrice weekly and IFN β-1a 30 μg IM once a week. GA 20 mg SC once daily was ranked second to last and placebo was ranked last.

When compared against placebo in the network meta-analysis, GA 20 mg SC once daily had a similar estimate of effectiveness (HR=0.82, 95% CI [0.53, 1.26]) as compared to the direct evidence, as did IFN β-1a 30 μg IM once a week (0.68, [0.49, 0.94]) and IFN β-1a pegylated 125 μg every two weeks (0.46, [0.26, 0.81]). Both IFN β-1a 44 μg SC thrice weekly (0.47, [0.24, 0.93]) and IFN β-1b 250 μg SC every other day (0.34, [0.18, 0.63]) showed evidence of delaying disability progression as compared to placebo. However, both of these estimates are based solely on indirect evidence, and findings from INCOMIN 2002,[194] which informed the contrast between IFN β-1b 250 μg SC every other day and IFN β-1a 30 μg IM once a week, relied on a hazard ratio estimated from summary statistics.

Comparisons between active drugs estimated from the NMA suggested that IFN β-1b 250 μg SC every other day is superior both to IFN β-1a 30 μg IM once a week (HR=0.50, 95% CI [0.29, 0.87]) and to GA 20 mg SC once daily (0.41, [0.21, 0.83]). The comparison between IFN β-1b 250 μg SC every other day and GA 20 mg SC once daily in particular was greater in magnitude than direct evidence suggested. No other comparisons between active drugs yielded statistically significant evidence of superiority of one drug over others.

Tests of inconsistency in the network did not suggest that direct and indirect evidence disagreed to a statistically significant level; however, the network was sparse and only one comparison included more than one study. An overall Wald test of inconsistency returned a statistically non-significant result (p=0.38).

Figure 15: Pairwise meta-analyses: time to disability progression confirmed at 6 months in RRMS

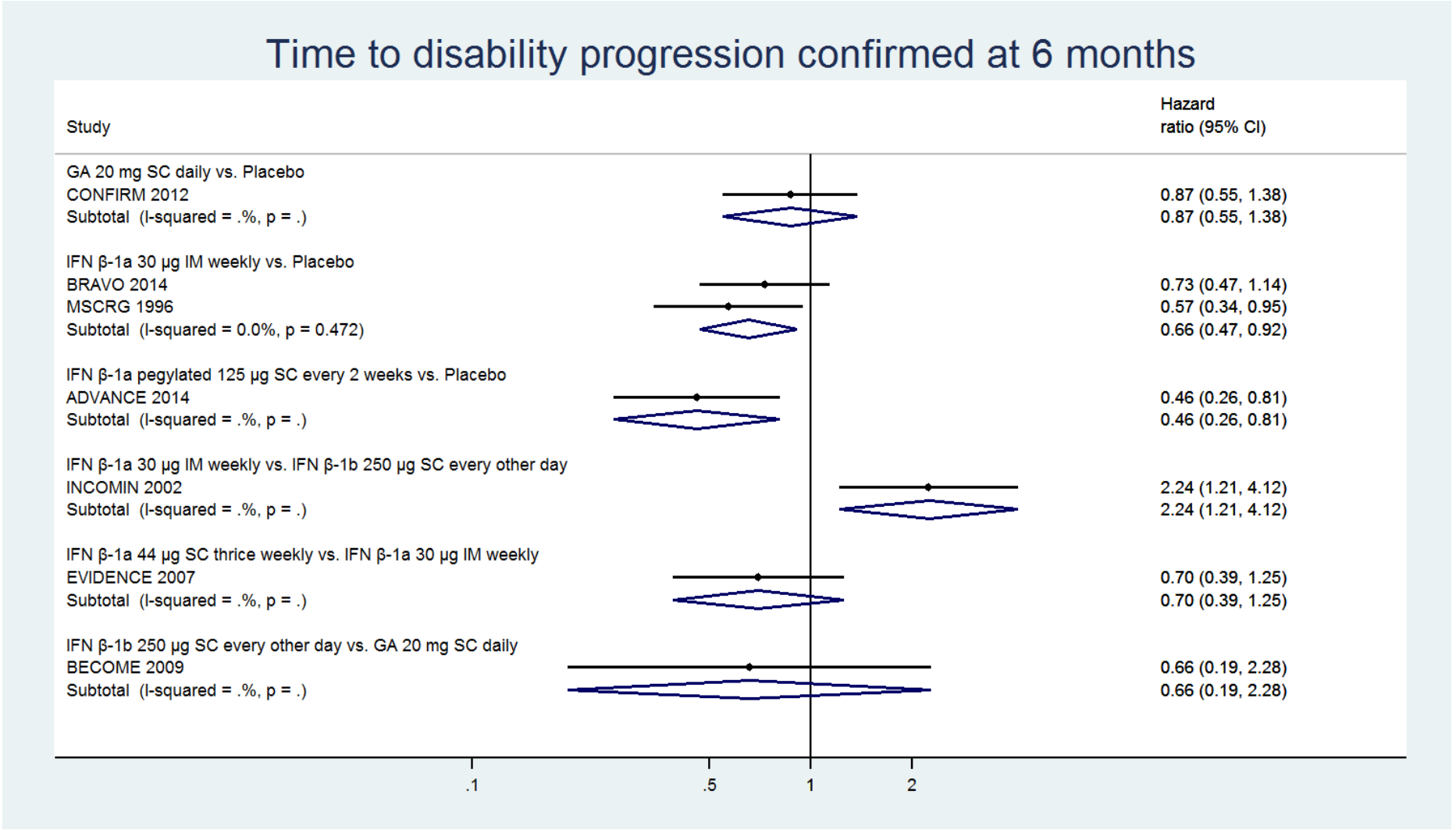


Figure 16: Network of studies, time to disability progression confirmed at 6 months in RRMS

ifn1a30: IFN β-1a 30 µg IM once a week; ifn1a44: IFN β-1a 44 µg SC three times weekly; ifn1b250: IFN β-1b 250 µg SC every other day; peg: IFN β-1a pegylated 125 µg SC every two weeks; ga20: GA 20 mg SC once daily; plac: placebo

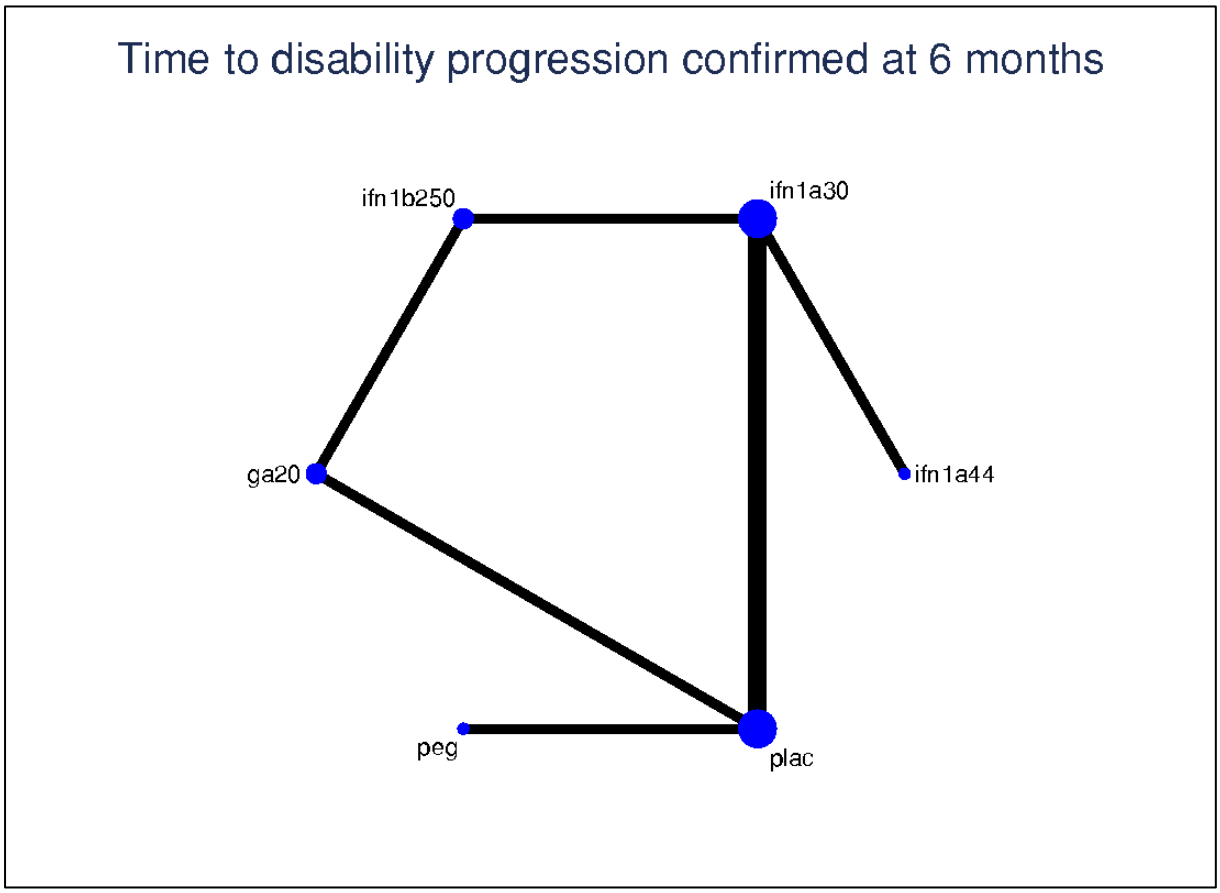


Table 12: Network meta-analysis: time to disability progression confirmed at 6 months in RRMS

Findings are presented as HR (95% CI).

Drug	**SUCRA**	**IFN β-1b 250 µg SC every other day**	**IFN β-1a pegylated 125 µg every 2 weeks**	**IFN β-1a 44 µg SC thrice weekly**	**IFN β-1a 30 µg IM weekly**	**Glatiramer 20 mg daily**	**Placebo**
IFN β-1b 250 µg SC every other day	0.90		0.74 (0.32, 1.71)	0.71 (0.32, 1.60)	0.50 (0.29, 0.87)	0.42 (0.21, 0.83)	0.34 (0.18, 0.63)
IFN β-1a pegylated 125 µg every 2 weeks	0.71			0.97 (0.40, 2.33)	0.68 (0.35, 1.31)	0.56 (0.28, 1.15)	0.46 (0.26, 0.81)
IFN β-1a 44 µg SC thrice weekly	0.70				0.70 (0.39, 1.25)	0.58 (0.27, 1.27)	0.47 (0.24, 0.93)
IFN β-1a 30 µg IM weekly	0.40					0.83 (0.49, 1.41)	0.68 (0.49, 0.94)
Glatiramer 20 mg daily	0.25						0.82 (0.53, 1.26)
Placebo	0.05						
Wald test for inconsistency (χ2, df, p)	1, 0.77, 0.38						

9.5.17 Meta-analyses: adverse events

Summary of adverse events meta-analyses

Full results for pairwise meta-analyses of AEs are available on request. Though the diversity and heterogeneity of AEs precludes detailed examination of each, several trends were apparent across pairwise comparisons.

- Comparing IFN β-1a 30µg (Avonex) vs. equivalent placebo, the IFN β-1a 30 µg was associated with more chills, flu-like symptoms, neutralising antibodies and myalgia.
- Comparing IFN β-1a 30µg (Avonex) vs. IFN β-1a 44 µg (Rebif), IFN β-1a 44 µg was associated with more injection site reactions, liver disorders, neutralising antibodies and white blood cell abnormalities, while the 30µg was associated with more fatigue.
- Comparing IFN β-1a 30µg (Avonex) vs. IFN β-1b (Betaferon/Extavia), the IFN β-1b was associated with more injection reactions and neutralising antibodies.
- Comparing IFN β-1a 30 µg (Avonex) vs. GA (Copaxone), there were no significant differences in AEs.
- Comparing IFN β-1a 44 µg (Rebif) vs. placebo, IFN β-1a 44 µg was associated with more injection reactions, flu-like illness, liver disorders, granulocytopenia, leucopenia, lymphopenia and neutralising antibodies
- Comparing IFN β-1a 44 µg (Rebif) vs. IFN β-1b (Betaferon/Extavia), the IFN β-1a 44 µg was associated with more ALT disorders and the IFNβ1b with more injection pain.
- Comparing IFN β-1a 44µg (Rebif) vs. GA (Copaxone), the IFN β-1a 44 µg was associated with more liver enzyme disorders, neutralising antibodies, headache, flu-like illness and myalgia, and the glatiramer with more injection reactions, immediate post-injection reactions and binding antibodies.
- Comparing IFN β-1b (Betaferon/Extavia) vs. placebo, IFN β-1b was associated with more injection site inflammation and neutralising antibodies.
- Comparing IFN β-1b (Betaferon/Extavia) vs. GA (Copaxone), IFN β-1b was associated with more flu-like symptoms, insomnia and disordered liver enzymes, and glatiramer with more injection site reactions, itching, pain, inflammation and induration, and immediate post-injection reactions.
- Comparing GA (Copaxone) vs. equivalent placebo, glatiramer was associated with more injection-site induration, itching, mass, erythema, pain, inflammation, and reactions, and more immediate post-injection systemic reactions.
- Comparing pegylated IFN β-1a (Plegridy) vs. placebo, pegylated IFN β-1a was associated with more injection-site erythema, pain, itching, chills and/or fever, headache, flu-like syndrome, myalgia, pyrexia, any AE possibly related to drug, patients who discontinued study due to AE and severe AE.

Discontinuation due to adverse events: modal follow-up

Pairwise meta-analyses

Pairwise meta-analyses for discontinuation due to AEs combined across studies at the modal follow-up are presented in Figure 17. The modal follow-up was approximately 24 months, and thus we included studies with intended follow-up around this point. We included 12 estimates in these meta-analyses. There was no visual

evidence of a systematic difference based on the strict definition of the outcome. In every pairwise meta-analysis, confidence intervals were wide, as would be expected. Three pooled estimates relied on multiple studies: GA 20 mg SC once daily vs. placebo, IFN β-1a 30 μg IM once a week vs. placebo, and IFN β-1b 250 μg SC every other day vs. GA 20 mg SC once daily. There was no evidence in this analysis for GA 40 mg SC three times weekly or IFN β-1a pegylated 125 μg every two weeks.

Despite visual evidence suggesting that discontinuation due to AEs was more likely in study arms testing active drugs as compared to study arms testing placebo, almost all individual study estimates and pooled estimates did not suggest that, to a statistically significant level, discontinuation was more likely in trial arms corresponding to one drug over another. The one exception was IFNB MSSG 1995, from which we used 24-month data.[208] In this study, which tested IFN β-1b 250 μg SC every other day against placebo, patients receiving the study drug were more likely to withdraw from the study due to an AE (risk ratio=9.92, 95% CI [1.29, 76.32]).

Network meta-analysis

The set of studies included in this analysis formed a connected network (see Figure 18). All drugs were compared to placebo. GA 40 mc SC three times weekly and IFN β-1a pegylated 125 μg every two weeks were not included in this analysis.

The NMA, which was estimated with random effects, generated estimates of each drug against placebo and against every other drug (see Table 13). Because confidence intervals were wide in pairwise, direct meta-analyses, confidence intervals were wide in the NMAs and estimates as compared to placebo were often numerically different. The NMA did not offer statistical evidence that any one drug was more likely to result in discontinuation due to AEs as compared to another. Based on SUCRAs, IFN β-1b 250 μg SC every other day was ranked highest for discontinuation due to AEs, followed by IFN β-1a 44 μg SC thrice weekly. Placebo was ranked last.

Figure 17: Pairwise meta-analyses: discontinuation due to AEs at 24 months in RRMS

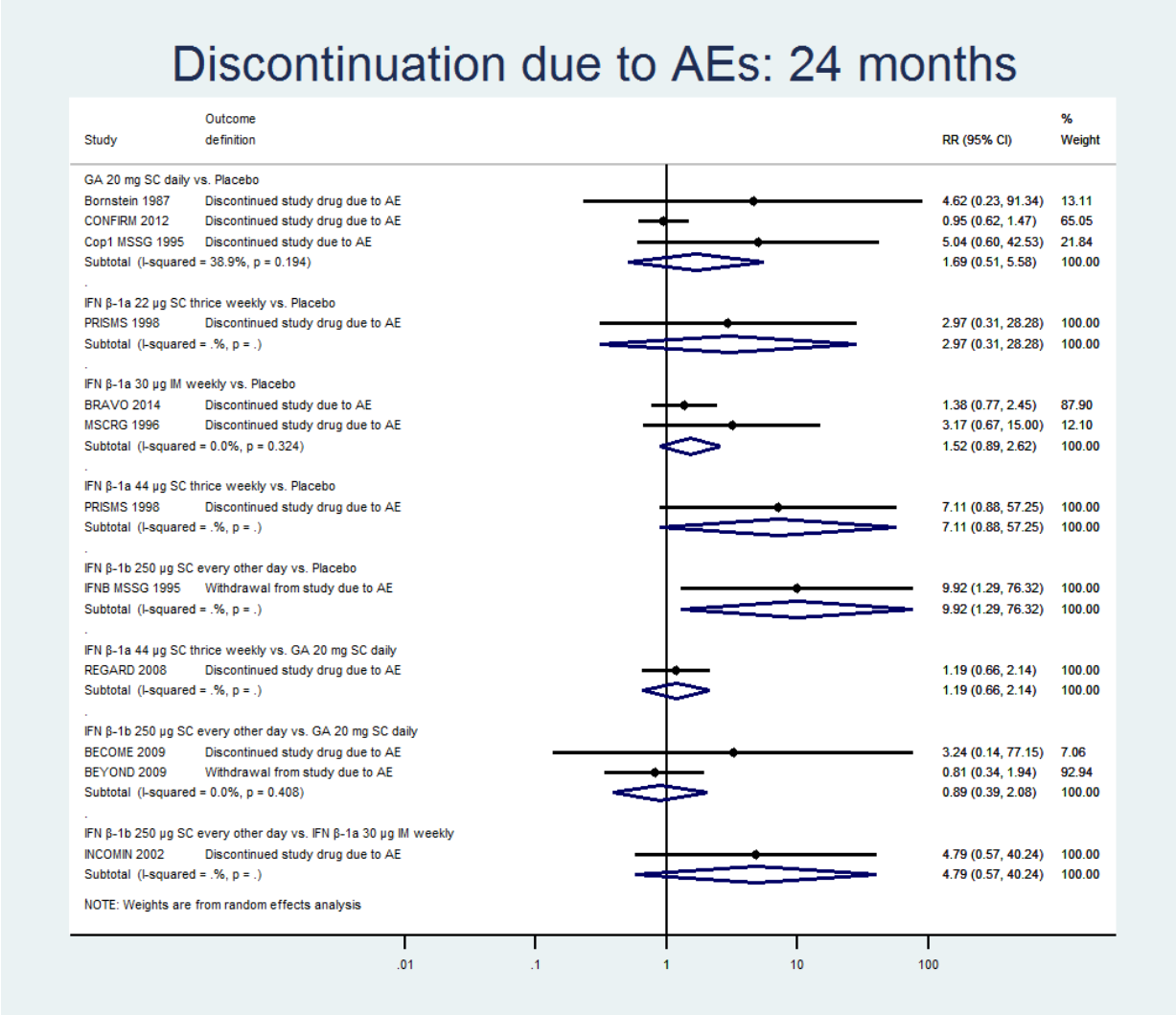


Figure 18: Network of studies, discontinuation due to AEs at 24 months in RRMS

ifn1a30: IFN β-1a 30 µg IM once a week; ifn1a44: IFN β-1a 44 µg SC three times weekly; ifn1a22: IFN β-1a 22 µg SC three times weekly; ifn1b250: IFN β-1b 250 µg SC every other day; ga20: GA 20 mg SC once daily; plac: placebo

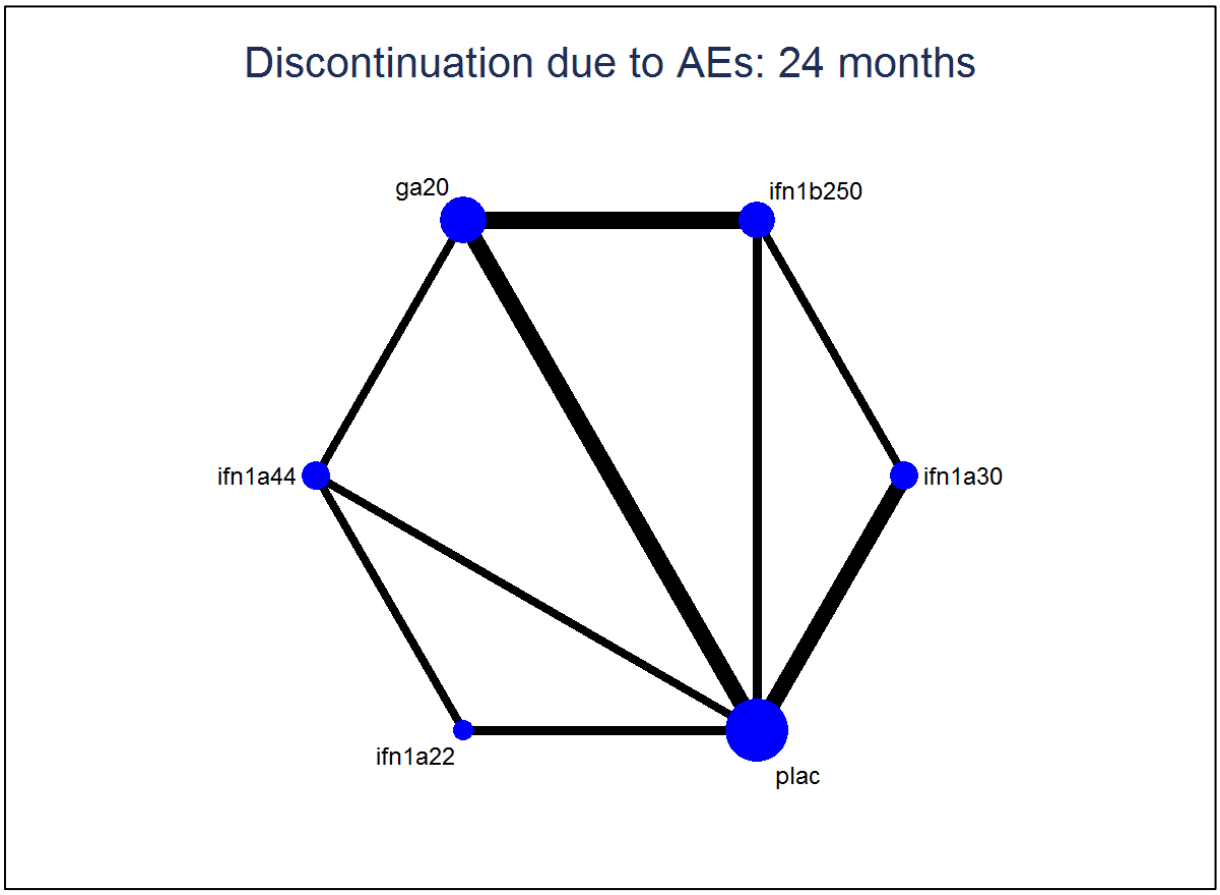


Table 13: Network meta-analysis: Discontinuation due to AEs at 24 months in RRMS

Findings are presented as risk ratios with 95% CI.

Drug	**SUCRA**	**IFN β-1b 250 µg SC every other day**	**IFN β-1a 44 µg SC thrice weekly**	**GA 20 mg daily**	**IFN β-1a 22 µg SC thrice weekly**	**IFN β-1a 30 µg IM weekly**	**Placebo**
IFN β-1b 250 µg SC every other day	0.79		1.15 (0.20, 6.56)	1.70 (0.50, 5.81)	2.37 (0.22, 25.84)	2.74 (0.56, 13.38)	4.41 (1.07, 18.29)
IFN β-1a 44 µg SC thrice weekly	0.76			1.48 (0.39, 5.57)	2.07 (0.32, 13.44)	2.39 (0.38, 15.22)	3.85 (0.81, 18.29)
GA 20 mg daily	0.57				1.40 (0.17, 11.76)	1.61 (0.38, 6.91)	2.60 (0.88, 7.64)
IFN β-1a 22 µg SC thrice weekly	0.41					1.15 (0.10, 13.09)	1.86 (0.21, 16.83)
IFN β-1a 30 µg IM weekly	0.35						1.61 (0.52, 5.02)
Placebo	0.12						
Wald test for inconsistency (χ2, df, p)	2.38, 3, 0.50						

In comparison with the direct evidence from IFNB MSSG 1995,[208] estimates for discontinuation due to AEs in IFN β-1b 250 μg SC every other day against placebo were lower but remained statistically significant (risk ratio=4.41, 95% CI [1.07, 18.29]). Estimates for IFN β-1a 44 μg SC thrice weekly were lower in the NMA (3.85, [0.81, 18.29]) than in pairwise estimate derived from PRISMS 1998[187] (7.11, [0.88, 57.25]), as were estimates for IFN β-1a 22 μg SC thrice weekly (NMA: 1.86, [0.21, 16.83] vs. PRISMS 1998: 2.97 [0.31, 28.28]). However, estimates for GA 20 mg SC once daily as compared to placebo were higher in the NMA (2.60, [0.88, 7.64]) as compared to the pairwise meta-analysis (1.69, [0.51, 5.58]).

An overall test for inconsistency across the network did not suggest the presence of inconsistency (p=0.50). However, a side-splitting test did find that direct and indirect evidence were in conflict for the comparison between GA 20 mg SC once daily and placebo, with indirect evidence suggesting that risk of discontinuation due to AEs was higher than presented in the direct evidence (p=0.037). Thus, there is some evidence of inconsistency in this network.

Discontinuation due to adverse events: all follow-up times

Pairwise meta-analyses

Pairwise meta-analyses for discontinuation due to AEs across all time points are shown in Figure 19. There was no visual evidence of a systematic difference based on the strict definition of the outcome. In every pairwise meta-analysis, confidence intervals were wide, as would be expected. Five pooled estimates relied on multiple studies: GA 20 mg SC once daily vs. placebo, IFN β-1a 30 μg IM once a week vs. placebo, and IFN β-1b 250 μg SC every other day vs. each of placebo, GA 20 mg SC once daily, and IFN β-1a 44 μg SC thrice weekly.

Despite visual evidence suggesting that discontinuation due to AEs was more likely in study arms testing active drugs as compared to study arms testing placebo, almost all individual study estimates and pooled estimates did not suggest that discontinuation was more likely in trial arms corresponding to one drug over another to a statistically significant level,. The one exception was IFN β-1a pegylated 125 μg every two weeks as compared to placebo, in which patients receiving the study drug were more likely to discontinue the study due to AEs (risk ratio=3.49, 95% CI [1.52, 7.99]). Estimates for GA 40 mg SC three times weekly were marginally non-significant (2.36, [0.99, 5.65]). Again, both estimates relied on one study. Of note is that comparisons between GA 20 mg SC once daily and placebo, which included five studies, did not suggest a substantial relationship between the study drug and discontinuation (1.07, [0.64, 1.79]), but this was driven (at least in part) by the null finding from CONFIRM 2012[214] (0.95 [0.62, 1.47]).

Network meta-analysis

The studies included in this analysis formed a connected network (see Figure 20). All drugs were compared to placebo, and all drugs were included in this analysis.

The NMA, which was estimated with random effects per the protocol, generated estimates of each drug against placebo and against every other drug (see Table 14). The NMA did not offer statistical evidence that any one drug was more likely to result in discontinuation due to AEs as compared to another. Based on SUCRAs, IFN

β-1a pegylated 125 μg every two weeks was ranked highest on risk of discontinuation due to AEs (i.e. greatest risk of discontinuation), followed by IFN β-1a 44 μg SC thrice weekly. Placebo was ranked last.

Because confidence intervals were frequently wide in pairwise, direct meta-analyses, confidence intervals were wide in the NMAs and estimates as compared to placebo were often numerically different. Compared with direct estimates from PRISMS 1998,[187] evidence from the NMA suggested a numerically lower risk of discontinuation due to AEs in IFN β-1a 44 μg SC thrice weekly as compared to placebo (NMA: risk ratio=2.49, 95% CI [0.89, 6.95]; PRISMS 1998: 7.11, [0.88, 57.25]). That is, the magnitude of the risk of discontinuation as compared to placebo was smaller in the NMA than in the one trial informing the direct comparison. The same applied for IFN β-1a 22 μg SC thrice weekly (NMA: 1.24, [0.21, 7.26]; PRISMS 1998: 2.97, [0.31, 28.28]). Similarly, estimates for discontinuation due to AEs in IFN β-1b 250 μg SC every other day vs. placebo were lower in the NMA than in the pairwise meta-analysis (NMA: 1.75, [0.63, 4.89]; pairwise meta-analysis: 4.93, [0.76, 32.00]). Estimates of discontinuation due to AEs were higher in the NMA for GA 20 mg SC once daily vs. placebo (NMA: 1.56, [0.77, 3.14]; pairwise meta-analysis: 1.07, [0.64, 1.79]).

An overall Wald test for inconsistency in the network did not reach significance, but suggested some conflict between direct and indirect evidence (p=0.09). Examination of the specific design effects from the design-by-treatment interaction model suggested that direct estimates of discontinuation due to AEs from IFN β-1b 250 μg SC every other day vs. placebo could be driving this result (design effect p=0.075). However, a side-splitting test did not suggest an obvious source of conflict between direct and indirect evidence. Thus, while there is no statistically significant evidence of inconsistency in this network, findings should be viewed with caution.

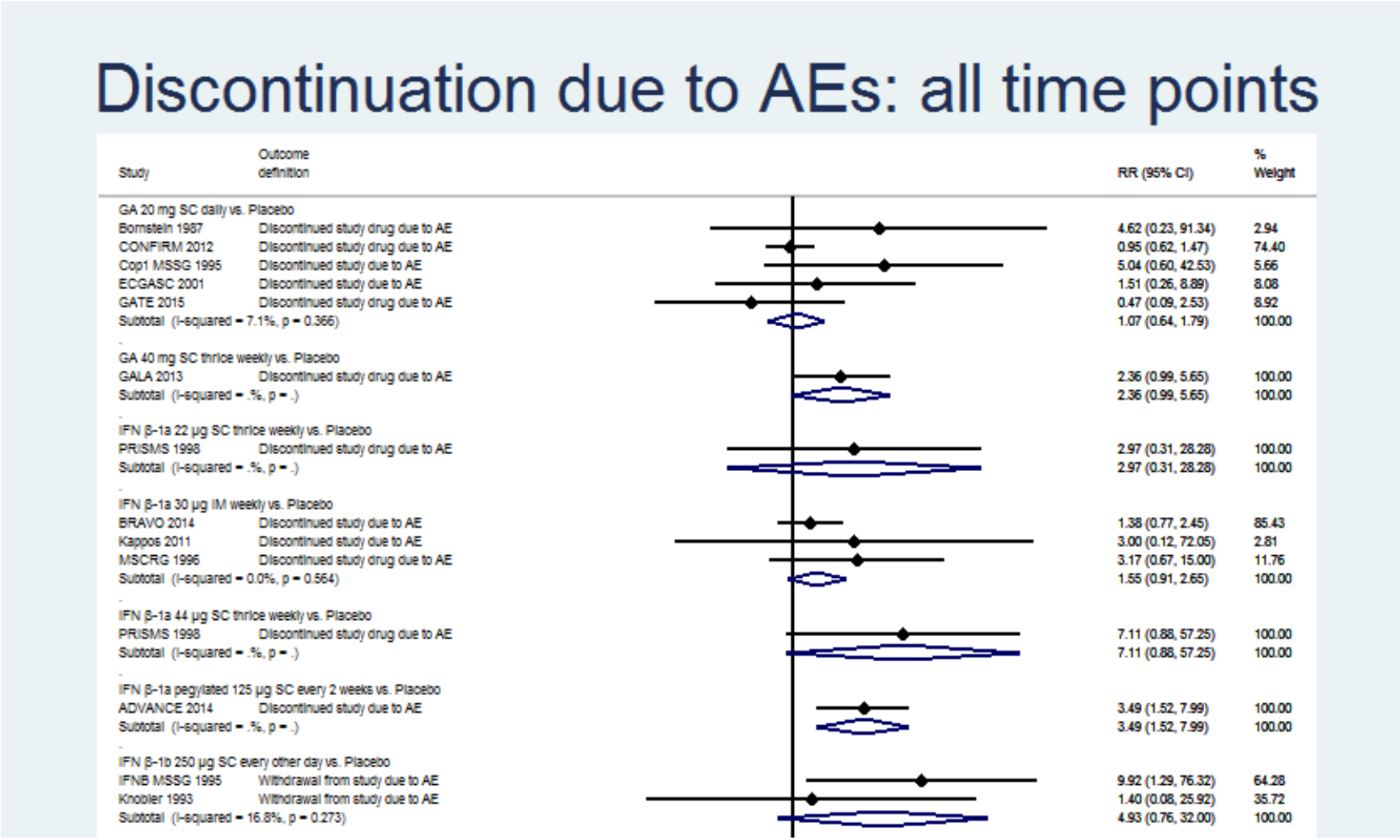
Comparison of network meta-analyses: modal follow-up vs. all time points

Neither NMA found evidence that one drug was superior to another.

However, estimates for discontinuation due to AEs for active drugs against placebo tended to be lower in the network including all time points, possibly since the majority of studies included in this analysis that were set aside in the modal follow-up analysis included shorter follow-up periods (generally of one year or shorter). Estimates were essentially unchanged for IFN β-1a 30 μg IM once a week vs. placebo (modal follow-up: risk ratio=1.61, 95% CI [0.52, 5.02]; all time points: 1.62, [0.82, 3.23]).

Figure 19: Pairwise meta-analyses: discontinuation due to AEs at all time points in RRMS

In this plot, RR=risk ratio.



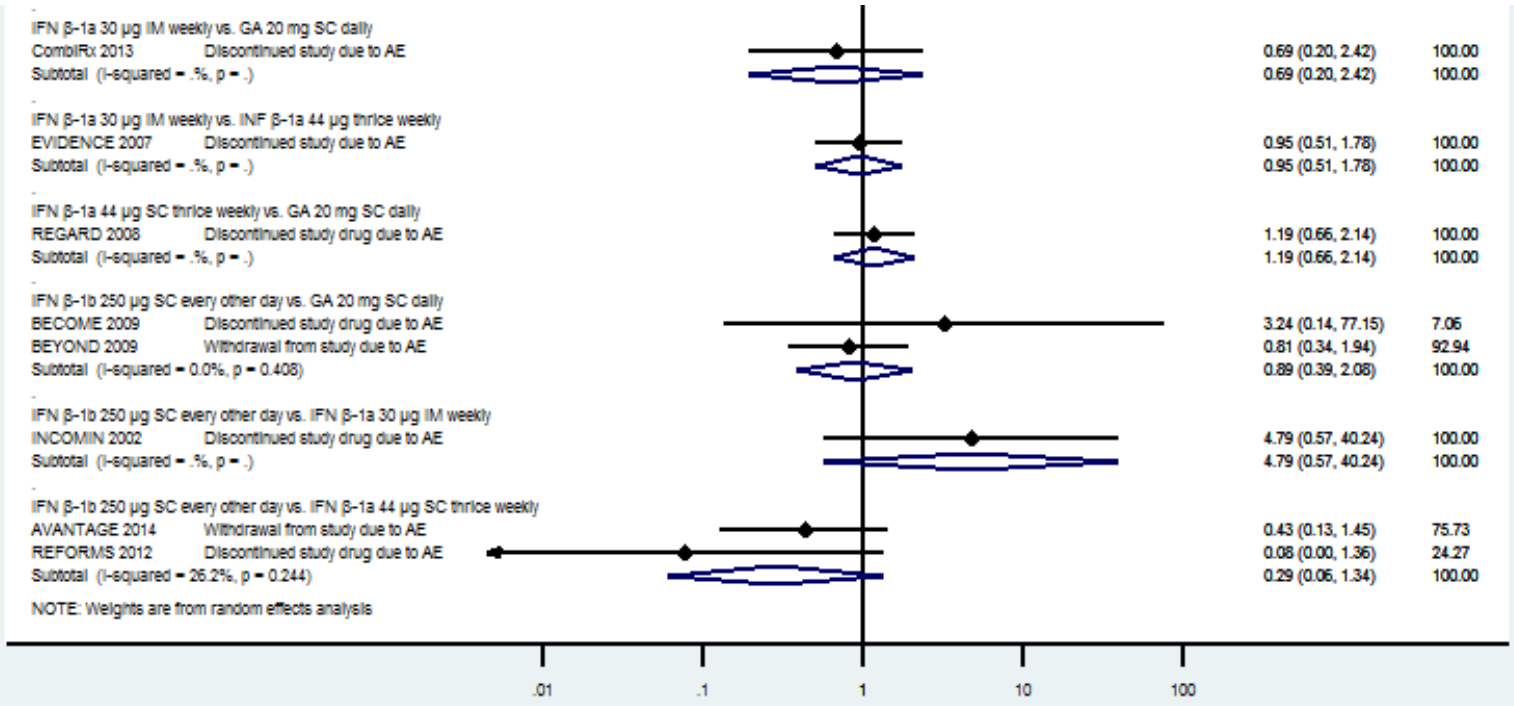

IFN β-1a 30 µg IM weekly vs. GA 20 mg SC daily
CombiRx 2013 Discontinued study due to AE 0.69 (0.20, 2.42) 100.00
Subtotal (I-squared = .%, p = .) 0.69 (0.20, 2.42) 100.00
IFN β-1a 30 µg IM weekly vs. INF β-1a 44 µg thrice weekly
EVIDENCE 2007 Discontinued study due to AE 0.95 (0.51, 1.78) 100.00
Subtotal (I-squared = .%, p = .) 0.95 (0.51, 1.78) 100.00
IFN β-1a 44 µg SC thrice weekly vs. GA 20 mg SC daily
REGARD 2008 Discontinued study drug due to AE 1.19 (0.66, 2.14) 100.00
Subtotal (I-squared = .%, p = .) 1.19 (0.66, 2.14) 100.00
IFN β-1b 250 µg SC every other day vs. GA 20 mg SC daily
BECOME 2009 Discontinued study drug due to AE 3.24 (0.14, 77.15) 7.06
BEYOND 2009 Withdrawal from study due to AE 0.81 (0.34, 1.94) 92.94
Subtotal (I-squared = 0.0%, p = 0.408) 0.89 (0.39, 2.08) 100.00
IFN β-1b 250 µg SC every other day vs. IFN β-1a 30 µg IM weekly
INCOMIN 2002 Discontinued study drug due to AE 4.79 (0.57, 40.24) 100.00
Subtotal (I-squared = .%, p = .) 4.79 (0.57, 40.24) 100.00
IFN β-1b 250 µg SC every other day vs. IFN β-1a 44 µg SC thrice weekly
AVANTAGE 2014 Withdrawal from study due to AE 0.43 (0.13, 1.45) 75.73
REFORMS 2012 Discontinued study drug due to AE 0.08 (0.00, 1.36) 24.27
Subtotal (I-squared = 26.2%, p = 0.244) 0.29 (0.06, 1.34) 100.00
NOTE: Weights are from random effects analysis
.01
.1
1
10
100

Figure 20: Network of studies, discontinuation due to AEs at all time points in RRMS

ifn1a30: IFN β-1a 30 µg IM once a week; ifn1a44: IFN β-1a 44 µg SC three times weekly; ifn1a22: IFN β-1a 22 µg SC three times weekly; ifn1b250: IFN β-1b 250 µg SC every other day; peg: IFN β-1a pegylated 125 µg SC every two weeks; ga20: GA 20 mg SC once daily; ga40: GA 40 mg SC thrice weekly; plac: placebo

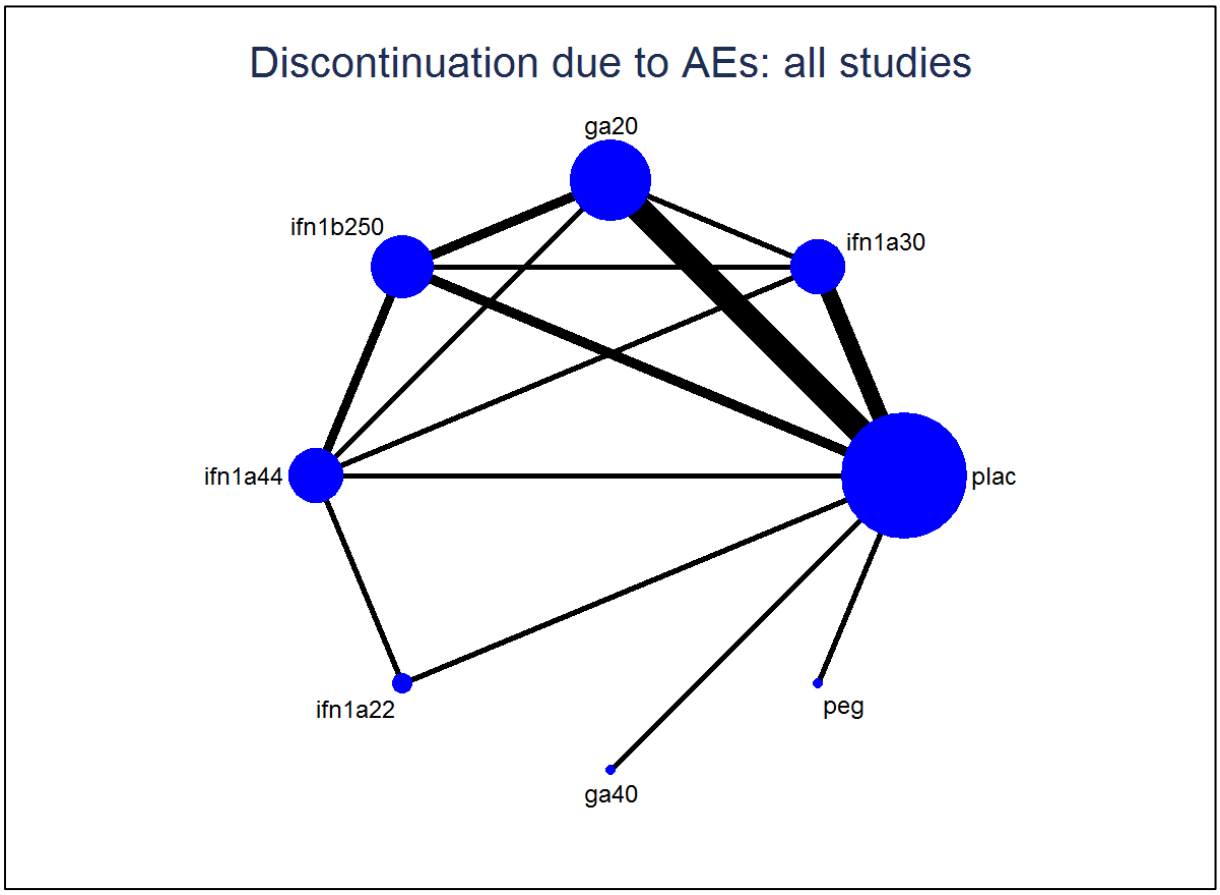


Table 14: Network meta-analysis: Discontinuation due to AEs at all time points in RRMS

Findings are presened as risk ratios with 95% CI.

Drug	SUCRA	IFN β-1a pegylated 125 µg every 2 weeks	IFN β-1a 44 µg SC thrice weekly	GA 40 mg thrice weekly	IFN β-1b 250 µg SC every other day	IFN β-1a 30 µg IM weekly	Glatiramer 20 mg daily	IFN β-1a 22 µg SC thrice weekly	Placebo
IFN β-1a pegylated 125 µg every 2 weeks	0.82		1.40 (0.31, 6.45)	1.48 (0.29, 7.43)	1.99 (0.43, 9.15)	2.15 (0.57, 8.04)	2.24 (0.59, 8.44)	2.82 (0.35, 23.04)	3.49 (1.13, 10.76)
IFN β-1a 44 µg SC thrice weekly	0.73			1.05 (0.22, 4.95)	1.42 (0.61, 3.30)	1.53 (0.65, 3.59)	1.60 (0.76, 3.36)	2.01 (0.45, 9.01)	2.49 (0.89, 6.95)
Glatiramer 40 mg thrice weekly	0.66				1.35 (0.29, 6.35)	1.45 (0.38, 5.60)	1.52 (0.39, 5.89)	1.91 (0.23, 15.88)	2.36 (0.74, 7.53)
IFN β-1b 250 µg SC every other day	0.50					1.08 (0.42, 2.79)	1.12 (0.51, 2.49)	1.42 (0.26, 7.71)	1.75 (0.63, 4.89)
IFN β-1a 30 µg IM weekly	0.45						1.04 (0.51, 2.13)	1.32 (0.24, 7.17)	1.62 (0.82, 3.23)
Glatiramer 20 mg daily	0.40							1.26 (0.24, 6.50)	1.56 (0.77, 3.14)
IFN β-1a 22 µg SC thrice weekly	0.33								1.24 (0.21, 7.26)
Placebo	0.12								
Wald test for inconsistency (χ2, df, p)	11.04, 6, 0.09								

9.5.18 Summary: relapsing remitting MS

Across drugs, studies suggested and meta-analyses confirmed that interferons and GA reduce relapse rate, reduce rate of severe relapses (both as measured by neurological rating scales and as measured by steroid treatment), and generally delay disability progression. However, findings were clearer for disability progression confirmed at 3 months as opposed to confirmed at 6 months. There was little evidence that any one drug was superior to others except for disability progression confirmed at 6 months, but networks were especially sparse. Findings for progression confirmed at 3 months did not match results from progression confirmed at 6 months. Findings for freedom from disease activity, MS symptoms and health-related quality of life were infrequently reported, and evidence for MS symptoms and health-related quality of life also suffered from poor reporting. Findings for discontinuations due to AEs, which are intended to be indicative, did not suggest that one drug was more likely to result in discontinuation than another, or, with few exceptions, against placebo. However, findings for discontinuation relied on networks with some limited evidence of inconsistency.

9.6 *Clinical effectiveness: secondary progressive MS*

Our analysis was informed by three included trials: European Study Group on Interferon β-1b in Secondary Progressive MS 1998 (referred to as ESG 1998[220]), North American Study Group on Interferon beta-1b in Secondary Progressive MS 2004 (referred to as NASG 2004[221]) and SPECTRIMS 2001.[222] It should be noted that while all studies included both relapsing and non-relapsing patients, only SPECTRIMS 2001 presented subgroup analyses by history of previous relapses in SPMS.

9.6.1 IFN β-1a 44 µg and 22 µg SC three times a week (Rebif) vs. placebo

One trial evaluated both 44 µg and 22 µg doses of IFN β-1a against placebo: SPECTRIMS 2001.[222]

Relapse outcomes

In SPECTRIMS 2001,[222] 618 patients were followed up for three years. Rate ratios (RaR) based on annualised relapse rates (ARRs) were numerically identical for both active arms as compared to placebo (44 µg: RaR=0.69, 95% CI [0.56, 0.85]; 22 µg: RaR=0.69, 95% CI [0.56, 0.84]).

Subgroup analyses stratifying by whether patients had history of relapse showed a pattern of significant results for those previously relapsing and non-significant results for those not previously relapsing.[222] For those previously relapsing, ARRs were significantly different from the placebo arm (1.08) in the 44 µg dose (0.67, $p<0.001$) and the 22 µg dose (0.57, $p<0.001$). For those not previously relapsing, ARRs were not significantly different from the placebo arm (0.39) in either dosage (44 µg: 0.43, $p>0.05$; 22 µg: 0.36, ns).

Both active arms also had similar delays in time to first relapse, though only the 44 µg dose had a significant effect against placebo (HR 0.77, 95% CI [0.61, 0.98]), corresponding to a difference in median time to first relapse of 494 days vs. 281 days.[222] Though the difference in median time to relapse of the 22 µg dose was similar (476 days vs. 281 days), this did not translate into a significant effect (HR=0.87, [0.69, 1.10]). The

difference between the two active arms was not calculated in this trial, though an approximation is that the HR of 44 µg vs 22 µg would be (0.77÷0.87)=0.89 and not statistically different from unity.

Relapse severity

Both arms showed similar reductions in the annualised rates of moderate or severe relapses (44 µg: RaR=0.68, 95% CI [0.44, 0.81]; 22 µg: 0.66, 95% CI [0.51, 0.86]).[222] Findings were similar for annualised rates of steroid courses used to treat relapses (44 µg: 0.66, 95% CI [0.49, 0.89]; 22 µg: 0.59, [0.44, 0.81]).

Disability progression

In SPECTRIMS 2001, disability progression was confirmed at 3 months.[222] Neither active drug arm was associated with a significant decrease in hazard for time to confirmed disability progression in the main analysis (44 µg: HR=0.83, 95% CI [0.65, 1.07]; 22 µg: 0.88, *p*=0.305), nor were active arms substantially different. However, an analysis controlling for disease characteristics found a significant difference in the 44 µg arm (0.78, [0.60, 1.00]).

Subgroup analyses combined the two dosages into one arm and stratified models by whether patients had history of relapse.[222] The hazard ratio for time to confirmed disability progression suggested a positive, though non-significant, effect in previously relapsing patients (0.74, *p*=0.055), while the hazard ratio approached unity in non-relapsing patients (1,01, *p*=0.934). However, amongst previously relapsing patients, *proportions* of patients with confirmed disability progression were significantly different between those receiving 44/22 µg and those receiving placebo (OR=0.52, 95% CI [0.29, 0.93]), but not amongst those not previously relapsing (OR=1.07, 95% CI [0.64, 1.78]).

Freedom from disease activity

We were unable to locate any relevant comparisons between IFN β-1a 44 µg or 22 µg SC three times a week and combined clinical-MRI outcomes for freedom from disease activity.

MS symptoms and health-related quality of life

We were unable to locate any relevant comparisons between IFN β-1a 44 µg or 22 µg SC three times a week and placebo for MS symptoms and health-related quality of life.

Adverse events and mortality

SPECTRIMS 2001[222] reported AEs and mortality. Full results are available on request. Differences on mortality were not significantly different between groups; one patient died in the placebo arm of SPECTRIMS 2001 whereas two patients died in the 44 µg arm and one patient died in the 22 µg arm.

9.6.2 IFN β-1b 250 µg SC every other day (Betaferon/Extavia) vs. placebo

Two trials evaluated IFN β-1b 250 µg SC every other day: ESG 1998[220, 223] and NASG 2004.[221] NASG 2004 included a dosing arm of IFN β-1b that is not recommended and thus not included in this analysis.

Relapse outcomes

In ESG 1998,[220, 223] 718 patients were followed for up to two years. Patients receiving the study drug had a significantly lower ARR (0.42) than those in the placebo arm (0.42 vs. 0.57, p=0.003). We approximated this as a rate ratio of 0.74 (95% CI 0.65, 0.83). Similarly, for the 623 patients enrolled in the relevant study arms in NASG 2004[221] and followed for up to three years before early study termination, patients receiving the study drug had a significantly lower ARR than placebo patients (0.16 vs. 0.28, p=0.009). We estimated this as corresponding to a rate ratio of 0.57 (0.43, 0.75).

Both studies also demonstrated statistically significant delays in time to first relapse. In interim data from ESG 1998,[220] median time to first relapse was 644 days in the study drug arm vs. 403 days in the placebo arm (log rank p=0.003). In NASG 2004,[221] end-of-study data demonstrated a time to relapse at the 30th percentile of 1051 days in the study drug arm vs. 487 days in the placebo arm (log rank p=0.01). However, proportions relapsing were not significantly different in ESG 1998[220] (57.5% in the study drug arm vs. 62.0% in placebo, p=0.083), though NASG 2004 did yield a significant difference (29% vs. 38%, p=0.018).

Relapse severity

Both studies showed significant differences between study drug and placebo in proportions of patients experiencing moderate or severe relapses (ESG 1998[220] interim data: 43.6% vs. 53.1%, p=0.0083; NASG 2004:[221] 21% vs. 30%, p=0.012). In NASG 2004, the annualised rate of moderate or severe relapses was significantly less in the study drug arm than in the placebo arm (0.10 vs. 0.19, p=0.022). However, it should be noted that outcome tables for NASG 2004 presented two estimates of relapse severity with markedly different results. Under the second set of estimates, neither proportion of patients with moderate or severe relapses (3% vs. 6%, p=0.056) or annualised rate of moderate or severe relapses (0.01 vs. 0.02, p=0.052) were significantly different between arms. Contact with study investigators did not yield clarification.

In both studies, the percentage of patients treated with steroids also decreased significantly (ESG 1998[220] interim data: 53.6% vs. 67.9%, p<0.0001; NASG 2004:[221] 37% vs. 46%, p=0.023).

Disability progression

In the final results of ESG 1998,[223] progression was measured using a variety of criteria, including progression of at least 1.0 EDSS points confirmed at 3 months and confirmed at 6 months, and progression of 2.0 EDSS points confirmed at 3 months. Each of these measures was estimated both excluding data collected during relapses (the default) and including relapse data, but proportions were similar in all cases between measures including and excluding data collected during relapses; thus we discuss only the default measures here. The proportion of patients progressing at least 1.0 EDSS point confirmed at three months was significantly less in the study drug arm than in the placebo arm (45.3% vs. 53.9%, p=0.031). Combined with estimated probabilities from a life table model (estimated non-progression at 33 months 53% vs. 44%) and a log rank p-value of 0.003, this yielded an approximate HR of 0.75 (95% CI [0.61, 0.92]). Proportions with confirmed progression at 6 months (40.8% vs. 48.6%, p=0.049) and with confirmed progression of at least 2.0 EDSS points at 3 months

(16.4% vs. 22.6%, *p*=0.032) showed similar trends. However, in NASG 2004,[221] disability progression was confirmed at 6 months and did not show a significant difference in terms of time to progression (study drug 32% vs. placebo 34%, log rank *p*=0.61).

Similarly, while patients in ESG 1998[223] did show significant differences in average points of EDSS progression between arms (0.47 vs. 0.69, *p*=0.003), patients in NASG 2004[221] did not (0.53 vs. 0.62, *p*=0.634).

Freedom from disease activity

We were unable to locate any relevant comparisons between IFN β-1b 250 μg SC every other day and combined clinical-MRI outcomes for freedom from disease activity.

MS symptoms and health-related quality of life

In NASG 2004,[221] change from baseline was not significantly different between patients in the study drug arm and patients in the placebo arm on fatigue (Environmental Status Scale change 1.7 vs. 1.2, *p*=0.125), cognition (composite neuropsychological score -0.28 vs. -0.32, *p*=0.42) or depression (Beck Depression Inventory score -0.5 vs. -1.0, *p*=0.652; percentage newly treated with antidepressants 29% vs. 29%, *p*=0.987). Changes in overall Multiple Sclerosis Quality of Life Inventory scores were not significantly different either (*p*=0.502).

Adverse events and mortality

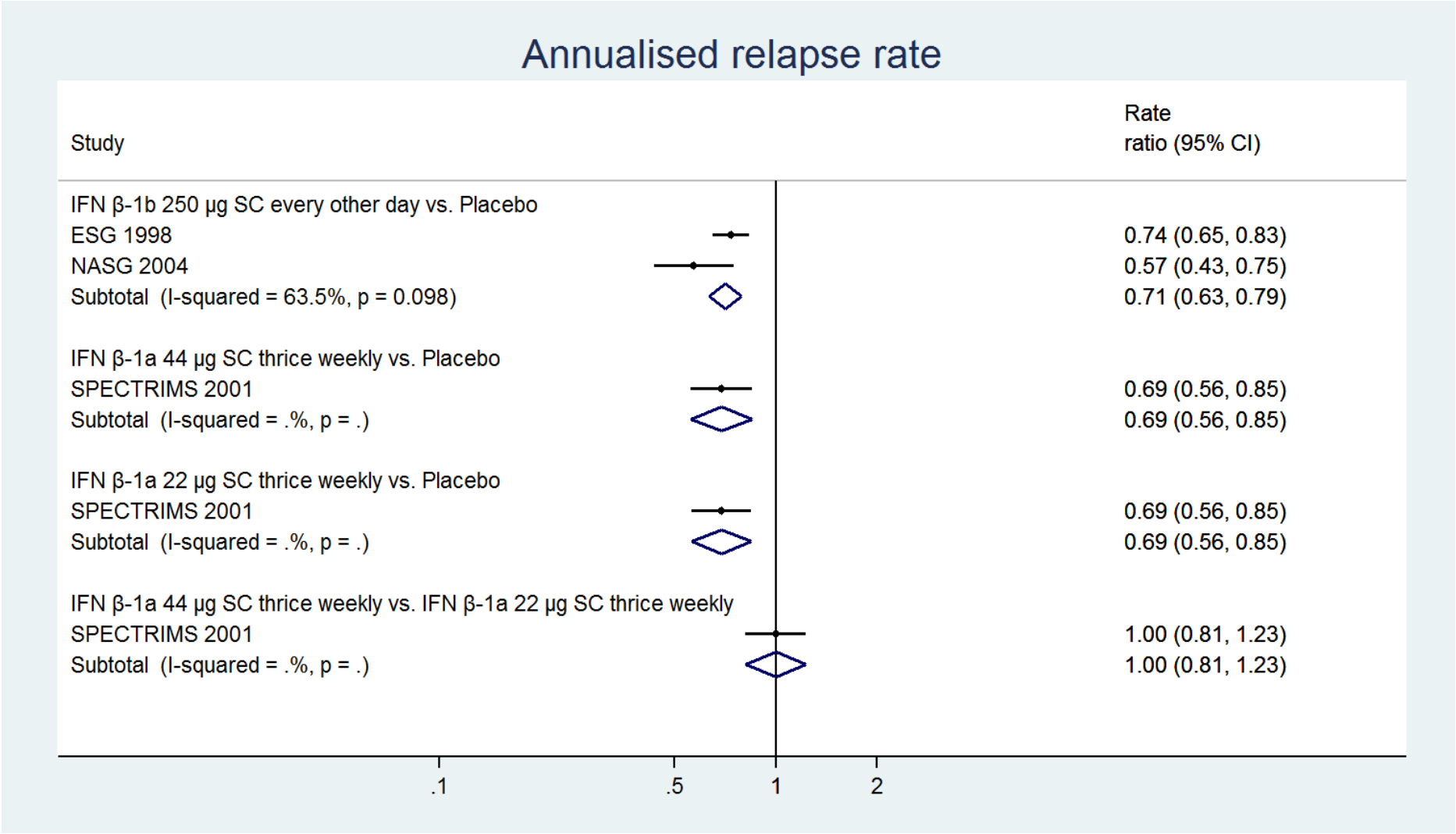
Both studies reported AEs and mortality. Full results are available on request. Studies were not significantly different on mortality, though there were a combined seven deaths in the IFN β-1b 250 μg SC every other day arms and a combined two deaths in the placebo arms of the two trials.

9.6.3 Meta-analyses: relapse rate

Pairwise meta-analyses

Direct evidence from comparisons is shown in Figure 21. Aside from SPECTRIMS 2001,[222] which compared IFN β-1a 44 μg SC thrice weekly, IFN β-1a 22 μg SC thrice weekly and placebo, the other two included studies compared IFN β-1b 250 μg SC every other day against placebo. The pooled effect of IFN β-1b 250 μg SC every other day against placebo suggested that the drug reduces the rate of relapse (RR=0.71, 95% CI [0.63, 0.79]).

Figure 21: Pairwise meta-analyses: ARR in SPMS



Network meta-analysis

Ranking of drugs in the resultant network suggested that IFN β-1b 250 μg SC every other day was superior to the equally ranked IFN β-1a 44 μg SC thrice weekly and IFN β-1a 22 μg SC thrice weekly (see Table 15). Placebo was ranked last. Findings for comparisons between active drugs and placebo were, as would be expected, essentially the same as in the direct evidence. Comparisons between IFN β-1b 250 μg SC every other day and both IFN β-1a 44 μg SC thrice weekly and IFN β-1a 22 μg SC thrice weekly did not suggest a statistical difference between the drugs in effectiveness (44 μg: HR=0.97, 95% CI [0.63, 1.50]; 22 μg: HR=0.97, 95% CI [0.63, 1.49]).

Because there was not the possibility for inconsistency in the network, we did not test for it.

Table 15: Network meta-analysis: annualised relapse rates in SPMS

Drug	SUCRA	IFN β-1b 250 μg SC every other day	IFN β-1a 44 μg SC thrice weekly	IFN β-1a 22 μg SC thrice weekly	Placebo
IFN β-1b 250 μg SC every other day	0.71		0.97 (0.63, 1.50)	0.97 (0.63, 1.49)	0.67 (0.52, 0.86)
IFN β-1a 44 μg SC thrice weekly	0.64			1.00 (0.71, 1.42)	0.69 (0.49, 0.98)
IFN β-1a 22 μg SC thrice weekly	0.64				0.69 (0.49, 0.98)
Placebo	0.01				

9.6.4 Meta-analyses: relapse severity

We did not undertake meta-analyses for relapse severity in SPMS because of the quality and scarcity of the data.

9.6.5 Meta-analyses: time to disability progression confirmed at three months

Pairwise meta-analyses

Direct evidence from comparisons is shown in Figure 22. Comparisons included two trials: SPECTRIMS 2001[222] and ESG 1998.[220, 223] Findings are the same as for the individual trials.

Network meta-analysis

Because of the shape of the network, in which there was no opportunity for inconsistency and in which no direct comparison was informed by more than one trial, the model was estimated using fixed effects instead of random effects as in the protocol. Ranking of drugs in the resultant network suggested that IFN β-1b 250 μg SC every other day was superior to IFN β-1a 44 μg SC thrice weekly and to IFN β-1a 22 μg SC thrice weekly (see Table 16). Placebo was ranked last. Findings for comparisons between active drugs and placebo were, as would be expected, essentially the same as in the direct evidence. Comparisons between IFN β-1b 250 μg SC every other day and both IFN β-1a 44 μg SC thrice weekly and IFN β-1a 22 μg SC thrice weekly did not suggest a statistical difference between the drugs in effectiveness (44 μg: HR=0.91, 95% CI [0.65, 1.25]; 22 μg: HR=0.85, 95% CI [0.62, 1.18]). Because there was no possibility for inconsistency in the network, we did not test for it.

Figure 22: Pairwise comparisons: time to disability progression confirmed at 3 months in SPMS

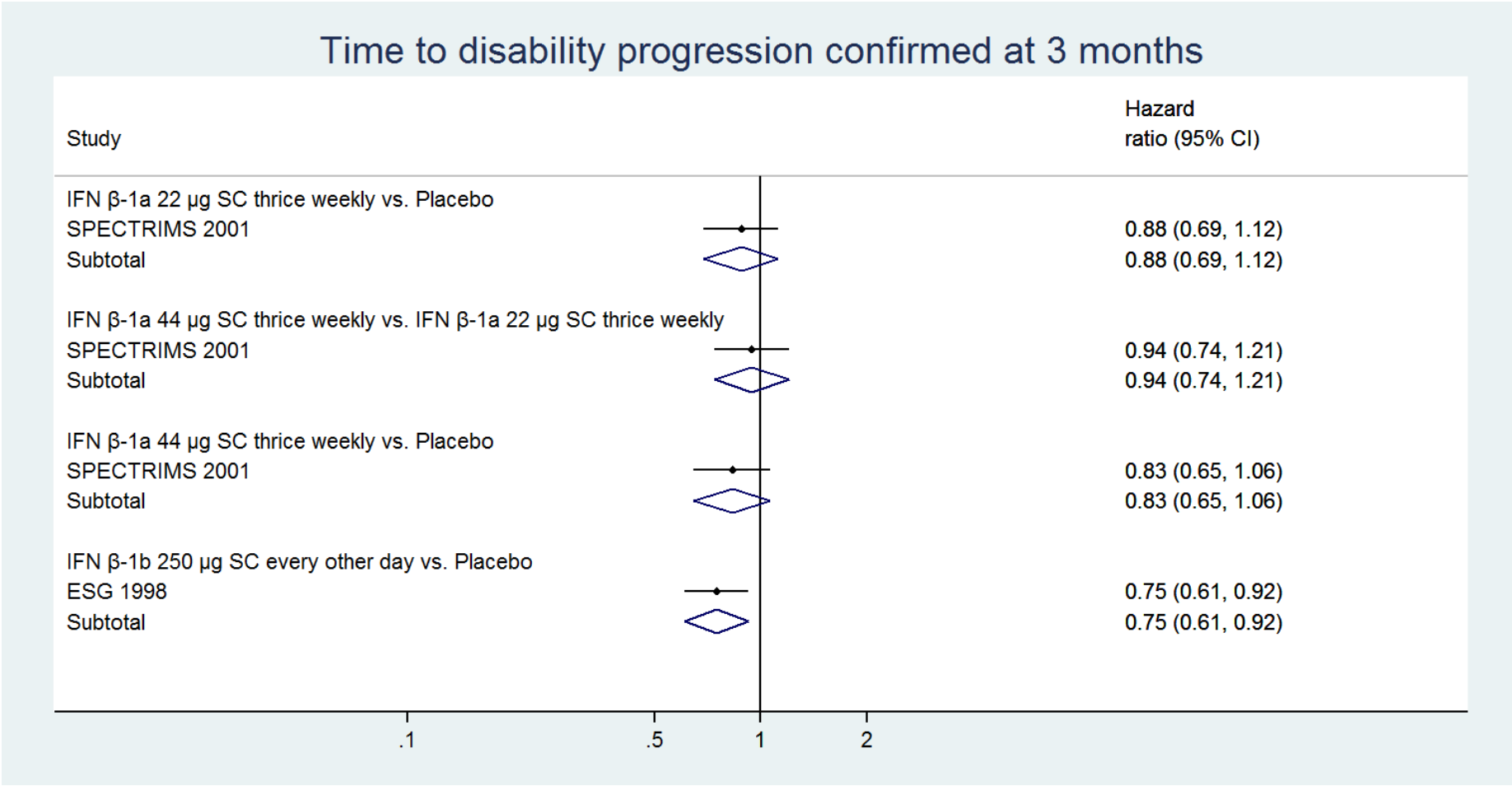


Table 16: Network meta-analysis: time to disability progression confirmed at 3 months in SPMS

Drug	SUCRA	IFN β-1b 250 µg SC every other day	IFN β-1a 44 µg SC thrice weekly	IFN β-1a 22 µg SC thrice weekly	Placebo
IFN β-1b 250 µg SC every other day	0.85		0.91 (0.65, 1.25)	0.85 (0.62, 1.18)	0.75 (0.61, 0.92)
IFN β-1a 44 µg SC thrice weekly	0.64			0.94 (0.74, 1.21)	0.83 (0.65, 1.06)
IFN β-1a 22 µg SC thrice weekly	0.44				0.88 (0.69, 1.12)
Placebo	0.07				

9.6.6 Meta-analyses: time to disability progression confirmed at six months

Only one study, NASG 2004,[221] reported an effect size for time to disability progression confirmed at six months. In their comparison of IFN β-1b 250 µg SC every other day and placebo, they did not find a statistically significant effect on time to disability progression. We imputed this hazard ratio as 0.93 (95% CI [0.71, 1.22]).

9.6.7 Meta-analyses: adverse events

Summary of adverse events meta-analyses

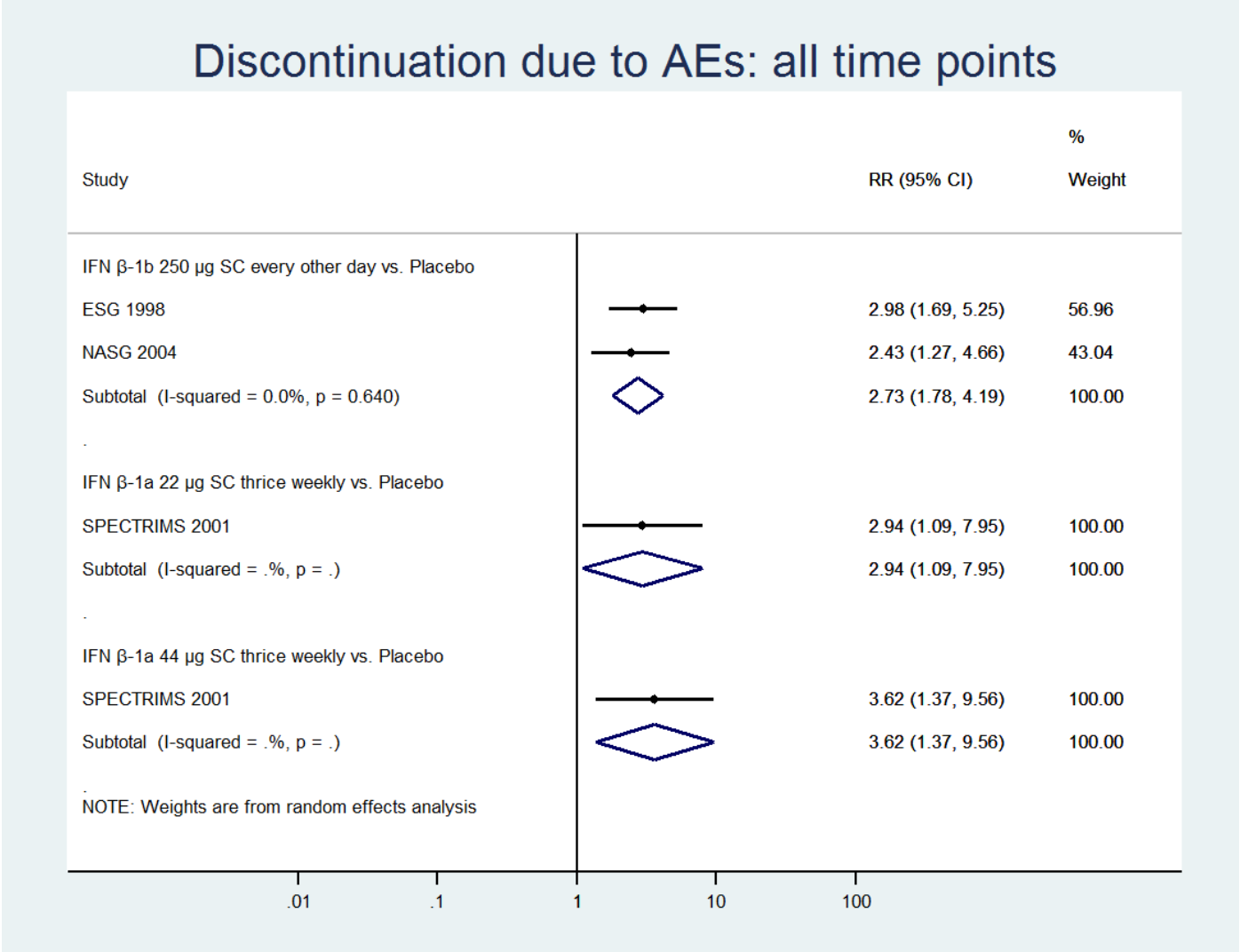
Full results for pairwise meta-analyses of AEs are available on request. Though the diversity and heterogeneity of AEs precludes detailed examination of each, several trends were apparent across pairwise comparisons. Comparing IFN β-1a SC thrice weekly vs. placebo, IFN β-1a was associated with more application site disorders, necrosis, increased alanine aminotransferase (SGPT), increased aspartate aminotransferase (SGOT), leucopenia, lymphopenia, neutralising antibodies and the numbers of patients who discontinued study treatment due to AE. Comparing IFN β-1b 250 µg SC every other day vs. placebo, IFN β1b was associated with more injection site inflammation, necrosis, pain, injection site reaction, chest pain, chills only, chills and fever, fever only, flu syndrome, hypertonia, leucopenia, lymphadenopathy, lymphopenia, neutralising antibodies, rash and the number of patients who discontinued study treatment due to AE.

Meta-analyses: discontinuation due to adverse events

Pairwise meta-analyses

All three studies presented data for discontinuation of the study drug due to AEs, and all studies included follow-up of 36 months. Pairwise estimates are in Figure 23. As compared to placebo, all drugs were associated with a significant increase in risk of discontinuation of the study drug due to AEs.

Figure 23: Pairwise meta-analyses: discontinuation due to AEs in SPMS



Network meta-analysis

Studies formed a star-shaped network. Examination of SUCRAs in the resultant network suggested that IFN β-1a 44 μg SC thrice weekly was ranked highest (i.e. associated with the greatest risk) for discontinuation of the study drug due to AEs, followed by IFN β-1a 22 μg SC thrice weekly and then IFN β-1b 250 μg SC every other day (see Table 17). Placebo was ranked last.

As would be expected, estimates from comparisons with placebo were unchanged in the NMA as compared to the pairwise meta-analysis. There was no evidence from the NMA that one drug was more likely to result in discontinuations due to AEs than any other drug.

Because there was no opportunity for inconsistency in the network, we did not test for it.

Table 17: Network meta-analysis: Discontinuation due to AEs in SPMS

Drug	SUCRA	IFN β-1a 44 μg SC thrice weekly	IFN β-1a 22 μg SC thrice weekly	IFN β-1b 250 μg SC every other day	Placebo
IFN β-1a 44 μg SC thrice weekly	0.81		1.23 (0.64, 2.37)	1.32 (0.46, 3.83)	3.62 (1.37, 9.56)
IFN β-1a 22 μg SC thrice weekly	0.60			1.08 (0.37, 3.18)	2.94 (1.09, 7.95)
IFN β-1b 250 μg SC every other day	0.58				2.73 (1.78, 4.19)
Placebo	0.01				

9.6.8 Summary: secondary progressive multiple sclerosis

Studies did not consistently report findings for SPMS patients with recent history of relapses. Thus, findings should be regarded with caution. Taken together, the three studies suggested that the included drugs reduced relapse rate and relapse severity relative to placebo, though we were unable to clarify issues with relapse severity data from one trial. Findings for disability progression were mixed. We were unable to locate any relevant comparisons on combined clinical-MRI measures of freedom from disease activity. One study reported MS symptom data and did not find evidence of differences between the study drug and placebo. There were no significant differences between study drugs and placebo on mortality. Each drug was associated with increased risk of discontinuation due to AEs.

NMAs for ARR and time to disability progression confirmed at three months did not suggest superiority of one drug over another, nor did NMAs for discontinuation due to AEs suggest that one drug was more likely to result in discontinuation over another. We did not undertake meta-analyses for relapse severity due to unresolved questions about one of the three included studies, and only one included study reported time to disability progression confirmed at six months.

9.7 *Overall summary of clinical effectiveness findings*

In clinically isolated syndrome, each included drug showed evidence of delaying time to clinically definite MS. The NMA did not show evidence of superiority of one drug over another, though the network was sparse and only one drug was represented by more than one trial. In RRMS, drugs showed good evidence of reducing relapse rate, including rate of moderate or severe relapses and in most cases, rate of steroid-treated relapses. There was little evidence of superiority of one drug over another in reducing relapse rate. Some drugs, but not all, delayed time to disability progression confirmed at three months, though there was no evidence of superiority of one drug over any other. The network meta-analysis for time to disability progression confirmed at six months indicated that most drugs showed improvement over placebo in delaying time to progression, but this analysis was sparse and several comparisons against placebo relied solely on indirect evidence. Finally, in SPMS, all drugs reduced relapse rate, though the network was sparse and relied on three studies. Time to confirmed disability progression at three months was measured in only two studies, which showed variable effects across treatments. Analyses for discontinuation due to AEs in RRMS and SPMS were indicative, but again did not point to one drug being more likely than another to result in discontinuation due to an AE.

We were unable to undertake meta-analyses for additional outcomes—MS symptoms, health-related quality of life and freedom from disease activity—due to heterogeneity, sparsity and poor reporting for these outcomes. Additionally, no studies reported discontinuation due to loss of effect attributed to neutralising antibodies.

Conclusions are tempered by several considerations. Analyses did not show a clear 'winner' across outcomes, and, again, comparisons between drugs estimated as part of NMA models were in the main inconclusive. Though the main model for ARR was best populated, analyses for relapse severity were sparse. Analyses for time to disability progression confirmed at six months were especially sparse. In particular, several comparisons of drugs vs. placebo estimated as part of this last model relied exclusively on indirect evidence. Moreover, analyses for time to progression confirmed at three and at six months did not show a consistent pattern except that all drugs were beneficial in delaying disability progression. This is particularly concerning, as progression confirmed at six months is considered to be a 'stronger' outcome than progression confirmed at three months. NMA models also had imbalanced risk of bias across the networks of studies. For example, most active vs. active trials were open-label. Finally, trials relied on short follow-up, mostly less than two years in duration.

Looking forward, we use drug-specific estimates for ARR, for disability progression sustained at 3 months, and for disability progression sustained at 6 months as derived from our NMAs in economic modelling presented in Chapter 12. Our NMAs inform key clinical parameters in sensitivity analyses for our base case model.

10 COMPANY SUBMISSIONS: CLINICAL EFFECTIVENESS

Three submissions were received, from:

- Merck for IFN β-1a 44 µg and 22 µg IM three times weekly (Rebif),
- Teva for GA 20 mg SC daily or 40 mg SC thrice weekly (Copaxone), and
- Biogen for pegylated IFN β-1a 125 µg SC every two weeks (Plegridy) and IFN β-1a 30 µg IM weekly (Avonex).

10.1 *IFN β-1a 44 µg and 22 µg IM three times weekly (Rebif): summary of Merck submission*

The clinical effectiveness section of the submission presents an overview of the relevant trials sponsored by the manufacturer, reporting the following clinical effectiveness data.

10.1.1 Clinical effectiveness of Rebif in RRMS

The company submission stated that in patients with RRMS, Rebif demonstrated short-term and long-term efficacy in reducing relapses and delaying disease progression when compared with best supportive care. The submission included findings from PRISMS 1998,[187] including its long-term and observational extensions, to support this claim. The company submission also presented head-to-head trials, including EVIDENCE 2007,[193] IMPROVE 2012[205] and REGARD 2008.[190]

10.1.2 Clinical effectiveness of Rebif in CIS

The company submission stated that in patients with CIS, Rebif demonstrated a reduction in the number of patients who progress to a diagnosis of MS over the short and long term when compared with best supportive care. The submission included findings from REFLEX 2012,[173] including its long-term and observational extension, to support this claim.

10.1.3 Clinical effectiveness of Rebif in SPMS

The company submission stated that in trials including subsets of patients with SPMS with relapses, Rebif has some, but not significant, effect on reducing time to disability progression, and a significant effect in reducing relapse rate. The submission included findings from SPECTRIMS 2001[222] to support this claim.

10.1.4 RSS findings on clinical effectiveness of Rebif

The year 10 analysis and data for Rebif were included in the submission. The company submission stated that the hazard ratios estimated from the RSS for disability progression in Rebif as compared to best supportive care ([redacted]) were within the 10% range for the target hazard ratio needed to result in clinical effectiveness. The company submission also noted that the RSS yielded an estimate of effectiveness for Rebif similar to estimates from the PRISMS 1998 trial.

10.1.5 Our assessment of the Merck submission

Our AMSTAR assessment of the company submission can be found in Table 18.

Table 18: AMSTAR appraisal of the Merck company submission

AMSTAR Checklist	**Manufacturer's submission**
1. Was an 'a priori' design provided?	Yes - The manufacturer's submission SR protocol was described in the CS Appendix.
2. Was there duplicate study selection and data extraction?	Yes - All abstracts were reviewed by two experienced systematic reviewers according to the eligibility criteria; any difference in opinion regarding eligibility was resolved through discussion with a third reviewer. The same process was applied to the subsequent review of full papers.
3. Was a comprehensive literature search performed?	Yes - Searches were performed in the following electronic databases: MEDLINE® and MEDLINE® In-process (OVID SP); EMBASE (OVID SP); The Cochrane Central Register of Controlled Trials (CENTRAL); PubMed (for E-publications ahead of print). Abstracts from the following key international conferences were searched: Americas Committee for Treatment and Research In Multiple Sclerosis (ACTRIMS) Annual Meeting (2015); European Committee for Treatment and Research In Multiple Sclerosis (ECTRIMS) Annual Congress (2015); ACTRIMS and ECTRIMS joint meeting (2014); American Academy of Neurology (AAN) Annual Meeting (2015); American Neurological Association (ANA) Annual Meeting (2014 and 2015). Searches were run on 5 October 2015.
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	No inclusion of grey literature
5. Was a list of studies (included and excluded) provided?	Included studies were listed; excluded studies were not listed in the main submission but those excluded from the NMA were listed in the NMA document
6. Were the characteristics of the included studies provided?	Intervention, dose, regimen, N, and the data arising from the review that was used to inform the network meta-analysis are shown in the Appendix. Comparison tables of patient baseline characteristics and for the outcomes of annualised relapse rate (ARR) and sustained disability progression in the identified RCTs are available on request.
7. Was the scientific quality of the included studies assessed and documented?	Quality appraisal tables are available on request; not supplied to due volume of pages.
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Not stated that quality of studies used in formulating conclusions; no mention of sensitivity analyses by study quality.
9. Were the methods used to combine the findings of	Methods appear appropriate

studies appropriate?	
10. Was the likelihood of publication bias assessed?	Not stated
11. Was the conflict of interest included?	Manufacturer's submission

10.1.6 Review of network meta-analysis methods

Model type

NMA models were estimated in the Bayesian framework. Both fixed effects and random effects models were assessed according to the relative treatment-specific effect. The fit of the fixed and random effects models was compared using the deviance information criterion (DIC). Lower DIC is indicative of better fit. The best-fitting model was identified for each analysis. Where the fit was similar between fixed and random effects models, the random effects model was adopted as a conservative approach. Moreover, the NMA included a comparison of the posterior distribution of between study standard deviations with the prior distributions to assess whether it was updated by the available evidence (i.e. the additional information had had an effect). Consistency was assessed using node-splitting analyses.

[redacted]

Prior distributions and estimation

The models were fitted using the OpenBUGS software package version 3.2.2. Models used 100,000 burn-in simulations with 150,000 simulations used. Flat priors were used in all cases for the treatment-specific, study-specific and between-study variance terms.

Interventions

The NMA included all trials testing licenced drugs with dosages at or below the recommended dose. Interventions and comparators of interest were immunosuppressives or immunomodulators: alemtuzumab (Lemtrada®), BG-12 (Tecfidera®), fingolimod (Gilenya®), glatiramer acetate (Copaxone® [GA]), intramuscular IFN-β1a (Avonex®), IFN-β1b (Betaferon®), pegylated IFN-β1a, natalizumab (Tysabri), and teriflunomide (Aubagio).

Outcomes and data preparation

The NMA included analyses for ARR and disability progression. Models for disability progression included progression confirmed at 6 months with additional data from confirmation at 3 months where 6 month data were not available, and the converse; i.e. disability progression confirmed at 3 months with additional data from confirmation at 6 months where 3 month data were not available. One potential issue with this method is that analyses are not strictly interpretable, and rely on an assumption that progression estimates from 3 months and 6 months are exchangeable, but this is unclear and may be questionable.

Authors used an optimisation algorithm to estimate person-years and number of relapses to be used with an exact Poisson likelihood. Authors also used summary hazard ratios in estimating disability progression models.

One strength of the reporting in this NMA was transparency about included effect sizes for each model.

Participants

The NMA included all patients with a diagnosis of RRMS or PRMS. The NMA included an informal assessment of similarity of baseline characteristics across trials. Authors did not undertake meta-regression or subgroup analyses.

Included trials

Unlike the assessment group's NMA, the company submission NMA included trials with comparators outside the NICE scope. However, even though the company submission NMA did not set explicit restrictions on duration of follow-up, several trials appeared to be missing from the NMA, including BRAVO 2014,[196] IMPROVE 2012,[205] Knobler 1993,[209] Kappos 2011,[197] and GATE 2015.[218] While some of these trials may have been published after the last search, it is not clear why they were excluded.

10.1.7 Findings from the network meta-analysis presented in the company submission

ARR findings

A lower ARR is indicative of better response. Though the submitted NMA covered a variety of doses and drugs, we summarise here only those results relating to licenced doses of the drugs under consideration.

[redacted]

Sustained disability progression findings

[redacted]

10.1.8 Results as compared to assessment group NMAs

For ARRs compared to placebo, the results for IFN β-1a 22 µg three times weekly and IFN β-1a 44 µg three times weekly were similar in the company's NMA and in the assessment group's NMA.

[redacted]

[redacted] This was also the case in the assessment group's NMA.

The 'blending' method used by the company submission NMA for analyses of sustained disability progression at 3 months and 6 months means that their analyses are not strictly commensurate with the assessment group's NMAs. Over both analyses, the assessment group's NMAs suggested a significant effect for IFN β-1a 22 µg three times weekly and IFN β-1a 44 µg three times weekly. [redacted]

10.1.9 Summary of the Merck submission

Quality of the submitted systematic review and NMA were reasonable and appropriate, and findings matched in magnitude and direction, though not always in significance, with corresponding findings from the assessment group's NMAs. The assessment group did note challenges with the interpretation of the combined disability progression models, and observed that several ostensibly relevant trials were not included in the NMA. Additionally, the company submission included trials of patients with PRMS, which was outside of the NICE scope for this submission. NMAs were not presented for CIS or SPMS.

10.2 *GA 20 mg SC daily or 40 mg SC thrice weekly (Copaxone): summary of Teva submission*

10.2.1 Clinical effectiveness of Copaxone in RRMS and CIS

The company submission states that GA in both of its doses (20 mg SC daily and 40 mg SC thrice weekly) reduces ARR and disability progression. It cites Bornstein 1987,[168] Cop1 MSSG 1995,[215] ECGASG 2001,[217] Calabrese 2012,[186] CONFIRM 2012[214] and GALA 2013[219] in support of this claim. It further notes that GA in its 20 mg SC daily dose delays progression to clinically definite MS, citing PreCISe 2009[172] and its extension.

10.2.2 RSS findings on clinical effectiveness of Copaxone

The company submission states that based on the year 10 RSS analysis, GA 20 mg SC once daily reduced EDSS disability progression at 10 years ([redacted]), with no evidence of a treatment waning effect at 10 years compared to the updated 6-year analysis. Based on the year 6 data, the company submission stated that as compared to the IFN β cohort together, the Copaxone cohort [redacted]

10.2.3 Our assessment of the Teva submission

Our assessment of the systematic review contained in the Teva submission can be found in Table 19.

Table 19: AMSTAR appraisal of the Teva company submission

AMSTAR Checklist	**Manufacturer's submission**
1. Was an 'a priori' design provided?	Yes - protocol in CS Appendix
2. Was there duplicate study selection and data extraction?	Not stated
3. Was a comprehensive literature search performed?	Yes - PubMed, Embase, Cochrane Library
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	No mention of grey literature
5. Was a list of studies (included and excluded) provided?	Included studies: yes in CS Appendix; excluded studies: no
6. Were the characteristics of the included studies provided?	Yes in CS Appendix
7. Was the scientific quality of the included studies assessed and documented?	Yes in CS Appendix
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	An analysis of the heterogeneity in the included studies was carried out and a number of potential sources of heterogeneity were identified. The main sources of heterogeneity and their impacts were investigated further through sensitivity analyses. The sensitivity analyses conducted were: exclusion of studies with less than two years follow-up, exclusion of studies with less than 50 patients *per* treatment arm, and a separate analysis was conducted of three-month and six-month confirmed disability progression. However, it does not appear that sensitivity analyses were carried out using overall quality scores. Results of RCTs were shown separately from non-randomised studies.
9. Were the methods used to combine the findings of studies appropriate?	Results tabulated but not combined in forest plots
10. Was the likelihood of publication bias assessed?	Not stated
11. Was the conflict of interest included?	Manufacturer's submission

10.2.4 Review of network meta-analysis methods

Model type

Models were estimated in the Bayesian framework. Both fixed effects and random effects models were estimated and then compared on fit. Authors also estimated pairwise meta-analyses and heterogeneity statistics.

Prior distributions and estimation

Authors used non-informative prior distributions. The authors used WinBUGS version 1.4.3 software (MRC Biostatistics Unit, Cambridge, UK) in all NMAs. In each model, two parallel chains were run, with a 50,000 iteration burn-in period. A total of 20,000 iterations against a thinning fact of 10 were sampled from each of the two chains. Convergence was assessed with Brooks-Gelman-Rubin diagnostics.

Interventions

All licenced drugs were included. Dosages were not specified, which poses significant ambiguity about whether all dosages in the literature were considered or only those which correspond to the marketing authorisation. It appears that both dosages of GA were pooled into one node in the analysis, but this was not clear.

Outcomes and data preparation

For disability progression, the authors estimated the number of events and the person-years of follow-up in each study and analysed data using a binomial likelihood with a complementary log-log link. Analyses used a model where disability progression confirmed at 6 months was preferred, with 3 months used when 6 month data were not available. Analyses of ARR used an arm-level data approach with a Poisson likelihood.

Though authors presented relevant arm-level data for trials including GA in the text of the company submission, it was not clear what the NMA inputs were. No forest plots for individual study estimates were presented.

Participants

Only participants with RRMS were included in the NMA.

Included trials

Unlike the assessment group's NMA, the company submission NMA included trials with comparators outside the NICE scope. However, authors also excluded studies with follow-up of less than 6 months. Within these restrictions, it appears that authors captured all relevant trials, though Knobler 1993[209] was not included in the analysis.

10.2.5 Findings from the network meta-analysis presented in the company submission

1.1.1.1 ARR findings

[redacted]

1.1.1.2 Sustained disability progression findings

[redacted]

10.2.6 Results as compared to assessment group NMAs

[redacted]. HRs for disability progression at 3 months and 6 months were blended and pooled across Copaxone doses in Teva's submission, but analysed separately in the assessment group NMA; thus, findings are not strictly commensurate.

[redacted] in the assessment group NMA the HR for disease progression for GA was significantly better than placebo at 3 months (0.76, [0.60, 0.97]) only, and not at 6 months (0.82, [0.53, 1.26]). Point estimates for disability progression were similar.

10.2.7 Summary of the Teva submission

Quality of the submitted systematic review and NMA were reasonable and appropriate, and findings matched in magnitude and direction, though not always in significance, with corresponding findings from the assessment group's NMAs. The assessment group did note challenges with the interpretation of the combined disability progression models, but found that inclusion of trials was reasonable and clear. However, there was a considerable lack of transparency about what inputs for each NMA model were, and no forest plots were presented. Additionally, it was not clear how dosages were used in the included models. NMAs were not presented for CIS.

10.3 *IFN β-1a 30 µg IM weekly (Avonex) and pegylated IFN β-1a 125 µg SC every two weeks (Plegridy) summary of Biogen submission*

10.3.1 Clinical effectiveness of Avonex in RRMS and CIS

The company submission stated that IFN β-1a 30 µg IM weekly is effective in reducing relapse rate and disability progression as compared to placebo, and cited MSCRG 1996[198] and its observational extension as evidence. The company submission further states that IFN β-1a 30 µg IM weekly is effective in delaying clinically definite MS in patients with CIS, and cites CHAMPS[170] and its open-label extensions in support of this.

10.3.2 RSS findings on clinical effectiveness of Avonex

Clinical effectiveness of Avonex in the RSS showed that in the year 10 analysis, [redacted]

10.3.3 Clinical effectiveness of Plegridy in RRMS

The company submission stated that pegylated IFN β-1a 125 μg SC every two weeks is effective in reducing relapse rate and disability progression as compared to placebo, and cited ADVANCE 2014,[211] as well as its extension, in support of this. Plegridy was not included in the RSS.

10.3.4 Our assessment of the Biogen submission

Our assessment of the systematic review contained in the Biogen submission can be found in Table 20.

Table 20: AMSTAR appraisal of the Biogen company submission

AMSTAR Checklist	**Manufacturer's submission**
1. Was an 'a priori' design provided?	Yes (Table 37 in the CS)
2. Was there duplicate study selection and data extraction?	Yes - the literature searches for this review were conducted as part of a wider program of research on treatments for MS. Search strategies included terms designed to identify studies of all EU approved treatments or treatments expected to be approved in the near future in either CIS, RRMS or SPMS patients. Identified studies were independently assessed by a reviewer in order to ascertain whether they met the pre-defined inclusion and exclusion criteria (based on population, interventions, comparators, and outcomes [PICOS]), and any uncertainties were resolved by discussion with a second reviewer. Data were extracted from eligible publications into a pre-defined table by a reviewer. All studies meeting the inclusion criteria described in Table 37 were initially included in the systematic review. These studies were then screened by two reviewers against the PICOS criteria of the NICE MTA of IFN-β and GA for treating multiple sclerosis to identify relevant studies for inclusion in meta-analyses and narrative syntheses.
3. Was a comprehensive literature search performed?	Yes - searches were conducted in October 2014 and updated on 9th November 2015 in MEDLINE (including MEDLINE In-process and MEDLINE Daily Update), Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Science Citation Index (SCI), with no restrictions on date. Using Boolean operators, the searches combined terms (including MeSH headings as appropriate) for the condition, the treatments and the outcomes of interest. A rapid appraisal was also conducted to identify relevant systematic reviews, technology appraisals, guidelines, and guidance in the following databases: Cochrane Database of Systematic Reviews (CDSR) Database of Abstracts of Reviews of Effects (DARE) Health Technology Assessment Database (HTA) National Institute for Health and Care Excellence (NICE)

	National Institute for Health Research (NIHR) Canadian Agency for Drugs and Technologies in Health (CADTH) International Prospective Register of Systematic Reviews (PROSPERO). In addition, searches were conducted in the clinical trial registers to identify data from ongoing or unpublished clinical trials: ClinicalTrials.gov, Current Controlled Trials, International Clinical Trials Registry Platform (ICTRP), PharmNetBund, and EU Clinical Trials Register (EUCTR). The full search strategies can be found in Appendix E. Hand searching of reference lists from included studies and relevant systematic reviews was also conducted.
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Unpublished trials were sought
5. Was a list of studies (included and excluded) provided?	Included: Yes - a summary of the 16 studies included in the MTC is provided in CS Appendix G (Table 55 in the CS). Details of studies included in the systematic review but excluded from the MTC are provided in CS Table 54 (CS Appendix F), along with rationale for their exclusion. Excluded: yes in CS Appendix
6. Were the characteristics of the included studies provided?	Yes – Appendix G in the CS
7. Was the scientific quality of the included studies assessed and documented?	Yes (Table 57 and Appendix G in the CS)
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Not stated
9. Were the methods used to combine the findings of studies appropriate?	Yes - sensitivity analyses took into account heterogeneity
10. Was the likelihood of publication bias assessed?	As stated in the report, 'Publication bias would have been assessed using funnel plots (e.g. SE (log [RR]) vs RR) where at least ten studies were included in an analysis; however, there were no head-to-head comparisons that included enough studies to produce a funnel plot.'
11. Was the conflict of interest included?	Manufacturer's submission

10.3.5 Review of network meta-analysis methods

Model type

Random effects and fixed effects models were both estimated and compared on the deviance information criterion, with random effects models preferred throughout. Further iterations were captured if convergence was in question.

Prior distributions and estimation

NMAs were estimated in the Bayesian framework using gemtc in the R environment. After 50,000 burn-in iterations, a further 50,000 iterations were captured. Convergence was assessed using the Brooks-Gelman-Rubin diagnostic. Prior distributions were non-informative.

Interventions

All studies testing comparisons between the drugs in the NICE scope and at the dosages contained in the marketing authorisation were included. Thus, dosages were clearly specified.

Outcomes and data preparation

Analyses included ARR for studies with follow-up of at least 12 months; HR for disability progression confirmed at 3 months and, separately, at 6 months, with follow-up data at 12 or 24 months; and for either any AE or serious AE. Data were analysed as log rate ratios, log hazard ratios or log odds ratios with corresponding standard errors. Authors do not provide a justification for models that were intended to be estimated at either 12 or 24 month follow-up, or why they chose to stratify estimates in this way. There is a lack of clarity regarding study inputs, and no forest plots for individual study estimates are presented.

Participants

Though the search included patients with RRMS, CIS and SPMS, it appears that only RRMS trials were meta-analysed.

Included trials

Studies excluded from the NMA and reasons for exclusion were clearly documented. However, the Biogen NMA excluded several studies on what would appear to be the basis of short-term follow-up. This is not made explicit.

10.3.6 Findings from the network meta-analysis presented in the company submission

The NMA found that IFN β-1a 30 µg IM weekly significantly reduced ARR relative to placebo, but not against other treatments. In fact, in the company submission NMA, GA 20 mg SC once daily was more effective in reducing ARR than IFN β-1a 30 µg IM weekly. Findings for disability progression confirmed at 3 or 6 months were not significant relative to other treatments or placebo.

The NMA found that for ARR, no significant treatment effects were observed between pegylated IFN β-1a 125 µg SC every two weeks and other treatments, or between pegylated IFN β-1a 125 µg SC every two weeks and placebo, though the last finding was marginally non-significant (RR=0.64, 95% CI [0.41, 1.04]). For sustained disability progression sustained for 3 or 6 months, no statistically significant differences were observed with pegylated IFN β-1a 125 µg SC every two weeks relative to other treatments or placebo.

Analyses for AEs were only conducted for IFN β-1a 30 µg IM weekly. No differences were found relative to placebo or other treatments.

Authors estimated a wide variety of sensitivity analyses summarised in CS Appendix H.

10.3.7 Results as compared to assessment group NMAs

Biogen's NMA on the whole did not identify statistically significant benefit from pegylated IFN β-1a 125 µg SC every two weeks or IFN β-1a 30 µg IM weekly on the key outcomes, which were ARR and disability progression confirmed at 3 months and at 6 months. However, both drugs demonstrated statistically significant effectiveness on each of these three outcomes in the assessment group's NMA. Point estimates were generally similar between the NMAs for ARR and time to disability progression confirmed at 3 months. This discrepancy may be due to the choice of prior distribution for between-trial variance in the base case of the company submission NMA, as well as the apparent exclusion of studies with short-term follow-up in the same. Notably, the assessment group considered several more drugs in the analysis of disability progression confirmed at 6 months than it would appear were included in the company submission's NMA for this outcome.

10.3.8 Summary of the Biogen submission

Quality of the submitted systematic review was both reasonable and appropriate. While a strength of the models was the explicit approach to dosages of comparators included, inputs in the NMA models were opaque and no study-level forest plots were presented with specific estimates. Moreover, the initial decision to stratify estimates by 12 or 24 months was not clearly explained, and apparent exclusions based on follow-up were not explicitly declared.

11 METHODS FOR ASSESSMENT OF COST EFFECTIVENESS STUDIES

11.1 *Identification of studies (clinically isolated syndrome)*

11.1.1 Introduction

The purpose of this systematic review was to identify existing cost-effectiveness model designs in CIS, and to identify parameter values (e.g. health state utilities and costs) suitable for use in a decision analytical model. We did not identify a suitable systematic review in CIS in the overview of systematic reviews (see Appendix 5) and scoping searches did not find many existing models. Therefore, our searches were broad and not limited by date.

11.1.2 Search strategy

The following electronic databases were searched: MEDLINE (Ovid); MEDLINE In-Process Citations and Daily Update (Ovid); Embase (Ovid); Cochrane Library (Wiley), including NHS EED, and HTA databases; Science Citation Index (Web of Knowledge), Research Papers in Economics (RePEC) and the Cost-effectiveness Analysis (CEA) Registry. The database searches were designed to be broad in nature, with search terms for CIS combined with terms for economic / HRQoL generic measures (based on recognised search filters[224-227]) where appropriate. A full record of searches is provided (see Appendix 6). The searches were not limited by publication date. All bibliographic records identified through the electronic searches and were collected in a managed reference database. The reference lists of included studies were also checked. Grey literature searches were undertaken using the online resources of various regulatory bodies, health service research agencies, professional societies and patient organisations and were undertaken concurrently for both clinical effectiveness and cost-effectiveness. For a record of these searches, see the clinical effectiveness record of searches in Appendix 1.

We undertook several additional searches. We checked the reference lists of primary studies identified through database searches for studies on the natural history of people with CIS, and CIS patient registries. We also undertook targeted database searches to identify any additional CIS patient registries including data from before 1995 (see Appendix 7). We searched studies citing included studies to identify more recent literature.

11.1.3 Inclusion and exclusion criteria

Studies meeting the following criteria were included in the review.

Population: Adults (≥18 years old) who have been diagnosed with CIS; defined as people who experienced a single demyelinating event in one or several areas of the central nervous system within the previous two months

Intervention: Disease modifying treatments (e.g. IFNβ-1a, IFNβ-1b) licensed for the treatment of CIS

Comparator: Best supportive care without DMTs or another DMT (e.g. IFNβ-1a, IFNβ-1b and glatiramer acetate) licensed for the treatment of CIS

Outcome: Cost per QALY, cost per life-year gained and cost per multiple sclerosis delayed

Study design: Economic analysis and included a decision analytical model

Language: English and Spanish

All publication types were included.

Other studies that contained information on parameter values (e.g. health state utilities, costs, natural history outcomes, etc.) suitable for use in a decision analytical model were identified at this stage and set aside for later review.

Studies in people diagnosed with relapsing remitting multiple sclerosis, secondary progressive multiple sclerosis, or primary progressive multiple sclerosis were excluded.

11.1.4 Study selection

Studies were first reviewed on title and abstract by two reviewers working independently (HM and PA). Subsequently, full-text studies were accessed and checked against the criteria for inclusion. As mentioned above, studies that presented information on costs and outcomes related to the natural history of or disease modifying treatment for people with CIS were also examined at this stage and set aside for later review.

11.1.5 Data extraction

Data extraction was conducted by two reviewers (HM and PA). Information extracted by one reviewer was cross-checked by the other. Any disagreements were resolved by discussion or by recourse to a third-party reviewer (JM). We extracted study details (title, author and year of study), background characteristics (population, intervention, comparator and outcomes), methods (study perspective, time horizon, discount rate, measure of effectiveness, assumptions and analytical methods), results (study parameters, base-case and sensitivity analyses), discussion (study findings, limitations of the models and generalisability) and other domains (source of funding and conflicts of interests). An example of the data extraction sheet is presented in Appendix 6.

11.1.6 Quality assessment

The studies were appraised using the Consolidated Health Economic Reporting Standards (CHEERS)[228] and Philips'[229] frameworks for best practice in economic evaluation and decision analytical modelling, respectively. The CHEERS assessment tool consists of six dimensions: title and abstract, introduction, methods, results, discussion and other. Under these dimensions/attributes, there are a series of questions to check whether these have been satisfactorily reported (see Appendix 6). The Philips reporting quality tool consists of two main dimensions: structure of the model and information used to parameterise the model. Under these dimensions/attributes there are a series of questions to check whether these have been satisfactorily conducted (see Appendix 6).

Reporting quality assessment was undertaken by two reviewers (HM and PA). Study quality assessed by HM was cross-checked by PA, and vice versa. Any disagreements were resolved by discussion or by recourse to a third-party reviewer (JM).

11.1.7 Data synthesis

Findings from included studies were synthesised narratively with the goal of summarising current modelling methods.

11.2 *Identification of studies (relapsing remitting multiple sclerosis)*

11.2.1 Introduction

The purpose of this systematic review was to identify existing cost-effectiveness model designs in RRMS, and to identify parameter values (e.g. health state utilities, costs etc.) suitable for use in a decision analytical model. We identified several related systematic reviews of cost-effectiveness evaluations in RRMS in the overview of systematic reviews.[230-238] Therefore, we performed searches for primary cost-effectiveness studies from the earliest search date found in these selected reviews (i.e. 2012) to April 2016. We performed separate searches for relevant HRQoL studies with no date limits applied. We used similar well-established methods which are used for undertaking systematic reviews of clinical studies,[162].

11.2.2 Search strategy

The following electronic databases were searched separately for cost-effectiveness studies and HRQoL studies: MEDLINE (Ovid); MEDLINE In-Process Citations and Daily Update (Ovid); Embase (Ovid); Cochrane Library (Wiley), including NHS EED, and HTA databases; Science Citation Index (Web of Knowledge), Research Papers in Economics (RePEC) and the Cost-effectiveness Analysis (CEA) Registry. The database searches were kept broad, with search terms for MS combined with terms for economics / HRQoL generic measures (based on recognised search filters[224-227]) where appropriate. A full record of searches is provided (see Appendix 7). The searches for primary cost-effectiveness studies were limited by publication date from January 2012 to April 2016. HRQoL searches were not limited by publication date. All bibliographic records identified through the electronic searches were collected in a managed reference database. The reference lists of included studies were also checked. Grey literature searches was undertaken using the online resources of various regulatory bodies, health service research agencies, professional societies and patient organisations.

The following additional searches were undertaken. We checked the reference lists of primary studies identified through the searches described in the paragraph above for studies on the natural history of people with RRMS, and RRMS patient registries. We also undertook targeted database searches to identify any additional RRMS patient registries that include data from before 1995 (see Appendix 7). Citation searches on any included studies was undertaken to identify more recent literature.

11.2.3 Inclusion and exclusion criteria

Studies meeting the following criteria were included in the review:

Population: Adults (≥18 years old) who have been diagnosed with relapsing remitting multiple sclerosis

Intervention: IFNβ-1a, pegylated IFNβ-1a, IFNβ-1b or GA

Comparator: Best supportive care without DMTs or another DMT (e.g. IFNβ-1a, IFNβ-1b and glatiramer acetate) licensed for the treatment of RRMS
Outcome: Cost per QALY, cost per life-year gained and cost per multiple sclerosis delayed
Study design: Economic analysis comprising of a decision analytical model

Other studies that contained information on parameter values (e.g. health state utilities, costs, natural history outcomes, etc.) suitable for use in a decision analytical model were identified at this stage and set aside for later review.

Studies were excluded if they included people diagnosed with clinically isolated syndrome. Additionally studies were excluded if they were reported in a form of an abstract or conference proceeding, or not published in the English language.

11.2.4 Study selection

Studies were first reviewed on title and abstract by two reviewers working independently (HM and PA). Subsequently, full-text studies were accessed and checked against the criteria for inclusion. As mentioned above, studies that presented information on costs and outcomes related to the natural history of or disease modifying treatment for people with RRMS were also examined at this stage and set aside for later review.

11.2.5 Data extraction

Data extraction was conducted by two reviewers (HM and PA). Information extracted by one reviewer was cross-checked by the other. Any disagreements were resolved by discussion or by recourse to a third-party reviewer (JM). We extracted study details (title, author and year of study), background characteristics (population, intervention, comparator and outcomes), methods (study perspective, time horizon, discount rate, measure of effectiveness, assumptions and analytical methods), results (study parameters, base-case and sensitivity analyses), discussion (study findings, limitations of the models and generalisability) and 'other' (source of funding and conflicts of interests). An example of the data extraction sheet is presented in Appendix 7.

11.2.6 Quality assessment

The studies were appraised against the Consolidated Health Economic Reporting Standards (CHEERS)[228] and Philips'[229] frameworks for best practice in economic evaluation and decision analytical modelling, respectively. The CHEERS assessment tool consists of six dimensions: title and abstract, introduction, methods, results, discussion and other. Under these dimensions/attributes, there are a series of questions to check whether these have been satisfactorily reported (see Appendix 7). The Philips' reporting quality tool consists of two main dimensions: structure of the model and information used to parameterise the model. Under these dimensions/attributes there are a series of questions to check whether these have been satisfactorily reported (see Appendix 7).

Reporting quality assessment was undertaken by two reviewers (HM and PA). Studies quality assessed by one reviewer was cross-checked by the other. Any disagreements were resolved by discussion or by recourse to a third-party reviewer (JM).

11.2.7 Data synthesis

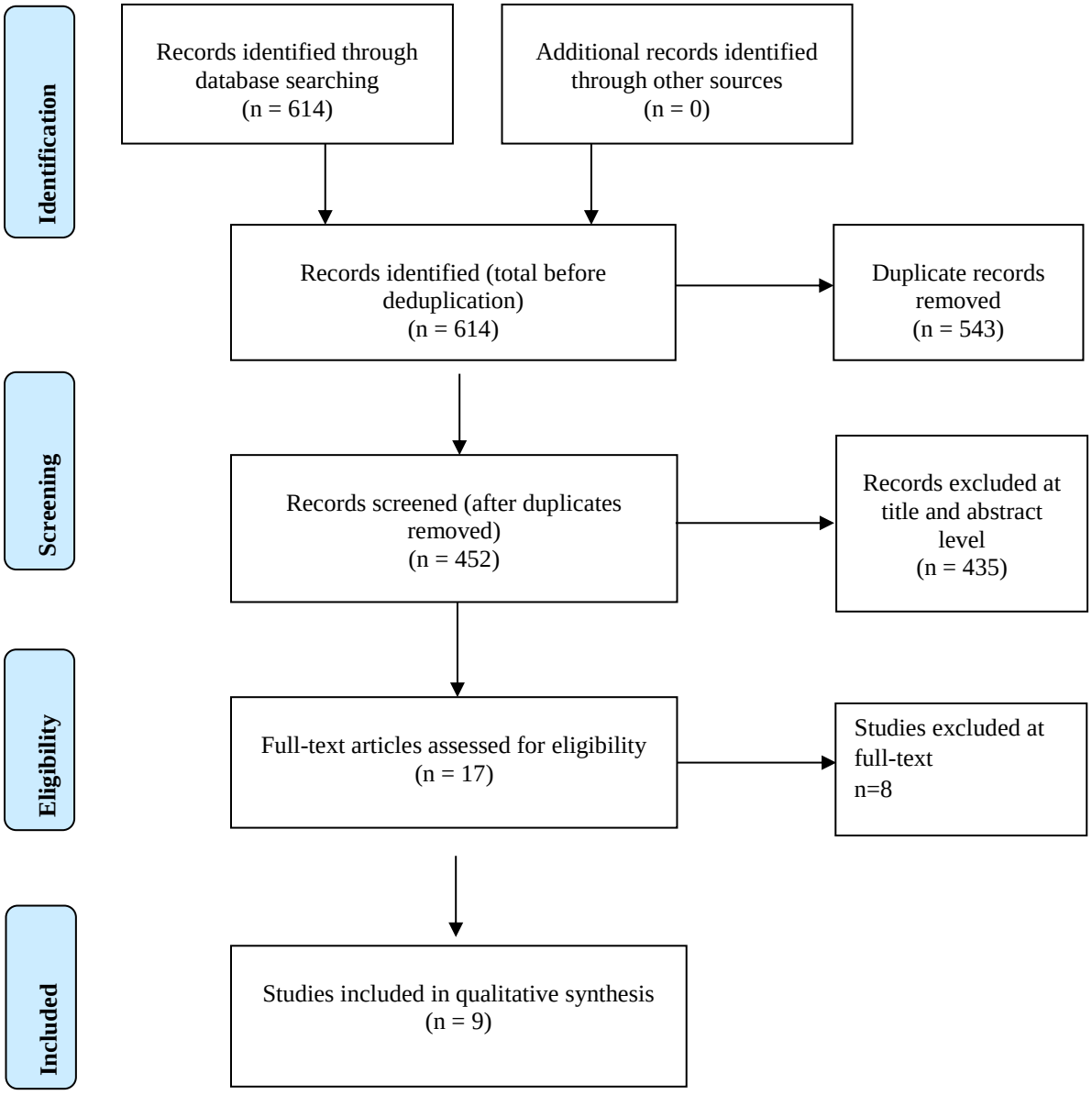
Information extracted from the included studies was summarised in a table. The findings from these studies have been compared narratively to show the current modelling methods used, and our recommendations for future modelling of RRMS are discussed.

12 RESULTS OF THE SYSTEMATIC REVIEW OF THE COST EFFECTIVENESS LITERATURE

12.1 *Results of search for clinically isolated syndrome studies*

The electronic database searches identified 614 records (Figure 24). After removing duplicates, 452 records were screened for inclusion. On the basis of title and abstract, 435 records were excluded and the remaining 17 records were included for full-text screening. A further 8 articles were excluded at the full-text stage, with the reasons for exclusion in Appendix 6, leaving nine studies[239-247]that included a decision-analytical model, which was used to estimate the cost-effectiveness of DMTs for treating people with CIS.

Figure 24: PRISMA flowchart for economic studies relating to CIS



12.2 *Description of included studies*

12.2.1 Summary of economic studies comparing DMTs for people with CIS

Fredrikson[239]

Fredrikson et al.[239] used a Markov model structure to assess the cost-effectiveness of subcutaneous IFNβ-1a three times weekly compared to no treatment for people who had experienced a single demyelinating event in one or several areas of the central nervous system within the previous two months. The model simulated the pathway for people with CIS who received disease modifying treatment versus no treatment, and the cost-effectiveness was estimated over the model's time horizon. The model started with a hypothetical cohort with a mean age of 31 years, which reflected the participants in the REFLEX trial and continued with those occupying/progressing to one of the following health states (CIS and on treatment, CIS no treatment or RRMS defined by the McDonalds 2005 criteria). Fredikson and colleagues made a number of simplifying assumptions (once people converted to RRMS, they could progress in single step increments, treatment effect was assumed to continue over the model time horizon, based on clinical judgment, a maximum duration of 25 years for treatment was applied, the probability of discontinuation of disease modifying treatment (DMT) was derived based on the three-year rate from the REFLEXION trial. This probability was applied from year 3 to the remainder of the model duration, authors assumed that 95% of people with CIS would convert to MS using the McDonald's criteria and people with MS who progressed to EDSS 7 or converted to SPMS were assumed to discontinue treatment).

Information required to populate the model was obtained from REFLEX and REFLEXION trials, and resource use and costs from published sources. Information was required on utility values associated with CIS and MS (by EDSS state), conversion rate from CIS to CDMS according to McDonald MRI criteria, annual average drop-out rate during 25 years, market share of disease modifying treatment for MS. Resource use and costs included: informal care, services, investments (house and car modifications, walking aides, wheelchairs), symptom management medication, tests (MRI scans of the brain and spinal cord in the first year of diagnosis and a brain MRI scan every year), ambulatory care, inpatient care, loss of productivity due to early retirement and short-term absence. The analysis was conducted from the societal perspective, and the results presented in terms of costs per progression-free life-years and costs per QALY gained over a 40-year time horizon. All costs were reported in Swedish Kronor, 2012 prices and converted to Euros using a historical average exchange rate from 2005. All costs and outcomes were discounted 3% per annum. Along with the cost-effectiveness analysis, Fredrikson and colleagues conducted univariate and probabilistic sensitivity analyses.

Results in terms of progression-free life-years gained, showed that there was an incremental gain of 1.63 progression-free life-years for people who received DMT compared with no treatment. Additional, the results showed that there was a 0.53 incremental QALY gain for people who received treatment. From the societal perspective, the base-case results showed cost-savings of approximately SEK 270,260.

Kobelt[240]

Kobelt and colleagues[240] used a Markov structure to assess the cost-effectiveness of using interferon beta-1b SC 250 µg every other day (betaferon) compared with no treatment for people with CIS. The model simulated the disease progression for a hypothetical cohort of people being treated for CIS and the cost-effectiveness was estimated over a 20-year time horizon. The model started with a cohort of people who received either interferon beta-1b SC 250 µg every other day (betaferon) or no treatment and continued with them remaining in the CIS health state or progressing to mild, moderate or severe multiple sclerosis disability. An illustrative Markov structure was not presented as this was an abstract.

Authors did not elaborate on the sources of information used to populate the model. All costs were reported in 2006 Euros. The primary outcome measure of effectiveness was QALYs gained over the 20-year time horizon; however, the author did not elaborate on the descriptive tools used to value these health states. All costs and benefits were discounted at 3% per annum. The analysis was conducted from the societal perspective and results were presented in terms of an incremental cost-effectiveness ratio (ICER) expressed as cost per QALYs gained. Kobelt[240] conducted sensitivity analyses by changing key model input parameters to determine the impact on the deterministic results. Additionally, a probabilistic sensitivity analysis (PSA) was undertaken.

Base-case results showed that interferon beta-1b dominated the no treatment arm. The results from the sensitivity analyses showed that the base-case results were robust to changes in model input parameters. Results from the probabilistic analysis showed that interferon beta-1b was the preferred option, with >0.5 probability of being cost-effective compared with no treatment at a willingness-to-pay threshold of 50,000€ per QALY.

Lazzaro[241]

Lazzaro and colleagues[241] developed an epidemiological/survival model to estimate the cost-effectiveness of interferon beta-1b SC 250µg every other day (Betaferon) for people with mono and multifocal CIS diagnosis compared with postponing disease modifying disease treatment until subsequent conversion to clinically definite multiple sclerosis.

Information required to populate the model was obtained from published sources. Information on incidence of CIS, utility value of CIS, conversion rate from CIS to CDMS according to McDonald magnetic resonance imaging (MRI) criteria, annual average drop-out rate during 25 years was obtained. All resource use and costs (disease modifying drugs and other drugs, outpatient diagnostic procedures, consultations and laboratory tests, hospitalization, physical therapy, walking aids, transport, working days lost by patients and their caregivers and informal care) were obtained from published sources and presented in Euros, 2006 prices. Results were presented in terms of an ICER and expressed as cost per QALYs gained over the 25-year time horizon. Measurement and valuation of preference-based outcomes have not been reported. The base-case analysis was undertaken from the Italian National Health Service (INHS) perspective and all costs and benefits were discounted at 3% per annum. To have a workable model, a number of simplifying assumptions were made. Authors undertook a number of one-way (annual consumption of and average annual compliance rate to IFN β-1b SC 250µg every other day (Betaferon); replacement of IFN β-1b with IFN β-1a SC 44 µg three days a week;

CDMS-related patient utility values) and multi-way (annual conversion rates to CDMS during year 1 and 2) sensitivity analyses, and also conducted probabilistic sensitivity analysis.

From the INHS perspective, the base-case results showed that the mean incremental costs per for people who received early treatment compared to delayed treatment was approximately 894€. Mean incremental gain for people who received early treatment compared to delayed treatment was 0.35, which equated to an ICER of approximately €2575 per QALY. From the societal viewpoint, early treatment dominated delayed treatment, meaning that early treatment was cheaper than delayed treatment and more effective. Results from the one-way and multi-way sensitivity analyses showed that the base-case results were sensitive to the change in the DMTs, and the lower limit 95% confidence intervals CDMS conversion rates during years 1 and 2 of the epidemiological model. Results from the probabilistic sensitivity analysis showed that at a €5500 willingness-to-pay for an incremental QALY, early treatment is likely to be cost-effective with a probability of 1.

Iskedjian[242]

Iskedjian 2005[242] used two Markov model structures to assess the cost-effectiveness of intramuscular IFN β-1a 30 µg once weekly (Avonex) compared to current treatment (methylprednisolone four intravenous injections of 1g for three days followed by 14 days of oral steroids 1mg twice daily) for people who had experienced a single, clinically diagnosed, demyelinating event. The model simulated the pathway for people with CIS who received DMTs versus symptom management, and the cost-effectiveness was estimated over a 12-year time horizon. The first model started with a hypothetical cohort of people receiving one of the two treatments and captured the costs and outcomes associated with the progression to clinically definite multiple sclerosis, and the second model estimated the long-term costs and outcomes of progression through various EDSS states [mild (EDSS ≤ 3.5), moderate (EDSS 4-5.5) and severe (EDSS ≥ 6)]. Iskedjian and colleagues made a number of simplifying assumptions; for example, people who progressed to clinically definite multiple sclerosis received no treatment benefit but accrued costs associated with their EDSS health states, people in both arms of the model received Avonex (IFN β-1a 30µg once weekly intramuscularly) once diagnosed with CDMS. Relapse rates were fixed to one every two years, relapses were assumed to last for two months and people did not discontinue from treatment (i.e. 100% compliance was assumed).

Information on transition probabilities resource use and costs were obtained from the literature. The analysis was conducted from the Canadian Ministry of Health and societal perspectives, and the results presented in terms of costs per Mono-symptomatic life years (MLY) gained, and QALYs gained over a 12-year time horizon. Utility values were derived based on the Health Utility Index (HUI) questionnaire, which was administered to Canadian MS patients. A separate analysis was undertaken, which used utility values derived from the EQ-5D questionnaire. All costs were reported in Canadian dollars, 2001 prices. All costs and outcomes were discounted by 5% per annum. Along with the cost-effectiveness analysis, Iskedjian and colleagues conducted univariate (20 and 30 year time horizons, using utility values based on EQ-5D questionnaire and varying the discount rate) and probabilistic sensitivity analyses.

Results from the Canadian Ministry of Health perspective showed that over the 12-year time horizon mean costs were CAN$173,000 and $108,000 for the Avonex (IFN β-1a 30µg once weekly intramuscularly) and the current

treatment arm, respectively. Expected mean mono-symptomatic life years gained were 4.69 and 3.48 for the IFN β-1a (Avonex) and the comparator arm, respectively, which equated to an ICER of CAN$53,110 per MLY gained. Results from the societal perspective showed that over the 12-year time horizon mean costs were CAN$317,000 and $262,000 for the Avonex and current treatment arms. Expected mean mono-symptomatic life years gained was 4.69 and 3.48 for the IFN β-1a (Avonex) and current treament arms. which equated to an ICER of approximately CAN$44,800 per MLY gained. The ICERs per QAMLY gained were approximately CAN$227,600 and CAN$189,300 from the Ministry of Health and societal perspective, respectively. Using utilities derived from the EQ-5D, the ICERs per QAMLY gained were approximately CAN$116,100 and CAN$91,200 from the Ministry of Health and societal perspective. Sensitivity analysis results demonstrated that in the progression to clinically definite multiple sclerosis model, the results were sensitive to the time horizon and the rate of progression the clinically definite multiple sclerosis. Using a six-year time horizon resulted in an incremental cost per MLY gained of CAN$85,100 and CAN$79,300 for the Ministry and societal perspective. Increasing the probability of progressing to clinically definite multiple sclerosis reduced the incremental cost per MLY gained to CAN$44,700 and CAN$35,600 for the Ministry of Health and societal perspective, respectively. Decreasing the probability to progression to clinically definite multiple sclerosis resulted in an increase in the incremental cost per MLY gained to CAN$67,800 and CAN$60,200 for the Ministry of Health and societal perspectives.

Arbizu[243]

The study by Arbizu et al.[243] was presented as an abstract from conference proceedings. Arbizu et al undertook a cost-utility analysis comparing the costs and consequences of providing supportive care to treatment with IFN β-1b in Spanish patients who have incident CIS. They estimated the costs from the societal perspective and adjusted to 2008 Euros. A 3% discount rate was applied to future costs and health benefits. They used a Markov model and EDSS scores defined initial health states. In their analyses they assumed that those who progressed to RRMS would start IFN β-1b and would remain on treatment until EDSS worsened to 6.5. The BENEFIT trial findings were used to model EDSS progression over time and transitions from CIS to MS. Cost and utility scores were predominantly obtained from published sources.

Their main findings suggest that when the model was run over a 50-year time horizon the ICER of IFN β-1b versus no treatment was €20,500/QALY gained. Their findings were sensitive to time horizon, IFN β-1b cost and risk of disease progression on treatment.

Caloyeras[245]

The study by Caloyeras et al.[245] is presented as an abstract of conference proceedings. Caloyeras et al[245] undertook a cost-utility analysis comparing the costs and consequences of providing supportive care to treatment with IFN β-1b in Australian patients who have incident CIS. They used findings from the BENEFIT study to determine initial EDSS scores for those with CIS, subsequent risk of progression in EDSS scores and risk of progressing to RRMS. They estimated the costs from the societal perspective and adjusted to 2007 Austrailian dollars (AUD). A discount rate of 5% was applied to discount future costs and health benefits, in accordance with Australian policy guidelines. They used a Markov model and EDSS scores defined initial

health states for CIS and RRMS. The costs and utilities attached to treatment health states for CIS and RRMS were identical, and dependent on the EDSS score. DMTs were assumed to discontinued, when disability worsened to EDSS score 6.5. Published sources were used to estimate costs and utility weights for health states.

When the model was run over a 25-year time horizon the ICER of IFNB-1b versus supportive care was AUD 20,000 (USD 14,000) per quality-adjusted life year (QALY) gained.

Caloyeras[244]

The study by Caloyeras et al[244] is presented as an abstract of conference proceedings, with poster presentation retrieved for appraisal. Caloyeras et al undertook a cost-utility analysis comparing the costs and consequences of providing supportive care to treatment with IFN β-1b in Australian patients with incident CIS. They used findings from the BENEFIT trial to determine initial EDSS scores for those with CIS, subsequent risk of progression in EDSS scores and risk of progressing to RRMS. They estimated the costs from the societal perspective and adjusted to 2007 AUD. A national guideline of 5% was applied to discount future costs and health benefits. They used a Markov model and EDSS scores defined initial health states for CIS and RRMS. The costs and utilities attached to treatment health states for CIS and MS were same, and dependent on EDSS score. DMTs were assumed not to discontinue, unless disability worsened to EDSS score 6.5. Patients were limited to one adverse event per annum.

Their main findings suggest that when the model was run over a 25-year time horizon the ICER of IFN β-1b versus no treatment was AUD 68,000 per QALY gained.

It is of note that these findings are presented by the same group as Caloyeras et al[245]. A different of cost per QALY was derived given even though it appears as though the same setting/perspective, time horizon, model structure and underlying trial data from the BENEFIT trial were used.

Caloyeras[246]

Caloyeras et al.[246] used a Markov model structure to assess the cost-effectiveness of IFN β-1b (250 μg once daily) compared to best supportive care for people with their first clinical event suggestive of MS. The model simulated the pathway for people with CIS who received DMTs versus best supportive care, and the cost-effectiveness was estimated over the model's time horizon. The model started with a hypothetical cohort of people 30 years old who were diagnosed with CIS and had an EDSS level of 0-5.5, and continued with people occupying/progressing to one of the following seven health states (Markov model with seven health states (EDSS 0.0, EDSS 1.0-1.5, EDSS 2.0-2.5, EDSS 3.0-3.5, EDSS 6.0-7.5 non-relapse, EDSS 8.0-9.5 non-relapse and EDSS 10 (MS-related death)). Caloyeras and colleagues made a number of assumptions (progression in EDSS levels modelled independently of progression to MS; two types of relapses modelled: relapse resulting in progression from CIS to MS and relapse after progression to MS; all–cause mortality estimated using life tables; MS specific mortality only when EDSS score 10 and people who discontinued treatment did not restart DMTs).

Clinical information (e.g. hazard ratios for DMTs compared with placebo) required to populate the model was obtained from the BENEFIT trial. Information on utility associated with EDSS levels was obtained from published sources. Resource use and costs included hospital inpatient care, ambulatory care, tests, drugs (DMTs

and other drugs), services, adaptations/investments and costs of informal care. Costs associated with relapses were estimated from a cross-sectional web-based survey. The analysis was conducted from the Swedish societal perspective, and the results presented in terms of costs per QALY gained over a 50-year time horizon. All costs were reported in Swedish kronor, 2009 prices. All costs and outcomes were discounted 3% per annum. Along with the cost-effectiveness analysis, Caloyeras and colleagues have undertaken one-way sensitivity analysis (acquisition costs, EDSS threshold for discontinuation, time horizon of the model, EDSS progression probability and discount rates) and probabilistic sensitivity analysis (drug acquisition costs, direct and indirect costs, utilities, EDSS progression probabilitieis, treatment discontinuation rate, relaspse rate) using uniform distribution and varying model parameters by ±2.5%.

Base case results showed that treatment with IFN β-1b dominated the best supportive care arm (commencing treatment when people progressed to RRMS). People who started on early treatment accumulated slightly higher direct medical costs per patient, but lower direct non-medical costs. Results from the sensitivity analyses demonstrated that the base case results were robust to changes made to model parameters. However, the model findings were sensitive to changes made to the time horizon of the analysis. Undertaking the analysis over a shorter 5-year time horizon found, early treatment was not cost-effective (1.32 million SEK).

Zarco[247]

Zarco and colleagues[247] used a decision tree structure to assess the cost-effectiveness of IFN β-1a or IFN β-1b compared to best supportive care for people who are diagnosed with clinically isolated syndrome. The model started with a hypothetical cohort of people with CIS and continued with a proportion of people having a relapse or not having a relapse at a one-year time horizon. At the two-year time horizon, the model considers the proportion of people who progressed to CDMS and those remaining in a CIS health state. The report was unclear on the assumptions made in the model.

Infromation on the progression from CIS to CDMS in an untreated population was obtained from the BENEFIT trial. Information on treatment efficacy of disease modifying treatments was obtained from clinical trials. Resource use and costs were estimated from a hospital-level micro-costing study and treatment costs were estimated from national health incurance. The analysis was conducted from the Columbian societal perspective, and the results presented in terms of costs per QALY and cost per diability adjusted life years over a 2-year time horizon. All costs were reported in USA dollars, 2011 prices. All costs and outcomes were discounted in the second year by 3%. Authors have undertaken univariate and probabilistic sensitivity analyses.

Base-case results in terms of cost per QALY showed that interferons were not cost-effective when compared to best supportive care for treating people with clinically isolated syndrome.

Table 21: Characteristics of included economic evaluations in CIS

Author, year and country	Attributes										
	Population	**Intervention and comparator**	**Perspective**	**Model type and cycle length**	**Health states**	**Time horizon**	**Evidence synthesis**	**Outcomes**	**Source of preference data**	**Discount rate**	**Sensitivity analysis**
Fredrikson et al.[239] Sweden	People who experienced a single demyelinating event in one or several areas of the central nervous system within the previous two months	SC IFN β-1a three-times weekly compared to no treatment	Societal perspective	Cohort Markov model with one-year cycle length	CIS and on treatment, CIS no treatment or relapsing-remitting multiple (RRMS) defined by the McDonalds 2005 criteria	40-year time horizon	Not based on a systematic review	Progression free life years, quality-adjusted life years	Not reported (authors suggested that utility values associated with each EDSS level were obtained from a study in MS patients	3% per annum for costs and outcomes	RRMS defined by the Poser criteria
Kobelt et al.[240] Sweden	People with a clinically isolated event	IFN β-1b compared to no treatment	Societal perspective	Cohort Markov model with one-year cycle length	Progression from CIS to mild, moderate and severe MS	20-year time horizon	Not reported	Quality-adjusted life-years gained	Not reported	3% per annum for costs and outcomes	Changes to time horizon, treatment duration and the proportion of people treated at conversion
Lazzaro et al.[241] Italy	People with mono and multifocal CIS diagnosis (McDonald criteria)	IFN β-1b SC 250µg every other day compared to no treatment	Italian National Health Service and Societal perspectives	Epidemiological/survival model	Not reported	25-year time horizon	Not reported	Quality-adjusted life-years gained	Not reported	3% per annum for costs and outcomes	Annual consumption of and average annual compliance rate to IFNβ-1b;

Author, year and country	Attributes										
	Population	**Intervention and comparator**	**Perspective**	**Model type and cycle length**	**Health states**	**Time horizon**	**Evidence synthesis**	**Outcomes**	**Source of preference data**	**Discount rate**	**Sensitivity analysis**
											replacement of IFN β-1b with 44 µg IFN β-1a SC three days a week; CDMS-related patient utility values), and PSA
Iskedjian et al.[242] Canada	People who experienced a single, clinically diagnosed, demyelinating event	IFN β-1a (Avonex) 30µg intramuscular injections once weekly compared to Methylprednisolone four intravenous injections of 1g for three days followed by 14 days of oral steroids 1mg twice daily	Ministry of Health and societal perspectives	Two cohort Markov models each with one-year cycle lengths	The first model captured costs and outcomes associated with progression to CDMS and the second model estimated the long-term costs and outcomes of progression through various EDSS states [mild (EDSS ≤ 3.5), moderate (EDSS 4-5.5) and severe (EDSS ≥ 6)]	12-year time horizon	Not reported	Mono-symptomatic life-years gained, quality-adjusted life- years gained	Utility values were derived based Health Utility Index (HUI) questionnaire and utility values derived based on EQ-5D questionnaire	5% per annum on costs and outcomes	20 and 30 year time horizons, using utility values based on the EQ-5D questionnaire, varying discount rates
Arbizu et al[243]	People with clinically isolated	IFN β-1b (250µg every other day) versus no treatment	Not reported	Not reported	Not reported	50 years	Not reported	QALYs	Not reported	3% per annum on costs	SA has been undertaken but it was

Author, year and country	Attributes										
	Population	**Intervention and comparator**	**Perspective**	**Model type and cycle length**	**Health states**	**Time horizon**	**Evidence synthesis**	**Outcomes**	**Source of preference data**	**Discount rate**	**Sensitivity analysis**
Spain	syndrome									and benefits	unclear on the extent
Caloyeras et al[244] Australia	Adults with clinically isolated syndrome	IFN β-1b (250µg every other day) versus best supportive care	Societal	Markov model	CIS health states and RRMS health states defined by same EDSS strata (0; 1-1.5; 2-2.5; 3-5.5; 6).	25 years	Based on results from a randomised controlled trial	QALYs	EQ-5D data from BENEFIT RCT and published literature	5% per annum on costs and benefits	Unclear but looks like one-way sensitivity analysis only
Caloyeras et al.[245] Australia	Adults with clinically isolated syndrome	IFN β-1b (250µg every other day) versus best supportive care	Australian perspective but unclear if health provider or societal	Markov model	Health states defined by EDSS levels	25 years	Based on results from a randomised controlled trial	QALYs	Obtained from published studies	5% per annum on costs and benefits	Unclear but looks like one-way sensitivity analysis only
Caloyeras et al.[246] Sweden	Patients with first clinical event suggestive of MS (CIS)	IFN β-1b (250mcg every other day) versus best supportive care	Societal	Markov model	First clinical event suggestive of MS (EDSS 0 to 5.5), RRMS (EDSS 0 to 5.5), Non-relapsing forms of MS (EDSS 6 to 9.5) and EDSS 10 (Dead) and Dead from all-causes	50 years	Based on results from a randomised controlled trial	QALYs	EQ-5D data from BENEFIT RCT and published literature	3% per annum on costs and benefits	Univariate and probabilistic sensitivity analyses
Zarco et al.[247] Columbia	People meeting standard indication for	IFN β-1a and IFN β-1b	Societal	Decision tree	Conversion to MS	Two years	Unclear	DALYs and QALYs	Obtained from published	3% on costs and outcomes in the	Relapse management, conversion probabilities,

Author, year and country	Attributes										
	Population	**Intervention and comparator**	**Perspective**	**Model type and cycle length**	**Health states**	**Time horizon**	**Evidence synthesis**	**Outcomes**	**Source of preference data**	**Discount rate**	**Sensitivity analysis**
	initiation of treatment with IFN β-1a, and have a diagnosis of CIS/MS								tables	second year	and indirect costs; probabilistic sensitivity analysis
CDMS, clinically definite multiple sclerosis; CIS, clinically isolated syndrome; EDSS, expanded disability status scale; EQ-5D, euroQol five dimensions; HUI, health utility index; RRMS, relapsing-remitting multiple sclerosis; SC, subcutaneous; RRMS,											

12.2.2 Characteristics of the included studies

The characteristics of the studies included in this review are presented in Table 21. All of the studies included an economic model to estimate the cost-effectiveness of using DMTs for treating people with CIS. The economic evaluations were conducted in Sweden[239, 240, 246], Australia[244, 245],Italy[241], Colombia[247], Spain[243] and Canada[242].

Studies[239-241, 244-246] mainly compared disease modifying treatments compared with no treatment. One study[247] compared IFNβ-1a with IFNβ-1b. Treatment included IFNβ-1a subcutaneous three-times weekly[239], subcutaneous IFNβ-1b[240, 241, 243-245]. However, one study[242] compared DMTs (INFβ-1a 30µg intramuscular injections once weekly) versus current treatment (methylprednisolone four intravenous injections of 1g for three days followed by 14 days of oral steroids 1mg twice daily).

Six studies[239, 240, 242, 244-246] used a cohort Markov model structure and one study[241] used an epidemiological/survival model and affixed costs and benefits accrued over time for occupying health states. One study[243] used a decision tree structure, and in the remaining study, it was unclear on the model structure used. Model cycle lengths ranged from six months[246] to one year, and time horizons ranged from 12 years[242] up to 50 years[246]. Most studies[239, 240, 242, 244-246] included longer term progression through to relapsing-remitting multiple sclerosis and estimated the cost-effectiveness.

Four studies[239, 240, 244, 246] analysed cost-effectiveness from the societal perspective, whereas two studies[241, 242] analysed from both the health service and the societal perspectives. Two studies[243, 245] were unclear on the perspective of the analysis. Five studies[239-241, 243, 246] used a discount rate of 3% per annum for costs and outcomes, while three studies[242, 244, 245] applied an annual 5% discount rate for costs and outcomes. Six studies[240, 241, 243-246] presented their results in terms of cost per QALY alone and the remaining two studies used progression-free survival[239] and mono-symptomatic life-years gained[242] in addition to cost per QALY.

12.2.3 Definition of clinically isolated syndrome

The definitions used to characterise people with CIS were consistent. The majority of the studies defined their hypothetical cohort as adults who had experienced a single demyelinating event suggestive of multiple sclerosis. Two studies[239, 241] elaborated on this definition and suggested their cohorts referred to adults who experienced a single demyelinating event in one or several areas of the central nervous system. To our knowledge, no studies included in this systematic review defined their population based on the McDonald 2010 criteria.

12.2.4 Characteristics of clinically isolated syndrome models

Four studies[239, 240, 242, 246] modelled the longer-term impact of treating CIS with DMTs incorporating progression to RRMS. No studies modelled conversion from RRMS to SPMS. All studies except the one conducted by Iskedjian and colleagues[242] considered progression until death in the analysis, but there was no justification for omitting this health state in the analysis. Disease progression in the RRMS health states was stratified by severity (mild, moderate and severe)[240, 242] or by predicting changes in EDSS levels[239, 241, 243-246]. In the majority of the studies the risk of death was obtained from country-specific lifetime tables for the general population. In one study[239], mortality rates were adjusted to reflect the increase risk of mortality associated with multiple

sclerosis. Here, background mortality was multiplied by EDSS-specific adjustment factors to reflect MS-specific mortality. All other studies accounted for death by assuming people died on progression to EDSS 10. Adjusting the background mortality and including progression to EDSS 10 leads to double counting of people who may die from MS-related causes.

12.2.5 Treatment effect of disease modifying treatments in the CIS health state

Three studies[239, 241, 246] clearly stated that treatment discontinuation was considered in analysis. One study[242] assumed that people did not discontinue treatment. The remaining studies[240, 243-245] were unclear on whether treatment discontinuation was included in the analysis. Treatment discontinuation was assumed to be a result of adverse events from drug utilisation, and/or progressing to EDSS ≥6. Discontinuation rates ranged from 6% every two years[239] to 17.7% annually[241]. It appeared that Fredrikson and colleagues[239] assumed a constant hazard over time for discontinuation of treatment in the first two years, and in subsequent years used information from a follow-on trial. In the analysis undertaken by Caloyeras and colleagues[246], these authors fitted a Weibull parametric model to Swedish registry data to derive time dependent transition probabilities for people discontinuing treatment. Here, discontinuation of treatment was assumed to be the same for both early and delayed treatment (waiting until people developed MS).

12.2.6 Quality assessment of the modelling methods in CIS studies

In this section we present a summary of the reporting quality of the studies included in the current review against the Philips' checklist presented in Appendix 6.

Structure

Models presented in full publications were generally of good quality. The studies clearly stated their decision problem, the perspective of the analysis, and the objectives of the model analysis, all of which were consistent with the decision problem and disease progression. However, analyses were often limited in scope. Most studies compared one DMT with best supportive care, thus not including and analysing all treatment options available for people with CIS. All studies clearly stated the time horizon of their analysis, but studies with shorter time horizons may not have been able to capture all the costs and conseqeunces of treating or not treating CIS with DMTs.

Information required for models

In general, methods used in the published studies to identify relevant information to populate the models were satisfactory[239, 241, 242, 246, 247]. As expected, less information was available from published abstracts[240, 243-245]. All studies provided references for their model inputs, but authors were not clear on how the evidence was synthesised (e.g. search strategy, quality assessment). In all studies, information was required on the effect of DMTs on disease progression, resource use and costs, outcomes and mortality. The effect of DMTs on delaying progression from CIS to RRMS was modelled using hazard ratios. The relative reduction in progression which was associated with DMTs was then applied to the predicted baseline cohort of people with CIS. All studies[239-246] except Zarco et al.[247] derived a hazard ratio directly from a trial. In contrast, Zarco and collegaues obtained

this hazard ratio by combining the treatment effects from a number of studies. However, these authors did not elaborate on the quality assessment of these RCTs or on how information on treatment effects was meta-analysed. The effect of DMTs can be applied to a baseline cohort of people to show the treatment effect on conversion to RRMS. Baseline information can be obtained from CIS registries, natural history cohort or from a placebo arm of a clinical trial. In all studies, information on disease progression in a baseline cohort was obtained from RCTs. Most studies have undertaken analyses based on a long time horizon, which is in line with the NICE reference case. However, only two studies[239, 246] elaborated on the techniques used to extrapolate treatment effects beyond the time horizon of the RCTs. These studies provided information on the parametric models chosen, and justified their choice of survival model.

Most studies[239, 241, 242, 246, 247] justified and referenced costs used in their analyses. Costs required for the models were mainly obtained from published sources, and these were inflated to current prices using the appropriate indices. In some studies[241, 246], authors provided detailed information on resource use. All authors stated the perspective of the analyses, and the resource use and costs reflected the viewpoint/perspective of the analyses. All authors discounted costs and benefits using the appropriate rates.

In the models that reported their results in terms of QALYs, authors provided the references used to obtain the utility weights. However, the majority of the authors did not elaborate on the descriptive tools/measures used to value these health states in these populations, or have not elaborated on the quality assessment or choices made between sources. Additionally, authors did not elaborate whether or not sources of utility information used were relevant to their population of interest. To our knowledge, utility weights were obtained primarily from studies undertaken in an RRMS population.

Uncertainty

All studies addressed parameter uncertainty in their analyses, but none attempted to address all types (methodological, structural, parameter and generalisability) of uncertainty. All studies made changes to key model input parameters to explore the impact on the results. Two studies[240, 242] ran their analysis over shorter time horizons to explore impact on ICER estimates. However, it was unclear if these studies also assumed that the duration of the treatment effect had been reduced.

12.3 *Summary of CIS cost-effectiveness evidence*

The evidence base offers insight into the decision analytical models used to estimate the cost-effectiveness of DMTs for reducing the conversion to multiple sclerosis. We identified nine studies, which included six full text articles and three abstracts.

In general, the modelling methodology appears to draw on current approaches to evaluating cost-effectiveness of DMTs in RRMS. The authors used EDSS levels to define health states for CIS, with DMTs impacting on progression from CIS to RRMS. Once individuals progressed to RRMS, their disease progression was modelled using increasing EDSS scores and progression to SPMS. This seems a reasonable approach as EDSS levels were commonly used to describe populations recruited in clinical trials evaluating DMTs in CIS. In addition, it enables cost and utility data for RRMS patients to be utilised in the CIS model. For example, utility weights for

EDSS levels amongst CIS patients could be assumed to be equivalent to utility weights for comparable EDSS levels amongst RRMS patients.

The shorter time horizons some studies used to evaluate costs and consqeunces were of concern. As CIS patients progress to RRMS, and DMTs reduce this progression, it would seem important to incorporate the long-term costs and consquences of RRMS (either treatment with DMTs or best supportive care) in a cost-effectivness analysis of treatment strategies for patients with CIS.

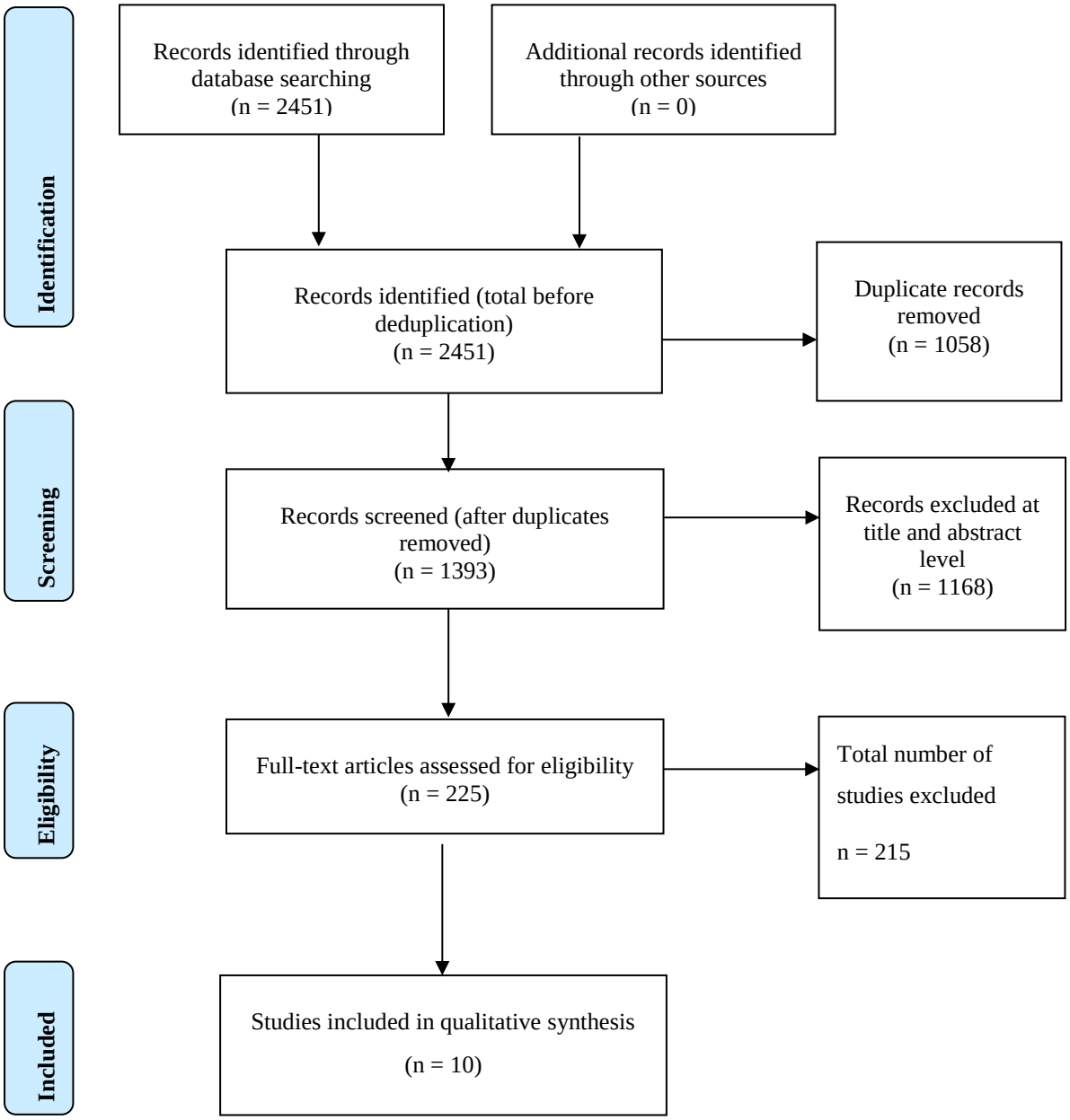
We appraised studies againgst the CHEERS and Philips' checklists on best practices for reporting economic evaluation and economic modelling studies. Based on our appraisal, the majority of the full text articles scored well in terms of defining the decision problem, outlining the study perspective, listing the intervention and comparators, presenting an illustrative model structure and providing a clear outline of the assumptions. Abstracts were limited in the amount of information that could be provided. From our review, we have raised some limitations/concerns, which mainly relate to the information required to populate the economic models. First, it was unclear on how authors made choices between data sources, especially utility values. It was unclear if utility values had been obtained from undertaking a systematic review. The, majority of the studies reporting their results in terms of QALYs provided references for these utility values. However, authors did not provide details on the descriptive tools/measure used to measure health-related quality of life, and also insufficient information is provided on who (CIS/MS patient or public) valued these health states. Second, the study undertaken by Zarco and colleagues[247] estimated treatment effect on conversion to MS from a number of trials. However, little information is provided on how a point estimate for the treatment effect was derived. Third, only two studies[239, 246] provided sufficient information on extrapolating the treatment effect beyond the trial time horizon. Finally, it was unclear if studies accounted for the uncertainty around extrapolating beyond the trail time horizon.

In Chapter 16, we have used information from this review to develop a de novo structure, which we used to estimate to cost-effectiveness of DMTs for treating people with clinically isolated syndrome.

12.4 *Results for the relapsing remitting multiple sclerosis studies*

The electronic database searches identified 2451 records (Figure 25). After removing duplicates, 1393 records were screened for inclusion. On the basis of title and abstract, 1168 records were excluded and the remaining 225 records were included for full-text screening. A further 215 articles were excluded at the full-text stage (see Appendix 7 for a list of excluded studies with reasons), leaving 10 studies[149, 248-256] that included a decision-analytical model used to estimate the cost-effectiveness of disease modifying treatments (DMTs) for treating people with relapsing-remitting multiple sclerosis (RRMS).

Figure 25: PRISMA flowchart for economic studies relating to RRMS



12.5 ***Description of the included studies***

12.5.1 Summary of economic studies comparing DMTs for people with RRMS

***Sanchez-de la Rosa*[248]**

Sanchez-de la Rosa and colleagues (2012)[248] used a Markov model structure to assess the cost-effectiveness of IM IFN β-1a (Avonex), SC IFN β-1a 44mcg (Rebif), SC IFN β-1b (Betaferon) and SC GA (Copaxone) compared to symptomatic treatment for people in Spain diagnosed with RRMS. The model simulated the pathway for people with RRMS who received DMTs as compared to symptomatic treatment, and cost-

effectiveness was estimated over the model's time horizon. The model started with a hypothetical cohort of adults diagnosed with RRMS, and continued with people occupying/progressing to one of the following health states (EDSS 0.0-2.5, relapse EDSS 0.0-2.5, EDSS 3.0-5.5, relapse EDSS 3.0-5.5, EDSS 6.0-7.5, EDSS 8.0-9.5, and dead). Sanchez-de la Rosa and colleagues made a number of simplifying assumptions: people could die from natural causes in all health states except EDSS 8.0-9.5, all people in the model received symptomatic treatment for MS, people who discontinued treatment were assumed to receive symptom management alone, treatment reduced the amount of sick leave and people regardless of EDSS level were always working).

The model required information on the starting distribution by EDSS level, probability of progression, incidence of neutralizing antibodies, resource use and costs, and utility values by EDSS level. Information on utilities associated with RRMS were obtained from an observational study that was undertaken in Spain, which used a sample of people with MS who responded to the EQ-5D questionnaire. Resource use and costs, stratified by EDSS level, were obtained from published sources. Resource use and costs included pharmacological, MS management, and loss of productivity costs. The analysis was conducted from the Spanish societal perspective, and the results presented in terms of cost per life-years gained and costs per QALY gained over a 10-year time horizon. All costs were reported in Euros, 2010 prices. All costs and outcomes were discounted 3% per annum. Sanchez-de la Rosa undertook one-way sensitivity analysis (applied a 0% and 5% discount rates; varied time horizon to 2, 4, 6 or 8 years; changed the incidence of neutralizing antibodies and loss of productivity costs).

Base-case results in terms of cost per QALY showed that IM IFN β-1a was a dominant strategy when compared to SC IFN β-1b. However, treatment with IM IFN β-1a was not cost-effective when compared to SC GA at a willingness-to-pay threshold of €30,000 per QALY. Results from the sensitivity analyses demonstrated that the base-case results were robust and stable to changes made to model parameters.

***Nikfar*[249]**

Nikfar et al.[249] estimated the cost-effectiveness of using symptom management in combination with IM IFN β-1a (Avonex), SC IFN β-1a (Rebif) or SC IFN β-1b (Betaferon/Extavia) compared with symptom management alone for the diagnosis of RRMS. The author developed a Markov structure to demonstrate the clinical pathway (RRMS defined by EDSS levels and transitioning to SPMS) that people would undergo for the treatment of RRMS. The model started with a hypothetical cohort of adults (30 years old) who received one of four treatment strategies. Some of the simplifying assumptions included people starting in EDSS 1-3.5. People could transition from RRMS to SPMS from the third cycle (approximately 5 years after diagnosis of RRMS, and it was assumed that this took place between EDSS 4-6 and EDSS 6-9.5). In case of withdrawal from IFNβ treatment in cycles 4 to 15, patients were allocated to the transition probabilities for relapse and disease progression used in the symptom management arm. Information required (probabilities of clinical events, and probabilities of switching to other IFN-β or symptomatic treatments and relapse rates) to populate the model was obtained from published sources through a literature review. Information on utility values, resource use and costs was obtained from a cross-sectional study undertaken by the authors. Briefly, 200 MS patients were recruited randomly from three referral hospitals of two cities, three private offices of MS specialists and members of the MS Iranian society. Authors elicited utility values directly from participants using the visual analogue scale, EQ-5D and Health Utility Index 3 (HUI-3) by in-house translated and validated questionnaires. Information on resource use and

costs was obtained using a retrospective approach in which information was collected at a single time point and covered the one-year period before inclusion in to the study. All prices were extracted from official tariffs, and reported in US dollars, 2012 prices. The analysis was conducted from the Iranian societal perspective and the base case results were expressed as an ICER based on the outcome of cost per QALY gained. All costs and outcomes were discounted at 7.2% per annum and 3% per annum, respectively. Base case results showed that when using the World Health Organization's recommendation on WTP thresholds (for developing countries, an ICER of less than three times the national GDP is considered cost-effective), all interventions except IM IFNβ-1a (Avonex) were cost-effective when compared to symptom management alone. However, using utility values based on EQ-5D, IM IFNβ-1a (Avonex) was shown to be cost-effective. Results from the sensitivity analyses showed that these results were robust except when changes were made to the use of copied biopharmaceuticals (CBPs) and biosimilars where these interventions were shown to be dominant.

Agashivala and Kim[250]

Agashivala and Kim (2012)[250] undertook a cost-effectiveness analysis using a decision tree. They simulated the costs and benefits of fingolimod or IFN-β for the first year and fingolimod in the second year as was done in the extension of the TRANSFORMS trial. They do not provide a description or diagrammatic representation of their model. They estimated costs of providing both treatments over the two years and compared these to the observed rates of relapse from the TRANSFORMS trial, and thereby estimated the additional costs per relapse avoided. Their definition of relapse, which was based on the definition used in the TRANSFORMS trial, was classified as new, worsening, or recurrent neurologic symptoms occurring 30 days from the onset of a preceding relapse and lasting for at least 24 hours without fever or infection. Relapses were confirmed if they were accompanied by an increase of at least one-half point on the EDSS, 1 point on 2 different functional systems of the EDSS, or 2 points on 1 of the functional systems (bowel, bladder, or cerebral functional systems were excluded). Resource use data were extracted from the literature and unit costs were obtained from the US 2010 Physician's Fee and Coding Guide. The costs were estimated from a US private payer perspective (health insurance), and included drug acquisition costs, and costs of monitoring and relapses. The analysis was undertaken over a time horizon of two years. Costs were adjusted to 2011 US Dollars, and future costs and outcomes were not discounted. The authors undertook one-way sensitivity analysis by varying input parameters by +/- 10%.

The estimated cost per relapse avoided was lower when fingolimod was started as first line treatment, than when it was started in the second year. They estimated the cost per relapse avoided to be $20,499 more in the delayed fingolimod group than in the early fingolimod group. Their findings are limited by the scope of the analysis undertaken. Their analysis does not take into account (or is not described) potential differences between the two treatments in terms of long-term health and cost impact, impact on disability/QoL, or consequences of adverse reactions to treatment. In addition, their parameter for risk of relapse was derived from a single clinical trial with inclusion and exclusion criteria that may limit generalisability to the general population. Their main findings are that it is more cost-effective to start fingolimod than to start IFN-β and then switch to fingolimod after one year of treatment. The findings have limited generalisability.

***Palace*[149]**

Palace and colleagues (Palace et al., 2015) developed a Markov model to simulate the long-term experience of people with RRMS. To model the natural history of RRMS, information from a baseline cohort was obtained from the British Columbia multiple sclerosis database. The clinical course of RRMS was modelled using health states which captured the long-term disability progression. Health states in RRMS were defined by EDSS levels 0-10. People who progressed to EDSS ≥ 6 were assumed to have converted to secondary progressive multiple sclerosis. From all health states people were subjected to risk of all-cause mortality or multiple sclerosis-related mortality. The treatment effect of DMTs (IFN-β or GA) on disability progression and relapse rates was obtained from the risk sharing scheme RSS Year 6 analysis. Transitions for both the treated and untreated cohorts occurred annually. In each model cyle, people incurred costs and accrued benefits based on the health state they occupied. Resource use and costs incurred were related to drug acquisition costs, cost for management by EDSS level and cost of relapse. Benefits accrued were measured in terms of health-related quality of life, and this information was obtained from a published sources.

Palace et al. (Palace et al., 2015) projected the cost-effectiveness of DMTs included in the RSS over a 20-year time horizon. The analysis was conducted from the UK NHS perspective, and the results presented in terms of an ICER and expressed as cost per QALY gained. All costs were reported in UK pounds and 2014 prices. All costs and benefits were discounted at 3.5% per annum. Authors undertook sensitivity analysis to determine if the base case results were sensitive to the choice of the natural history cohort.

***Pan*[251]**

Pan and colleagues used a Markov model and estimated the cost-effectiveness of IFN β-1b 250 µg (Betaferon/Extavia) compared to no treatment for people with RRMS. The model simulated the pathway for two cohorts (intervention versus no treatment) and cost-effectiveness was estimated over a 70-year time horizon. The model started with a hypothetical cohort of people who were ≥18 years old with clinically definite or laboratory–supported definite multiple sclerosis for >1 year, and who were ambulatory with EDSS ≥5.5, with at least two acute relapses during the previous two years. In the Markov model structure, the authors considered seven health states (EDSS 0.0-1.5, EDSS 1.0-2.5, EDSS 3-3.5, EDSS 4-5.5, EDSS 6-7.5, EDSS 8-9.5 and dead). In the model, people remained or progressed to more severe RRMS health states over six-monthly cycles. To have a workable model structure, the following assumptions were made: people who received mixed treatments during the post-trial period were assumed to have the same treatment efficacy as those who received IFNβ-1b during the trial period, a utility decrement of 0.0235 was applied to people who relapsed and this was assumed to last for six months, the model assumed no backward/regressive transitions, i.e. MS was seen as a progressive disease, the effectiveness of treatment was assumed to last for the duration of treatment, people who discontinued treatment were assumed to progress at the same rate as people in a natural history cohort, the model assumed that people with RRMS (EDSS <6.0) received treatment, and people who discontinued treatment were assumed not to re-initiate treatment.

Data required to populate the model were obtained from published sources. Clinical information on the risk of EDSS progression and relapse rates were based on a meta-analysis undertaken by the authors. Information on

utility values was obtained from a published source, and these were derived based on the EQ-5D. Utility values were allocated according to EDSS health state. Utility decrements were applied to people who relapsed independent of EDSS state. No disutilities for carers were included in the analysis. Resource use and costs stratified by EDSS level included were obtained from published sources. Resource use and costs included drug treatment costs, health state costs stratified by EDSS state, informal care costs and indirect (loss of productivity costs) costs. Authors applied a 10% discount to drug prices for IFN β-1b and mixed DMTs. The analysis was conducted from the USA societal perspective, and the results presented in terms of an ICER and expressed as cost per QALY gained. All costs were reported in USA dollars and 2011 prices. All costs and outcomes were discounted at 3% per annum. Pan and colleagues undertook one-way sensitivity analyses on key model input parameters (changing the time horizon, exclusion of productivity losses due to premature deaths, discount rate, and starting EDSS distribution) but did not undertake probabilistic sensitivity analysis.

The base case results in terms of life years gained showed that the discounted mean incremental gain was approximately US$86,200 with a reduction in life years loss of 2.8 year, which equated to an ICER of approximately US$31,000 per LYG. Results in terms of QALYs gained showed that the discounted mean incremental gain was approximately US$86,200 with a 1.9 years increase in quality–adjusted life years, which equated to an ICER of approximately US46,400 per QALY gained. Changes made to treatment discontinuation rate together with discounting on DMT drug costs resulted in moderate changes to the incremental cost effectiveness ratio. However, changes made to the time horizon (from 70 years to 20 years) resulted in the ICER (approximately US$163,600) becoming less cost-effective. Additionally, changing the starting distribution to 50% in EDSS 0.0-1.5 and 50% EDSS 2.0-2.5, resulted in a more cost-effective ICER of approximately US$19,600.

***Darba*[252]**

Darba et al undertook a cost-effectiveness analysis and compared the costs and consequences of treating RRMS with GA, IM IFN β-1a (Avonex), and combination therapy with GA and IFN. They undertook the analysis from the Spanish payer perspective, discounted future costs and outcomes, and adjusted costs to 2013 Euros. They built a Markov model with five health states relating to outcomes observed in the CombiRx RCT and estimated the incremental costs per relapses avoided. The model was run over 10 years with one-year cycle length. Transition probabilities were derived from the CombiRx RCT, whilst healthcare resource-use was obtained from other published sources. They assume the risk of exacerbation/relapses decreased over time (for the years after the end of the RCT). They undertook one-way and probabilistic sensitivity analysis.

Their main finding was that treatment with GA monotherapy dominated (less costly and fewer relapses) the other treatment options. They did not take into account the costs associated with adverse events, and it is unclear what the health state ‘information lost’ represents. It is likely it represents drop out from the main trial. These two issues may impact on the findings. The findings have limited generalisability as no other DMTs were considered, and disability and quality of life were not included in the model.

***Imani and Golestani*[253]**

Imani and Golestani undertook a cost-effectiveness analysis to estimate the incremental costs and benefits of four DMTs in comparison to best supportive care in Iran. They used a Markov model structure, and estimated costs and consequences over a lifetime horizon and from the Iranian societal perspective. Costs were estimated in 2011 US Dollars, and discount rates used reflect Iranian policy. Direct health provider costs included cost of treatment, monthly costs associated with EDSS states and cost of relapses. They are unclear as to whether they included other medical costs, for example costs of adverse drug events. Indirect costs included loss in productivity from absenteeism. In their model, nearly 75% of those modelled started with some degree of disability (EDSS score>2.5). In addition, they use fewer health states, noted by EDSS score, to model disability progression and to assign costs/utilities to, however, they provide no diagrammatic representation of their model.

They found that of the DMTs, treatment with IFN β-1a (Avonex) was the most cost-effective option. However, the ICER of IFN β-1a in comparison to best supportive care was 2011 US$607,397/QALY gained at the societal level. Their one-way sensitivity analysis found that the ICER was higher when analysis was undertaken over a shorter time horizon. The findings have limited generalizability due to the analysis setting, as resource-use reflects care and costs for Iran.

***Dembek*[254]**

Dembek et al[254] undertook a cost-effectiveness analysis to estimate the incremental costs and benefits of injectable DMTs in comparison to best supportive care in Spain. They compared three different regimens of IFN and glatiramer acetate (GA). They used a Markov model structure, and estimated costs and consequences over a 30 year time horizon and from the Spanish societal perspective. Costs were estimated in 2010 Euros. Direct health provider costs included cost of treatment, monitoring, adverse events and relapses. Indirect costs included loss in productivity from absenteeism and early retirement. They also included other non-medical costs (e.g. walking aids; informal care; and transportation). In their model, they assumed most MS patients start DMTs early, with minimal or no disability, and stop once EDSS score progresses to 6.0. In addition, they used fewer health states by EDSS score to model disability progression and to assign costs/utilities to, and assumed no additional mortality risk from MS.

They found that of the DMTs, treatment with IM IFNβ-1a (Avonex) was more cost-effective than SC IFNβ-1a 44 μg (Rebif), IFN β-1b (Betaferon/Extavia) or GA. The PSA showed that IM IFN β-1a was most cost-effective in 79-97% of simulations. However, the ICER of IM IFN β-1a in comparison to best supportive care was €168,629/QALY gained at the societal level. Their one-way sensitivity analysis found the findings were sensitive to DMT costs, cycle utilities, and disutility weights assigned to relapse events. They discuss their findings in relation to previous economic analysis but do not discuss the policy implications of the high ICER for DMT in comparison to best supportive. Their findings are also limited by not presenting findings from the health payer perspective as well.

Chevalier[255]

Chevalier et al[255] undertook a cost-effectiveness analysis to estimate the incremental costs and benefits of other DMTs in comparison to delayed-release dimethyl fumarate (DMF). They compared DMF to three different dosing regimens of IFN and three other DMTs. They used the same model structure as in previous NICE HTA of DMTs in MS, and estimated the cost-effectiveness from the French societal and payer perspectives. The model was run over 30 years with one-year cycle length and followed French guidelines for discounting. Costs were estimated in 2013 Euros, although the costs of drugs were for 2015. Direct health provider costs included the cost of drugs, monitoring, adverse events and management costs associated with EDSS health states and for relapses. Indirect costs included loss in productivity from absenteeism and early retirement.

They found that in comparison to DMF, glatiramer acetate, IFN β-1a 30 μg (Avonex), IFN β-1b 250 μg (Betaferon/Extavia), fingolimod and teriflunomide were dominated (i.e., higher costs and lower QALYs) by IFN β-1a 44 μg (Rebif) and DMF at both the societal and health payer perspective. The ICER for IFN β-1a 44 μg, in comparison to DMF, was €29,047/QALY and €13,110/QALY from the health payer and societal perspectives, respectively. The PSA found that at a WTP threshold of €30,000, the probability DMF was the most cost-effective option was 0.65. The one-way sensitivity analysis suggests that under the majority of scenarios they investigated, DMF continued to dominate other DMTs except IFN β-1a 44 μg. The found the ICER was most influenced by DMF disability progression rate, DMF acquisition cost, EDSS state cost and DMF relapse rate. Their main findings were that DMF is the optimal choice of DMTs.

Lee[256]

Lee et al.[256] undertook a cost-effectiveness analysis to estimate the incremental costs and benefits of fingolimod in comparison to IM IFN β-1a (Avonex). They estimated the cost-effectiveness from the USA societal perspective. The model was run over 10 years, with one-year cycle length and followed USA guidelines for discounting, with costs adjusted 2011 US Dollars. The model simulated costs and outcomes for hypothetical MS patients aged 37 years with minimal or no disability (EDSS score<2.5). Health states in the model reflected current EDSS score and whether the patient was on treatment. They assumed relapses lasted only for one month, and graded the severity of relapse, and assumed treatment was stopped once EDSS score>5.5. The direct health provider costs included the cost of drugs, monitoring and management costs associated with EDSS health states and for relapses. Indirect costs included loss in productivity from absenteeism, but it was unclear if this also included costs of early retirement. Quality of life weights were derived from US based studies.

They found that in comparison to intramuscular IFN β-1a 30 μg once weekly (Avonex), the ICER for treatment with fingolimod was US$73,975 per QALY gained from the societal level. The ICER was higher from the health payer perspective (US$81,794/QALY). The probabilistic sensitivity analysis found that fingolimod was not cost-effective at a willingness-to-pay (WTP) threshold of US50,000/QALY, but would be cost-effective if the cost of the drug were to drop.

Table 22: Characteristics of included economic evaluations in RRMS

Author, year and country	Attributes										
	Population	**Intervention and comparator**	**Perspective**	**Model type and cycle length**	**Health states**	**Time horizon**	**Evidence synthesis**	**Outcomes**	**Source of preference data**	**Discount rate**	**Sensitivity analysis**
Sanchez-de la Rosa et al., 2012[248] Spain	People with RRMS in Spain	IM IFN β-1a (Avonex); SC IFN β-1a (Rebif); SC IFN β-1b (Betaferon); SC glatiramer acetate (Copaxone) versus symptomatic treatment	Spanish societal perspective	Markov model with one month cycle lengths	Relapse EDSS 0.0-2.5, Relapse EDSS 3.0-5.5, EDSS 0.0-2.5, EDSS 3.0-5.5, EDSS 6.0-7.5, EDSS 8.0-9.5, and dead	10 years	Clinical information on disease progression and relapses obtained from a published study	Relapse rate estimation, disease progression estimation for EDSS 0.0-2.5 to EDSS 3.0-5.5 and disease progression estimation for EDSS 3.0-5.5 to EDSS 6.0-7.5	Utility values obtained from observational study undertaken in Spain, based on participant with MS who completed an EQ-5D questionnaire	3% per annum for both health outcomes and costs 7.5% for drug costs	Discount rate was set to 0% and 5%, the incidence of neutralizing antibiotics appearance, time horizon was set to 2,4,6 and 8 years
Nikfar, 2013[249] Iran	People with RRMS	Symptom management in combination with IM IFN β-1a, SC IFN β-1a or SC IFN β-1b compared to symptom management alone	Iranian societal perspective	Markov model with biennial cycle lengths	RRMS (EDSS 1-3.5, EDSS 4-6, EDSS 6.5-9.5), SPMS (EDSS 6.5-9.5), withdrawal, switching, Dead	30 years	Treatment effects were obtained from randomised controlled trials and long term follow-up studies	Number of people remaining in the RRMS state, number of people remaining relapse free, QALYs gained, total costs and productivity losses	Directly elicited from people with MS using the VAS, EQ-5D and HUI-3 instruments	7.2% per annum for costs and 3% for outcomes	Authors assessed the impact of using copied biosimilars and biosimilars in the analysis, using different sources of utility estimates, and sensitivity of discounting costs and outcomes
Agashivala and Kim 2012[250] USA	People with RRMS who had experienced at	Two years of fingolimod therapy versus IFN β-1a for one year followed by one	United States of America commercial health plan	Decision tree	No clear description or diagram with the modelling	Two years	Clinical evidence from the TRANSFORMS	Relapses avoided	Not applicable	Not reported	Univariate sensitivity analyses undertaken

Author, year and country	Attributes										
	Population	**Intervention and comparator**	**Perspective**	**Model type and cycle length**	**Health states**	**Time horizon**	**Evidence synthesis**	**Outcomes**	**Source of preference data**	**Discount rate**	**Sensitivity analysis**
	least one documented relapse in the last two years	year of fingolimod therapy	(private insurance perspective)		approach reported		clinical trial				
Palace, , 2015[149] UK	RRMS, ≥ 18 years, two clinically significant relapses in the previous two years, and EDSS level ≤5.5, and for SPMS, ambulant with relapses as the main driver of advancing disability	IFN β or glatiramer acetate	NHS and PSS perspective	Markov model with annual cycle lengths		20 years	Clinical information from RSS	Loss of utility (primary outcome) EDSS progression (secondary outcome)	Health-related quality of life information was collected from the EQ-5D questionnaire	3.5% per annum for both health outcomes and costs	Scenario analyses around discontinuation of DMTs, loss to follow-up, inclusion of SPMS at baseline, using information up to four years from the RSS, and changing the natural history cohort
Pan, 2012[251] USA	People age ≥18 years with clinically definite or laboratory – supported definite MS >1 year, are ambulatory with EDSS ≥5.5, and have had at least two acute relapses during the previous two years	IFN β-1b (250 µg) compared with no treatment	Societal perspective	Markov model with six month cycle length	EDSS 0.0-1.5, EDSS 1.0-2.5, EDSS 3-3.5, EDSS 4-5.5, EDSS 6-7.5, EDSS 8-9.5 and death	70 years	Authors have stated that risk of EDSS progression and relapse rates were obtained from published sources	Life years gained and quality-adjusted life years (QALYs) gained	Utility values obtained from a published source and these were based on information collected on EQ-5D	3% per annum applied to costs and outcomes	one-way sensitivity analyses: changing the time horizon, exclusion of productivity losses due to premature deaths, discount rate, and starting EDSS distribution
Darba,	Spanish	Combination Disease	Spanish	Markov	No relapses,	10	Clinical	Relapses	Not	3% per	Authors have

Author, year and country	Attributes										
	Population	**Intervention and comparator**	**Perspective**	**Model type and cycle length**	**Health states**	**Time horizon**	**Evidence synthesis**	**Outcomes**	**Source of preference data**	**Discount rate**	**Sensitivity analysis**
2014[252] Spain	patients aged 18-60 with established RRMS. EDSS score 0-5.5 and who had experienced at least two exacerbations.	Modifying Treatments (GA and IFN β-1a)	National Health Service (NHS)	model with annual cycle lengths	suspected exacerbations, non- protocol defined exacerbations, protocol defined exacerbations, and information lost	years	evidence from the CombiRx clinical trial	avoided	applicable	annum for both health outcomes and costs 7.5% for drug costs	undertaken one-way sensitivity analysis and probabilistic sensitivity analysis
Imani and Golestani, 2012[253] Iran	Multiple sclerosis patients in Iran	DMTs for MS (Avonex, Betaferon, Rebif and CinnoVex) versus symptom management/supportive care	Iranian MoH perspective, but costing perspective societal (incl. lost worker productivity)	Markov model	Four RRMS states determined by EDSS score (0-2.5; 3-5.5; 6-7.5; 8-9.5) Two relapsed states by EDSS score (0-2.5; 3-5.5) Death	Until death	Unclear	Time spent in EDSS 0.0-5.5, time spent relapse-free, life-years gained and QALYs gained	Published literature	3% per annum for both health outcomes and costs	Unclear on the type of SA (e.g. one way) undertaken
Dembek, 2014[254] Spain	MS patients aged 30 and with no or minimal disability (57 % with EDSS scores of 1–1.5 and 43 % with EDSS scores of 2–2.5)	IM IFN β-1a (30µg administered once weekly) SC IFN β-1a (44µg administered every other day) IFN β-1b (125 µg administered thrice weekly) GA (20 mg administered daily)	Societal	Markov model with annual cycle lengths	Four RRMS states determined by EDSS score (0-2.5; 3-5.5; 6-7.5; 8-9.5) Two relapsed states by EDSS score (0-2.5; 3-5.5)	30 years	Unclear	QALYs	Published literature	3% per annum for health outcomes and costs	Univariate sensitivity analysis and probabilistic sensitivity analysis

Author, year and country	Attributes										
	Population	**Intervention and comparator**	**Perspective**	**Model type and cycle length**	**Health states**	**Time horizon**	**Evidence synthesis**	**Outcomes**	**Source of preference data**	**Discount rate**	**Sensitivity analysis**
					Death						
Chevalier, 2016[255] France	People with RRMS	IFN β-1a 44 µg dose IFN β-1a 30 µg dose IFN β-1b 250 µg dose GA teriflunomide; fingolimod versus delayed-release DMF	Health payee and societal perspectives	Markov model with annual cycle lengths	RRMS and SPMS health states	30 year	Information on risk of adverse events obtained from a systematic review undertaken by the authors	QALYs	EQ-5D responses from a study undertaken amongst MS patients in France, and utility scores derived using French tariff set	4% per annum for first 30 years then 2% thereafter	Probabilistic sensitivity analysis
Lee, 2012[256] USA	People with RRMS with a mean age of 37 years	Fingolimod 0.5mg orally once a day versus intramuscular IFN β-1a 30mcg once weekly	USA societal perspective	Markov model with annual cycle lengths	RRMS non-treatment states determined by EDSS score (0-2.5; 3-5.5; 6-7.5; 8-9.5) Two treatment states by EDSS level (0-2.5; 3-5.5) Temporary relapse health state Death	10 years	Unclear	QALYs	Unclear	3% per annum for both costs and outcomes	One-way and probabilistic sensitivity analysis

CDMS, clinically definite multiple sclerosis; CIS, clinically isolated syndrome; DMTs, disease modifying treatment; EDSS, expanded disability status scale; EQ-5D, euroQol five dimensions; HUI, health utility index; MoH, Ministry of Health; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SA, sensitivity analysis; SC, subcutaneous; VAS, visual analogue scale

12.6 *Summary of overall cost-effectiveness evidence*

The characteristics of the studies included in this review are presented in Table 22. All of the studies included an economic model to estimate the cost-effectiveness of using DMTs for treating people with RRMS. The economic evaluations were mainly conducted in the USA[250-252, 254, 256] and Spain.[248] Two studies[249, 253] were undertaken in Iran, and the remaining studies in the UK[149] and France.[255] Studies[248, 249, 253, 254] mainly compared IFN β-1a 30µg intramuscular injections once weekly (Avonex), IFN β-1a three-times weekly (Rebif), IFN β-1b subcutaneous (Betaferon) or glatiramer acetate (Copaxone) with symptom management. Two studies[149, 252] compared IFN β-1a 30 µg IM once weekly (Avonex) with glatiramer acetate, one study[251] compared IFN β-1b subcutaneous (Betaferon) with symptom management, the two studies[250, 256] included IFN β-1a 30 µg IM once weekly (Avonex) in their intervention compared to fingolimod. The remaining one study[255] included comparisons between IFN β-1a, IFN-β 1b, or glatiramer acetate with dimethyl fumerate.

All studies[248, 249, 251-256] except Agashivala and Kim 2012[250] used a Markov cohort model structure to determine the cost-effectiveness of DMTs for RRMS. Agashivala and Kim 2012[250]used a decision tree structure. For those studies[149, 248, 249, 251-256] using a Markov model structure, model cycle lengths were one month[248], six months[251], annual[149, 252-256], or biennial[249] and time horizons ranged from two years[250] up to to death[253]. Five studies[248, 249, 251, 254, 256] analysed from the societal perspective alone, two studies[149, 252] from the national health service perspective, two studies[253, 255] from both a health service and the societal perspectives, and one study[250] from the third-party provider persepctive. Six studies[248, 251-254, 256] used a discount rate of 3% per annum for costs and outcomes, one study[255] applied an annual 4% discount rate for costs and outcomes, one study[149] applied a 3.5% annual discount rate, one study[249] used a discount rate of 7.2% for costs and 3% for outcomes, and the final study[250] did not explicitly state the discounting approach. Additionally, two studies[248, 252] included a discount rate of 7.5% for cost of drugs. Results were mainly presented in terms of relapses avoided, life years gained and QALYs.

12.6.1 Definition of relapsing remitting multiple sclerosis

The definitions used to characterise people with relapsing remitting multiple sclerosis were consistent across all studies. However, to our knowledge no studies elaborated on the definitions used to define multiple sclerosis from the clinical studies that were used to obtain treatment effects of disease modifying treatments.

12.6.2 Characteristics of relapsing remitting multiple sclerosis

All studies considered disease progression based on the use of EDSS to capture disability progression in people with RRMS. All models also captured the relapsing nature of MS. Nine studies[248-256] grouped EDSS health states (e.g. EDSS 1-3.5[249]) but authors did not provide justification on how these groupings were derived. In contrast, Palace and colleagues[149] modelled each EDSS level to show disease progression. One study[249] clearly presented definitions for each health state included in their model. Three studies[149, 249, 256] included the conversion of relapsing remitting multiple sclerosis to secondary progressive MS. Only one study[149] allowed for people to transition to less severe health states. In studies[149, 249, 256] that considered relapses in their models,

authors assumed that relapses occurred up to EDSS 5.5. At this level, authors assumed that people discontinued treatment and followed the same pathway as people who were at the same EDSS level but untreated.

In general the risk of death was obtained from country-specific lifetime tables for the general population. Two studies[248, 256] assumed that people were at risk of MS-related death at EDSS 8-9.5. However, it was unclear if Sanchez-de la Rosa et al.[248] varied the risk of death by age. Nikfar and colleagues[249] used another method to account for death. These authors assumed that multiple sclerosis increased the risk of death by threefold across age and sex adjusted mortality rates. Pan et al. modelled mortality based on extrapolating survival data from an observational study. These authors fitted a Weibull parametric model to the placebo (no treatment) group, then adjusted by using estimates on a hazard ratio derived from a comparison between treatment and a placebo group. Evidence on other parametric model fits were not presented by the authors.

12.6.3 Treatment effect of disease modifying treatment in relapsing remitting multiple sclerosis

The effect of treatment on disability progression and frequency of relapses was considered in all studies by applying a hazard ratio/relative risk to a baseline cohort of people with RRMS. All studies drew on the evidence from randomized controlled trials. However, only one study[248] was clear on the meta-analytical methods used to estimate the treatment from clinical trials. These authors used log-linear regression in order to estimate the treatment effect of disease modifying treatment on disease progression and relapse frequency.

It was unclear if studies modelled the direct impact of DMTs in the conversion to secondary progressive multiple sclerosis. All studies considered an indirect impact of disease modifying treatments on mortality by showing that disease modifying treatments delays disease progression.

It was not clear whether any studies accounted for the waning effect of disease modifying treatment. One study[248] considered the effect of neutralising antibodies on the efficacy of disease modifying treatments.

12.6.4 Discontinuation of treatment in relapsing remitting multiple sclerosis

Discontinuation rates were considered in all [149, 248-256] analyses except the study undertaken by Agashivala and Kim [250]. Treatment discontinuation was assumed to be a result of adverse events from drug utilisation, and/or progressing to EDSS ≥6 or perceived lack of efficacy[249]. To our knowledge, no studies fitted a parametric model to long-term data in order to derive time dependent transition probabilities for people discontinuing treatment. Studies used short-term information on discontinuation rates from trials and assumed a constant hazard over time for the duration of the model.

12.7 *Quality assessment*

We present a summary of the reporting quality of the studies included in the current review assessed against the Philips et al.[229], which covers model structure, information required for the model, and uncertainty. Details of the quality assessment of each study are presented in Appendix 7.

12.7.1 Model structures

Structures of the models included in this review were generally of satisfactory quality. In accordance with best practice for developing model structures, studies clearly stated their respective decision problems and the viewpoint/perspective of the analysis, and the objectives of the model, all of which were consistent with the decision problem. Additionally, illustrative structures captured the relapsing nature of multiple sclerosis and followed the pathway for people treated for RRMS. Whilst good reporting quality was noted in most studies, there were some structural issues noticed. These related to the time horizon, the model structure, half-cycle corrections, and the generalisability of the results. In four studies[149, 248, 250, 256], the time horizon was possibly too short to capture all costs and benefits of treatment with DMTs. Agashivala and Kim (2012)[250] used a decision tree structure and affixed probability estimates for progression at discrete/fixed timepoints. As a result, this does not reflect the true nature of RRMS. A Markov model would have been more appropriate because of the chronic nature of the disease and the long time horizons for progressing to more severe EDSS levels. Additionally, the health states included in the model structure were not clearly described. One study[248] used a one-month cycle length in their model, but this does not reflect the routine follow-up for people with RRMS; an annual cycle length would have been more appropriate. On the other hand, Nikfar and colleagues used a model cycle over two years, although it was unclear if these authors used a half-cycle correction.

In general, all studies[149, 248-256] stated the location of the analyses but not the settings, which prevents assessment of the generalisability of the results.

12.7.2 Information required

The methods used to identify relevant information to populate the models were satisfactory in most studies[248-250, 252, 254-256]. All studies provided references for their model inputs but quality appraisal and selection of relevant inputs was rarely made transparent. In all studies [149, 248-256], information was required on the treatment effect of DMTs on progression and relapse rates, resource use and costs, outcomes and mortality.

The effects of treatment with DMTs on disease progression compared to no treatment were modelled using hazard ratios. The relative reduction in disability progression associated with DMTs was applied to the predicted baseline cohort of people with RRMS. In some analyses, studies obtained this hazard ratio directly from a trial or have obtained this hazard ratio through reviewing the clinical effectiveness literature. However, studies that used the latter approach did not elaborate on the quality assessment of these RCTs or provide sufficient detail on how the hazard ratio had been derived. Information on a baseline chort of people could be obtained from MS registries, natural history cohort or from a placebo arm of a trial. In all studies, information on disease progression in a baseline cohort were obtained from RCTs. All models considered the treatment effect on a reduction in relapses. The treatment effect on the average number of relapses experienced by EDSS level, was obtained from published sources. Most studies undertook analyses based on a long time horizon, which is in line with the NICE reference case. However, authors have not elaborated on the techniques used to extrapolate the treatment effects beyond the time horizon of the RCTs. Studies using a shorter time horizon, for example Lee et al. (2012)[256], did not assume treatment benefit beyond the length of the follow-up study.

Information on resource use and costs was obtained from published sources, and these were well documented in some studies. Details of resource use, by EDSS level were well documented in the study undertaken by Nikfar and colleagues[249].

12.7.3 Uncertainty

All studies included one-way sensitivity analysis, undertaken by changing key model inputs to determine the robustness of their base case results. In sensitivity analyses authors made changes to discount rates, time horizon, initial EDSS distribution of people in the starting cohort, perspective of the analysis, discontinuation rate, and utility values. To our knowledge, authors did not use information from a natural history cohort of people to model disease progression as part of their sensitivity analyses, or allowed for waning treatment effect over time.

12.8 *Summary of the RRMS cost-effectiveness evidence*

We identified 10 recent studies[149, 248-256] that used an economic model to estimate the cost-effectiveness of disease modifying treatment for treating people with relapsing remitting multiple sclerosis. The evidence offers insight on the modelling methodology, which includes the illustrative structures to depict multiple sclerosis progression, key model inputs, and assumptions made in order to assess the cost-effectiveness. These methods appear to be feasible across all studies.

We appraised studies against the CHEERS[228] and Philips'[229]) checklists on best practices for reporting economic evaluation and economic modelling studies. Based on our appraisal, studies performed well against these checklists in terms of reporting sufficient information on the decision problem, outlining the study perspective, listing the intervention and comparators, presenting an illustrative model structure and providing a clear outline of the assumptions. Our review highlights some limitations of the studies, and these are related to the structure and the information required to populate. In terms of the structure, the time horizon was short in some studies, and the choice of model structure did not accurately reflect or capture the disability progression associated with multiple sclerosis. Limitations associated with model information relate to the lack of detail on quality assessment of clinical effectiveness studies and lack of detail on the methods used to meta-analyse information from clinical studies, and insufficient information on extrapolating treatment effect beyond trial time horizons. Additionally, we noted some limitations in the methods used to model mortality.

In Chapter 15, we draw on the information from this review in terms of model design and model inputs, to estimate the cost-effectiveness of disease modifying treatments for treating people with RRMS.

13 RISK SHARING SCHEME SUBMISSION

13.1 *Overview of Risk Sharing Scheme model*

In the RSS model, an economic analysis was conducted to assess the cost-effectiveness of the combined treatment effect of disease modifying treatments, IFN β-1a 44 or 22 μg SC thrice weekly (Rebif), GA 20 mg SC daily (Copaxone), IFN β-1b 250 μg SC every other day (Betaferon) and IFN β-1a 30 μg IM weekly (Avonex) included in the Risk Sharing Scheme (RSS) compared with best supportive care for people with relapsing-remitting multiple sclerosis.[149]

In the analysis, a Markov model was used to depict the natural history of people with RRMS, including progression to secondary progressive multiple sclerosis (SPMS). Information required on the natural history of people with RRMS was based on the British Columbia multiple sclerosis (BCMS) cohort. Two sets of transition probabilities were reported: transitions based on the age of onset of RRMS below (subgroup 1) and above (subgroup 2) the median age. In both the natural history and RSS cohorts, disability progression was characterized by using the Expanded Disability Status Scale (EDSS), which ranges from 0 to 10 (Death). In addition to progressing to more severe EDSS states, people were allowed to regress to less severe EDSS states, which reflected the natural course of the disease. In the model, only people in EDSS state 7-9 could progress to EDSS 10 (death). Additionally, it was assumed that the standardized mortality rate increased by two-fold, regardless of the age of onset or severity of MS.

In the treatment arm (RSS model), it was assumed that each year 5% of people would discontinue DMTs, and that this might be due to adverse events or progression to EDSS 7-9. It was assumed that people who discontinued treatment would remain off treatment for the remainder of their life.

The analysis was undertaken from the UK NHS perspective in a primary care setting. Health outcomes were measured in quality-adjusted life-years, and the analysis was undertaken over a 50-year time horizon. Information on utilities by EDSS state were obtained from pooling utility estimates from the 2002 and 2005 MS Trust surveys, based on information collected on the EQ-5D, which was subsequently converted to an EQ-5D index score. Information on resource use and unit costs was obtained from the ScHARR[257] report and subsequently inflated to current prices. The results were presented as an ICER and expressed as cost per QALYs gained. Both costs and benefits were discounted at 3.5% per annum.

Base case results showed that for people in subgroup 1, mean cost per person in the treatment arm was approximately £357,100 with a mean of 7.987 QALYs gained per person. For best supportive care, the mean cost per person was approximately £328,800 with a mean of 6.947 QALYs per person. Consequently the incremental cost-effectiveness ratio (ICER) was approximately £27,200 per QALY. In subgroup 2, the mean cost per person in the treatment arm was approximately £379,300 with 8.022 QALYs gained compared to the best supportive care arm of approximately £355,500 with 7.028 QALYs gained. This gave an incremental cost-effectiveness ratio (ICER) of approximately £23,900 per QALY. Overall, the mean incremental cost of DMTs compared to best supportive care was approximately £25,600 with a corresponding 1.013 QALYs gained, and an ICER of approximately £25,300 per QALY.

A number of sensitivity analyses were undertaken:

1. Excluding EDSS scores for people who switched to a non-scheme DMT from the analyses
2. Using imputation techniques for missing values in the multi-level model.
3. Changing the assumption made in the Markov model about the treatment effect of DMTs on backward transitions
4. Supplementing transition probabilities derived from the BCMS with imputed values

Results for sensitivity analysis 1 showed a marginal increase in treatment effect for the base run. For sensitivity analysis 2, slight differences were seen between treatment effects. No probabilistic sensitivity analyses were undertaken. Table 23 gives a summary of the RSS model.

Table 23: Summary of the RSS model

Parameter	**Risk sharing scheme model**
Natural history cohort	British Columbia cohort
Population	People initially diagnosed with RRMS and those who progress to SPMS
Intervention	Disease modifying treatments available in the RSS: • IFN β-1a 30 µg IM once a week (Avonex) • IFN β-1a 44 or 22 µg SC three times per week (Rebif) • IFN β-1b 250 µg SC every other day (Betaferon) • Glatiramer acetate 20 mg SC daily (Copaxone)
Comparator	Best supportive care
Type of model and health states	Markov model
Hazard ratio	Targeted outcomes were agreed on for each of the four DMTs included in the RSS, expressed as hazard ratios of disability progression for treated compared to no treatment
Resource use and costs	Disease modifying treatment costs, health state/EDSS costs and cost of relapses
Health-related quality of life	Utility values were pooled from the 2002 and 2005 MS Trust surveys
Discontinuation of treatment	Assumed that 5% people would discontinue treatment every year.
Relapse	Weighted average of the frequency of relapses for people with RRMS and SPMS, irrespective of EDDS level
Adverse events	Utility decrement of 0.02 associated with adverse events from disease modifying treatments. It was assumed that this decrement would only apply to the first year of commencing treatment
Mortality	MS-related death for people in EDSS 7-9. For all states, a standardised mortality rate estimated and multiplied by two to take into account MS-related and non-MS related mortality
Time horizon	50-year time horizon
Base-case analysis results	Using the 'base run' model, an ICER of approximately £25,300 per QALY was derived. Using the 'time-varying model', an ICER of approximately £33,700 per QALY was derived
Sensitivity analysis (and PSA) results	No PSA was undertaken
EDSS, expanded disability status scale; ICER, incremental cost-effectiveness ratio; MS, multiple sclerosis; NICE, National Institute for Health and Care Excellence; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-years; RRMS, relapsing-remitting multiple sclerosis; RSS, Risk Sharing Scheme; SPMS, secondary progressive multiple sclerosis	

13.1.1 Evidence used to parameterise the Risk Sharing Scheme (RSS) multiple sclerosis model

The model was populated with clinical information from the Risk Sharing Scheme and secondary sources. Information required to parameterise the model included evidence on the natural history of people with relapsing remitting multiple sclerosis, aggregate treatment effect of disease modifying treatments, adverse events, resource use and costs, mortality, and health-related quality of life.

13.1.2 Natural history of relapsing remitting multiple sclerosis

The natural history of RRMS and SPMS was estimated using the British Columbia multiple sclerosis (BCMS) database. Details of the BCMS cohort have been published elsewhere (Palace et al., 2014). In brief, the BCMS cohort is a population-based database established in the 1980s which captures about 80% of people with multiple sclerosis in British Columbia, Canada (Palace et al., 2015). EDSS scores were recorded by MS specialists after face-to-face consultation with patients, and this usually occurred at the annual visit to the MS clinic. In the database, people who progressed to secondary progressive multiple sclerosis were not censored. However, all patients were censored in 1996 as a result of the introduction of disease modifying treatments in British Columbia, Canada. This database is considered to be large (by 2004, the BCMS had over 5900 participants), with prospectively collected information (e.g. EDSS scores, relapses, adverse events) and a long term follow-up (>25,000 cumulative years), and the database covers a relatively recent time period[149].

13.1.3 EDSS progression in the British Columbia cohort

The 'method of Jackson'[258] was used to depict the natural history of MS, based on the observation of people with relapsing-remitting multiple sclerosis in the BCMS. Transition matrices were derived for people whose age of onset of MS was below and above the median age. Table 24 and Table 25 show the transition matrices derived for people whose age of onset of RRMS was below (subgroup 1) and above (subgroup 2) the median age, respectively. Disability progression was characterized using the EDSS. In addition to progressing to more severe EDSS states, people were allowed to improve to less severe EDSS states, which reflects the natural course of the disease. From the transition matrix, only people in EDSS state 7-9 could progress to EDSS 10 (MS-related death).

Table 24: Natural history transition matrix based on information from British Columbia multiple sclerosis database (below the medium)

		EDSS state										
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
EDSS state	**0**	0.6870	0.0612	0.0169	0.0062	0.0018	0.0005	0.0001	0.0000	0.0000	0.0000	0
	1	0.2110	0.6787	0.1265	0.0522	0.0225	0.0056	0.0014	0.0002	0.0000	0.0000	0
	2	0.0720	0.1664	0.5955	0.1165	0.0662	0.0291	0.0045	0.0005	0.0000	0.0000	0
	3	0.0224	0.0646	0.1729	0.5439	0.1210	0.0594	0.0252	0.0026	0.0003	0.0000	0
	4	0.0043	0.0170	0.0454	0.0945	0.4874	0.0915	0.0321	0.0073	0.0006	0.0000	0
	5	0.0014	0.0047	0.0184	0.0573	0.1009	0.4727	0.0424	0.0042	0.0005	0.0000	0
	6	0.0018	0.0067	0.0219	0.1148	0.1664	0.2810	0.7283	0.1220	0.0187	0.0014	0
	7	0.0001	0.0005	0.0018	0.0107	0.0262	0.0396	0.1151	0.6814	0.0570	0.0045	0
	8	0.0000	0.0001	0.0005	0.0037	0.0069	0.0191	0.0457	0.1628	0.8544	0.1301	0
	9	0.0000	0.0000	0.0000	0.0004	0.0007	0.0014	0.0052	0.0189	0.0608	0.6252	0
	10	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001	0.0077	0.2387	1

Table 25: Natural history transition matrix based on information from British Columbia multiple sclerosis database (above the medium)

		EDSS state										
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
EDSS state	**0**	0.6954	0.0583	0.0159	0.0059	0.0017	0.0005	0.0001	0.0000	0.0000	0.0000	0
	1	0.2029	0.6950	0.1213	0.0496	0.0221	0.0053	0.0013	0.0001	0.0000	0.0000	0
	2	0.0725	0.1578	0.6079	0.1201	0.0666	0.0294	0.0044	0.0005	0.0000	0.0000	0
	3	0.0217	0.0609	0.1680	0.5442	0.1152	0.0587	0.0250	0.0025	0.0003	0.0000	0
	4	0.0042	0.0164	0.0446	0.0911	0.4894	0.0874	0.0307	0.0073	0.0005	0.0000	0
	5	0.0014	0.0046	0.0185	0.0584	0.1039	0.4869	0.0408	0.0038	0.0005	0.0000	0
	6	0.0018	0.0064	0.0216	0.1165	0.1681	0.2731	0.7407	0.1168	0.0187	0.0013	0
	7	0.0001	0.0005	0.0017	0.0103	0.0258	0.0388	0.1089	0.6926	0.0553	0.0043	0
	8	0.0000	0.0001	0.0005	0.0036	0.0067	0.0188	0.0438	0.1606	0.8964	0.1326	0
	9	0.0000	0.0000	0.0000	0.0003	0.0006	0.0010	0.0042	0.0156	0.0205	0.6230	0
	10	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001	0.0077	0.2387	1

13.1.4 Types of multiple sclerosis

The model includes people who commenced in a RRMS health state and who progressed to SPMS. People with clinically isolated syndrome, primary progressive multiple sclerosis or benign disease were not included in the RSS as treatment options included in the Scheme were not licensed for these types of multiple sclerosis (Tappenden et al., 2001).

13.1.5 Interventions

The RSS model compares the combined treatment effects of using IFN-β and glatiramer acetate compared to best supportive care for people with RRMS. Table 26 shows the drugs and dose regimes with their licensed indications in the UK. The Y10 analyses included people whose EDSS scores were recorded after they had switched to non-scheme DMTs. The assessment group was not clear on the non-scheme DMTs included in the RSS. Sensitivity analysis was conducted around the treatment effect, which was to censor people whose EDSS scores were recorded after switching treatment. Censoring these people resulted in an increase in the combined treatment effect (HR=0.7666).

Table 26: Interventions included in the RSS

Company	Drug	Dose regime	Route of administration	Licensed indications
Avonex	IFN β-1a	30 µg once a week	Intramuscular	RRMS
Rebif		RRMS: 44 µg three times per week (22 µg three times per week for patients who cannot tolerate the higher dose)	Subcutaneous	RRMS SPMS
Betaferon/Extavia	IFN β-1b	250 µg every other day		RRMS SPMS
Copaxone	Glatiramer acetate	20 mg once daily		RRMS
IFN, interferon; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis				

13.1.6 Population

The population included in the RSS model is similar to the population in the BCMS. In the RSS, the population was stratified by age of onset of RRMS and by EDSS score. The initial distribution of people in each EDSS state is presented in Table 27.

Table 27: Baseline distribution of people in the RSS

EDSS	Age of onset below median	Age of onset above median	Total
0	61	74	135
1	295	394	689
2	411	677	1088
3	401	569	970
4	273	379	652
5	162	279	441
6	76	166	242
7	0	0	0
8	0	0	0
9	0	0	0
10	0	0	0
Total	1679	2538	4217

13.1.7 Mortality rate

Two types of mortality were included in the economic model, MS-related death (EDSS 10), and death from other causes. General population mortality was obtained from the Office of National Statistics (ONS) 2010, and a weighted average was taken to represent the distribution of males and females in the economic model. People with RRMS and SPMS were assumed to have a higher mortality rate than those in the general population. It was assumed that the standardized mortality rate increased two-fold, regardless of the age of onset or severity of MS, and EDSS level. The assessment group noted that the same transition probabilities from EDSS 7-9 to MS-related death were used for both natural history subgroups and also for both active therapy subgroups. The assessment group were concerned that MS-related mortlity may have been overestimated, as individuals in the model also die as a result of progression to EDSS 10 (death).

13.1.8 Resource use and costs

All costs included in the analysis were those directly related to the NHS and PSS perspective, and were reported in UK pounds (£) sterling in 2015/16 prices. The RSS model included the following resource use and costs in order to conduct analyses:

1. Disease modifying treatment costs
2. Health state/EDSS costs
3. Cost of relapse

13.1.9 Disease modifying treatment costs

Table 26 shows the DMTs included in the RSS model. A weighted average of these treatments was taken and a mean cost of £7300 per year was derived for people who received treatment. Drug prices were agreed as part of the Risk Sharing Scheme. However, it was not clear how these weighted averages were derived.

13.1.10 Health state/EDSS costs

Information on resource use and costs associated with treating multiple sclerosis from a UK perspective were obtained from a cross-sectional observational study (Working Paper) undertaken by Kobelt and colleagues (Kobelt et al., 2000).[259] The Kobelt study obtained resource use information in order to derive costs of multiple sclerosis from a societal perspective (direct and indirect costs), but also provided disaggregated information relating to the direct costs (detection, treatment, rehabilitation and long-term care of illness). The direct costs included inpatient care, ambulatory care, social care, drug treatment, investments made to the home and informal care (care provided in the absence of family). The study reported that direct costs (including informal care) accounted for 54% of the total costs, and the remaining 46% represented indirect costs. However, excluding informal care from the analysis, direct costs accounted for 38% of the total costs per patient per year. The costs were estimated for each individual patient in the study, and an average cost per patient was reported with respect to the different levels of disability (mild, moderate, severe). All costs were reported in UK pounds (£) sterling at 1999/00 prices.

The previous report submitted by ScHARR[257] suggested that 244 out of the 622 records were excluded because respondents had primary progressive multiple sclerosis, benign multiple sclerosis or information on EDSS state was missing. Mean direct costs by EDSS state and mean cost of a relapse reported in the current submission were based on information supplied to the ScHARR team in confidence, and the assessment group did not have access to this information. Costs in the ScHARR submission were subsequently inflated to current prices (2015/16) using the appropriate indices from the Hospital and Community Health Services (HCHS) pay and price index 2015/16[260], and the assessment group believes that these have been appropriately derived. Table 28 shows the costs included in the model.

Despite these mean costs being correctly derived, the RSS report assumes that resource use and patient management have not changed since 1990/00. The assessment group believes that a systematic review could have been conducted to obtain more recent information on resource use.

The assessment group is unable to provide comment on:

1. The resource use information valued to derive mean unit costs per EDSS state
2. The number of people reporting on resource use in each health state
3. The percentage of people receiving each drug treatment
4. Distribution of resource use, and the techniques used to account for skewness of costs, if this existed
5. The techniques used to account for missing data, if this existed
6. ‘Mapping’ from mild, moderate, and severe disability onto the EDSS

Table 28: Mean unit costs included in the RSS model

EDSS state	Unit costs, £ 1999/00 prices	Unit costs, £ 2015/16 prices
0	756	1164
1	756	1164
2	756	1164
3	1394	2147
4	1444	2225
5	5090	7840
6	5678	8746
7	17, 327	26, 688
8	26, 903	41, 439
9	34, 201	52, 679
10	0	0

13.1.11 Cost of relapse

The cost of a relapse included in the RSS model was obtained from the ScHARR analysis[257], and subsequently inflated to current prices using the Hospital and Community Health Services (HCHS) pay and price index 2015/16[260]. The cost represents an average cost regardless of the severity of the relapse. The cost of a relapse was the same in the treatment and no treatment arms of the model. As with health state costings, the assessment group noted that the original cost year was 1999/00 and assumptions are made that resource use and management have not changed since the base year. Despite this assumption, the assessment group considers the cost of relapse (£4263) to have been derived correctly. However, the assessment group is unclear on the components/resources costed in order to derive this cost. Additionally, the assessment group believes that a review of the literature could have been undertaken to obtain more recent information.

The costs included in the model were related to drug treatment costs, health state/EDSS costs, and relapse costs. The assessment group was not clear if the cost of treating adverse events, administering the drugs or monitoring treatments were included in the analysis. For example IFN β-1a (Avonex) is administered intramuscularly, and would incur additional directs costs (e.g. training patients or carers to administer injections).

13.1.12 Health state utility values

The primary outcome measure used in the model was a 'deviation score of the average observed loss of utility.' Health outcomes were measured in QALYs, with utility weights assigned to the health states in the model. The utilites used in the RSS model were derived by first pooling values from two MS Trust surveys (2002 and 2005) and then substracting the carer's disutility. Utilities obtained from Boggild et al. as used in the ScHARR report[257] were derived based on information from a two-stage survey of 1554 respondents from the MS Trust database. To our understanding, these three sets formed the three-pooled dataset. Utility estimates, by EDSS, were derived based on information collected on the EQ-5D, which was subsequently converted to an EQ-5D

index score. Alternative utility values were derived based on pooled datasets from the ScHARR model, and also from the UK MS RSS cohort. Table 29 shows the utility values used in the RSS model.

Table 29: Mean utility values used in the model

EDSS state	Boggild dataset	Three-pooled dataset	Two-pooled dataset	Carer's disutility
0	0.7850	0.8722	0.9248	-0.002
1	0.7480	0.7590	0.7614	-0.002
2	0.6900	0.6811	0.6741	-0.002
3	0.5827	0.5731	0.5643	-0.002
4	0.5827	0.5731	0.5643	-0.045
5	0.5790	0.5040	0.4906	-0.142
6	0.4740	0.4576	0.4453	-0.167
7	0.3650	0.2825	0.2686	-0.063
8	0.2640	0.0380	0.0076	-0.095
9	-0.1770	-0.2246	-0.2304	-0.095
10	0	0	0	0

13.1.13 Carer's disutility

An analysis was undertaken which included carer's disutilities by EDSS state. Table 29 shows the disutility values used in the model. Initially, the assessment group was unclear on the source of these disutilities. However, on clarification the Department of Health suggested that these values were obtained from a study by Acaster and colleagues (2013).[261] The assessment group examined the literature review to identify other potential sources of disutilities associated with providing care for people with MS.

13.1.14 Treatment effect

The effect of treatment with disease modifying treatments was modelled for the relative reduction in the annual frequency in relapses and the relative risk of disease progression between EDSS states. In the RSS model, both treatment effects were estimated based on observed relapses and progressions in EDSS scores in people in the Risk Sharing Scheme. Though not clear, it appeared that similar methods used to derive transition matrices from the BCMS cohort were used to derive transition matrices for the RSS model. From the comparison between both cohorts, a mean hazard ratio of 0.7913 for disability progression was derived, based on the RSS Y10 analyses. The model assumed that the treatment effect reduced the instantaneous rate of forward transitions by this hazard ratio, independent of EDSS, and that there was no effect on backward transitions. The report suggested that the hazard ratios for backward transitions wase similar to that as for forward transitions, however, these ratios were not reported. Additionally, in the model (base run) it was assumed that the hazard ratio remained the same over the entire duration (50 years) of the model time horizon.

13.1.15 Relapse frequency

In the RSS model, a weighted average of the frequency of relapse for people with RRMS and SPMS, irrespective of EDDS level was derived based on information obatained from the 2002 survey by the MS Trust

(see Table 30). However, due to the paucity of information reported on the aggregate treatment effect of DMTs in reducing relapse frequencies, we are unable to provide further commentary on this estimate.

Table 30: Relapse frequency by EDSS state

EDSS	Relapse frequency		Relapse frequency (%)		Untreated	Treated
	RRMS	SPMS	% RRMS	% SPMS	Mean frequency	Mean frequency
0	0.8895	0.0000	1.000	0.000	0.8895	0.6405
1	0.7885	0.0000	0.861	0.139	0.6790	0.4888
2	0.6478	0.6049	0.861	0.139	0.6418	0.4621
3	0.6155	0.5154	0.806	0.194	0.5961	0.4292
4	0.5532	0.4867	0.545	0.455	0.5230	0.3765
5	0.5249	0.4226	0.343	0.657	0.4577	0.3295
6	0.5146	0.3595	0.270	0.730	0.4014	0.2890
7	0.4482	0.3025	0.053	0.947	0.3103	0.2234
8	0.3665	0.2510	0.000	1.000	0.2510	0.1807
9	0.2964	0.2172	0.000	1.000	0.2172	0.1564
10	0.0000	0.0000	0.000	0.000	0	0

13.1.16 Treatment discontinuation

In the treatment arm of the economic model it was assumed that 5% of people discontinue treatment every year as a result of adverse events, and that treatment would be discontinued amongst individuals progressing to EDSS ≥7. However, the reasons for this were unclear; for example people may discontinue treatment because the therapy is no longer working.[257]

The assessment group noted that no sensitivity analyses or probabilistic sensitivity analysis was undertaken around these key assumptions about discontinuation. The justification for this assumption was based on the proportion of people discontinuing treatment as seen in the RSS. However, published evidence suggests thatthe proportion of people discontinuing treatment in clinical trials of the DMTs included in the RSS may range from 0% (Singer et al., 2012).[195] to 10% (Fox et al., 2012).[214] Additionally, it appears that people who discontinued treatment continued to accrue treatment benefits without additional costs. When people progressed to EDSS 7-9, the model used 'on treatment' transition probabilities. The assessment group would expect that people who discontinued treatment would progress to more severe health states in a similar way to people in the natural history cohort.

13.1.17 Analysis (cycle length, time horizon and perspective)

For the base case analysis, a Markov model was developed and programmed to assess the cost-effectiveness of the combined treatment effect of DMTs in the RSS compared to no treatment for people with RRMS. The model cycled yearly, with a starting age of 30-years and estimated the mean costs and effects associated with treatment compared with no treatment (best supportive care) over a 50-year time horizon. The analysis was conducted from the NHS and Personal Social Services (PSS) perspective and the results reported in terms of an incremental cost-effectiveness ratio, expressed as costs per QALYs gained. Both costs and benefits were discounted at 3.5% per annum.

13.1.18 Time varying model

The RSS submission also included a sensirtivity analysis using a 'time varying model' to take account of a perceived lack of fit of the RSS in taking account of trajectories of patients with higher EDSS at baseline. The model had two sets of transition probabilities, one for years 0-2 and one for all subsequent years.

13.2 *Summary of the critical appraisal of the RSS model*

In general, the assessment group considered the model submitted by the RSS to be appropriate in order to estimate the cost-effectiveness of DMTs compared to best supportive care. In most cases, the model draws on the best available evidence on progression through RRMS and SPMS by EDSS levels, resource use and costs, and utility values. We haveconsidered and provided a critique of the RSS model against the NICE reference case, and of the economic model inputs and we checked the model used to estimate the cost-effectiveness. However, e some uncertainties remain, which are presented below. Additionally in Chapter 15, we describe alternative analyses, which address our concerns. Our concerns are summarised below:

1. The model applied a constant rate of 5% for people discontinuing treatment. However, there is little evidence to support this assumption.
2. The difference between combined DMTs and best supportive care in reducing the frequency of relapses was 0.72, but it was unclear how this value was derived. The report suggested that a weighted average of the frequency of relapses for people with RRMS and SPMS, irrespective of EDDS level, was used and that this was derived from information obtained from the 2002 survey undertaken by the MS Trust.
3. The assessment group noted that there was an increased risk of mortality for people with MS when compared to the general population, as well as transition probabilities to EDSS 10 (MS-related death). Using this assumption would lead to double-counting MS-related deaths in the model.
4. The model considers the agreed price between the companies and the Department of Health. However, it was unclear to the assessment group how these prices were derived.
5. In the analysis, the model included carers' distutilities. The assessment group agrees that people may experience a loss in utility for caring of people with multiple sclerosis. However, in this instance, the perspective of the analysis is from the NHS and PSS perspective.
6. A probabilistic sensitivity analysis, to incorporate uncertainty in the estimates for model parameters, was not undertaken.

14 COMPANY SUBMISSIONS

14.1 Biogen Idec Ltd

14.1.1 Background

This section focuses on the economic evidence submitted by Biogen Idec Ltd. This section is set out as follows: first, we present an overview/summary then a critique of the economic model submitted which describes in detail the evidence (e.g. natural history information, effectiveness of interventions included in the analysis, resource use and costs, mortality and health-related quality of life) used to parameterise the models. In the Biogen Idec Ltd. model, an economic analysis was conducted to assess the cost-effectiveness of disease modifying treatments—IFN β-1a 30 µg IM once weekly (Avonex), IFN β-1a 44 or 22 µg SC three times weekly (Rebif), IFN β-1b 250 µg SC every other day (Betaferon/Extavia), pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy) and GA 20 mg SC daily or 40 mg SC three times weekly (Copaxone)—compared with best supportive care for people with RRMS.

In the analysis, a Markov model was used to depict the natural history of people with RRMS through the progression to secondary multiple sclerosis. Information required on the natural history of people with RRMS was based on extrapolating the ADVANCE placebo arm data with the British Columbia cohort.

In the intervention arms, it was assumed that treatment with DMTs was not discontinued due to reaching a particular EDSS level, which the authors suggested is in accordance with the current Association of British Neurologists (ABN) guidelines.[262] It was assumed that people would only discontinue treatment having progressed to the secondary progressive multiple sclerosis health state.

The analysis was undertaken from the payer perspective. The outcome measure used in the analysis was quality-adjusted life-years (QALYs) gained, over a 50-year time horizon. Treatment effects were assumed to delay the progression of the disease and reduce the frequency of relapses. Information on utilities for RRMS by EDSS level were based on information from the ADVANCE trial[211] and Orme et al. (2007),[105], which were derived from utility values from the UK MS survey. Utility values for SPMS by EDSS level were based on information from the UK MS survey as cited in the company submission. Carers' disutilities were based on information obtained from the manufacturer's submission to NICE for TA127.[263] Utility values for adverse events associated with each DMD were included in the economic analysis.

Information on resource use and unit costs were obtained from various sources. The results were presented as an ICER and expressed as cost per life years gained (LYG) and cost per QALYs gained. Both costs and benefits were discounted at 3.5% per annum. Authors have undertaken a number of sensitivity analyses (societal perspective, patient baseline characteristics, transition probabilities, treatment efficacy, relapse rates, discontinuation rates, utility values, mortality multipliers, patients' out-of-pocket costs, carers' costs, loss of productivity for people with MS and adverse events) and probabilistic sensitivity analysis to determine the robustness of the base-case results.

Base-case results showed that treatment with pegylated IFN β-1a SC 125µg every two weeks resulted in the highest mean life-years gained (20.658) and mean QALYs (9.642) compared to all other interventions included

in the analysis. Pegylated IFN β-1a SC 125 µg every two weeks compared to best supportive care had a mean incremental cost of approximately £25,200 with corresponding incremental 0.810 QALYs, which equated to an ICER of approximately £31,000 per QALY.

Results from the sensitivity analyses showed that the base-case results were robust to univariate changes made to key input parameters except the hazard ratio for the confirmed disability progression, which had the greatest impact. The probabilistic sensitivity analysis suggested that at a £30,000/QALY willingness to pay threshold, pegylated IFN β-1a 125 µg SC every two weeks had a <0.4 probability of being cost-effective when compared to best supportive care.

14.1.2 Types of multiple sclerosis

The model includes people who commenced in a relapsing-remitting multiple sclerosis health state and progressed to secondary progressive multiple sclerosis. People with clinically isolated syndrome, primary progressive multiple sclerosis or benign disease were not included in the analysis.

14.1.3 Model structure

The illustrative Markov model structure submitted by the company was based on the original ScHARR model,[257] with developments to include other interventions. The company used a cohort-based Markov model to depict the natural history of people with RRMS. The model simulated the disability progression, progression from RRMS to SPMS, and the relapsing nature of the disease. People with RRMS were able to occupy one of the EDSS health states, which ranged from 0 to 10, and in increments of 0.5. The model allowed for people to progress, regress or stay in the same EDSS health state, or progress from EDSS to SPMS. When people progress to SPMS, they either remained or progressed to more severe SPMS EDSS states.

In the model, people incurred costs and accrued benefits depending on the EDSS state for RRMS and SPMS. Benefits were measured using quality-adjusted life years, whereby each model cycle a utility is assigned to people occupying a specific health state.

The assessment group was uncertain if the review of the economic literature was undertaken to inform the model design and/or its inputs. Based on our review there appears to be some inconsistency in the model structures that have been used to estimate the cost-effectiveness of DMTs for people with RRMS. These discrepancies may be a result of the complex nature of multiple sclerosis. In Biogen Idec's model, people could progress from health states EDSS ≥1 to SPMS. However, in some models identified in the review people could only progress from EDSS ≥6 to SPMS.

14.1.4 Interventions

The interventions considered in the economic analyses included IFN β-1a 30 µg IM once weekly (Avonex), IFN β-1a 44 or 22 µg SC three times weekly (Rebif), IFN β-1b 250 µg SC every other day (Betaferon/Extavia), pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy) and GA 20 mg SC daily or 40 mg SC three times weekly (Copaxone). These comparisons are all in line with the NICE scope. The interventions are compared

against best supportive care for people with RRMS. The company suggested that best supportive care would not currently be offered as a start point to RRMS patients.

14.1.5 Population

The population included in the economic analysis was similar to the population included in the ADVANCE trial (i.e. 71% of females with a starting age of 36 years with relapsing-remitting multiple sclerosis). The initial distribution of people in each EDSS state is presented in Table 31.

Table 31: Baseline distribution of people by EDSS state, Biogen model

EDSS	Distribution (%)
0	6%
1	26%
1.5-2	28%
2.5-3	24%
3.5-4	12%
4.5-5	4%
5.5-6	0%
6.5-7	0%
7.5-8	0%
8.5-9.5	0%
10	0%

14.1.6 Transitions

To simulate how people transitioned between the health states in the model, information was required on transitions between RRMS health states, progressing from RRMS to SPMS and transitions between SPMS, for both the comparator and intervention arms (discussed in the treatment efficacy section). In the comparator arm (natural history receiving best supportive care), in the base case, transitions were derived from information from the ADVANCE trial,[211] and supplemented with information from the British Columbia dataset.[151] Table 32 shows the annual transition probabilities between RRMS health states used in the natural history arm. In sensitivity analysis, the company has derived other transit probabilities, using information from the ADVANCE trial extrapolated with the British Columbia dataset or London Ontario dataset.[84] For the transition probabilities from RRMS to SPMS these were based on information from the London Ontario dataset. The company suggested that these values were not available in the British Columbia MS cohort and, they have not elaborated on how these transition probabilities were derived. Table 33 shows the transitions between RRMS to SPMS by EDSS level. Transition probabilities for people progressing within SPMS health states were estimated from the British Columbia cohort. These annual probabilities were derived using a multistate model. Table 34 shows the transitions between SPMS states.

Table 32: Natural history matrix based on information from ADVANCE trial and British Columbia dataset, Biogen model

EDSS From/to		EDSS state (to)										
		0	**1**	**1.5-2**	**2.5-3**	**3.5-4**	**4.5-5**	**5.5-6**	**6.5-7**	**7.5-8**	**8.5-9.5**	**10**
EDSS state (from)	**0**	0.850	0.050	0.100	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0
	1	0.024	0.830	0.114	0.024	0.000	0.000	0.006	0.001	0.001	0.000	0
	1.5-2	0.014	0.152	0.670	0.104	0.048	0.000	0.010	0.001	0.001	0.000	0
	2.5-3	0.000	0.008	0.125	0.693	0.084	0.017	0.064	0.005	0.004	0.000	0
	3.5-4	0.000	0.022	0.000	0.216	0.519	0.086	0.141	0.009	0.007	0.000	0
	4.5-5	0.000	0.000	0.000	0.000	0.041	0.532	0.375	0.028	0.023	0.000	0
	5.5-6	0.000	0.000	0.000	0.000	0.000	0.000	0.894	0.049	0.056	0.001	0
	6.5-7	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.807	0.189	0.004	0
	7.5-8	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.995	0.006	0
	8.5-9.5	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000	0
	10	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1

Table 33: Annual transition probabilities for RRMS to SPMS, Biogen model

EDSS	Probability of transition to SPMS (one EDSS higher)
1	0.003
1.5-2	0.032
2.5-3	0.117
3.5-4	0.210
4.5-5	0.299
5.5-6	0.237
6.5-7	0.254
7.5-8	0.153
8.5-9.5	1.000

Table 34: Annual transition probabilities between SPMS health states based on information from the British Columbia dataset, Biogen model

EDSS From/to		EDSS state (to)										
		0	**1**	**1.5-2**	**2.5-3**	**3.5-4**	**4.5-5**	**5.5-6**	**6.5-7**	**7.5-8**	**8.5-9.5**	**10**
EDSS state (from)	**0**	0.695	0.203	0.073	0.022	0.004	0.001	0.002	0.000	0.000	0.000	0
	1	0.058	0.695	0.158	0.061	0.016	0.005	0.006	0.000	0.000	0.000	0
	1.5-2	0.016	0.121	0.608	0.168	0.045	0.018	0.022	0.002	0.001	0.000	0
	2.5-3	0.006	0.050	0.120	0.544	0.091	0.058	0.116	0.010	0.004	0.000	0
	3.5-4	0.002	0.022	0.067	0.115	0.489	0.104	0.168	0.026	0.007	0.001	0
	4.5-5	0.001	0.005	0.029	0.059	0.087	0.487	0.273	0.039	0.019	0.001	0
	5.5-6	0.000	0.001	0.004	0.025	0.031	0.041	0.741	0.109	0.044	0.004	0
	6.5-7	0.000	0.000	0.001	0.002	0.007	0.004	0.117	0.693	0.161	0.016	0
	7.5-8	0.000	0.000	0.000	0.000	0.001	0.001	0.019	0.056	0.903	0.021	0
	8.5-9.5	0.000	0.000	0.000	0.000	0.000	0.000	0.002	0.006	0.174	0.818	0
	10	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1

14.1.7 Treatment effects of IM IFN β -1a 30µg

For disability progression the company derived a hazard ratio based on a Cox proportional hazard model as a measure of relative risk. In the RSS model, the treatment effect of IFN β-1a 30µg IM once weekly (Avonex) was shown to be [redacted].
The year 10 implied hazard ratio of [redacted] for IFN β-1a 30µg IM once weekly (Avonex) was used in the company's model. Assuming no waning, the transition matrices are presented in Table 35 and Table 36, for age of onset <28 and >28 years, respectively. The implied hazard ratio was applied to the model to show the relative effect of treatment on disability progression.

Table 35: Transition matrix for IFN β-1a 30 µg IM once weekly, age at onset <28 years, Biogen model

EDSS		EDSS state (from)										
		0	1	1.5-2	2.5-3	3.5-4	4.5-5	5.5-6	6.5-7	7.5-8	8.5-9.5	10
EDSS state (to)	0											
	1											
	1.5-2											
	2.5-3											
	3.5-4											
	4.5-5											
	5.5-6											
	6.5-7											
	7.5-8											
	8.5-9.5											
	10											

Table 36: Transition matrix for IFN β-1a 30 µg IM once weekly, age at onset >28 years, Biogen model

EDSS		EDSS state (from)										
		0	1	1.5-2	2.5-3	3.5-4	4.5-5	5.5-6	6.5-7	7.5-8	8.5-9.5	10
EDSS state (to)	0											
	1											
	1.5-2											
	2.5-3											
	3.5-4											
	4.5-5											
	5.5-6											
	6.5-7											
	7.5-8											
	8.5-9.5											
	10											

14.1.8 Resource use and costs

All costs included in the analysis were those directly related to the NHS and PSS perspective, and were reported in pounds sterling in 2015/16 prices. The model included the following resource use and costs in order to conduct their analyses:

- Drug acquisition costs
- Administration costs
- Monitoring costs
- Health state/EDSS costs
- Cost of relapse
- Treatment-related adverse event costs

14.1.9 Drug acquisition costs

Treatment costs for IFN β-1a 30 µg IM once weekly (Avonex) and pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy) along with the other DMTs are presented in Table 37. Annual costs were presented for the list and net price for each DMT available at the time of the RSS. From the Excel model submitted, costs of treatments were based on the dosage (per week and year), price per packet, and the annual costs for each drug was derived. The assessment group considered these acquisition costs to be correctly derived.

Table 37: Annual treatment costs in the Biogen model

Treatment	Administration	Doses per year	Annual acquisition costs (list price: £, 2014/15 prices)		Annual acquisition costs (net price: £, 2014/15 prices)	
			Year 1	Subsequent years	Year 1	Subsequent years
IM IFN β-1a (Avonex)	30 µg once weekly	52.18	8502	8502	[redacted]	[redacted]
SC IFN β-1a (Plegridy)	125 µg every two weeks	26.1	8502	8502	8502	8502
SC IFN β-1a (Rebif)	22 µg three times weekly	156.18	7914	7976	7513	7513
SC IFN β-1a (Rebif)	44 µg three times weekly	156.18	10,311	10,572	8942	8942
SC IFN β-1b (Betaferon)	250 µg every other day	182.63	7239	7239	7259	7259
SC IFN β-1b (Extavia)	250 µg every other day	182.63	7239.11	7239.11	7239.11	7239.11
GA (Copaxone)	20 mg once daily	365.25	6681	6681	5823	5823
GA (Copaxone)	40 mg once daily	156.18	6681	6681	6681	6681
GA, glatiramer acetate; IM, intramuscular; SC, subcutaneous						

Where no net prices for DMTs were available the list price of these drugs were used in the analysis. The ERG noted that the annual drug acquisition costs for IFN β-1b 250 µg SC every other day (Betaferon) are reported in Table 37 as £7239 but the model used £7239.11 in the analysis.

14.1.10 Administration costs

Annual administration costs included costs associated with training/teaching people self-administration. The administration costs are presented in Table 38. The assessment group considered the resource use and costs to be appropriate.

Table 38: Administration costs for each intervention, Biogen model

Treatment	Annual administration cost for Year one (£, 2014/15)	Resource use	Annual administration cost for subsequent years (£, 2014/15)	Resource use
IFN β-1a 30 µg IM once weekly (Avonex)	177.00	3 hours of nurse's time to teach self-administration	0.00	None
IFN β-1a 44 or 22 µg SC three times weekly (Rebif)				
IFN β-1b 250 µg SC every other day (Betaferon/Extavia)				
Pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy)				
GA 20 mg SC daily or 40 mg SC three times weekly (Copaxone)				

14.1.11 Monitoring costs

Annual monitoring costs for each treatment were presented in Appendix K of the main report. The company clearly outlined the resource use, used to derive monitoring costs. Monitoring costs were presented for Year one and for subsequent years. The monitoring costs for all interventions are presented in Table 39. These annual monitoring costs appeared to have been derived and used in the model correctly.

Table 39: Annual costs for monitoring each treatment, Biogen model

Drug intervention	Monitoring costs for Year 1 (£, 2014/15)	Monitoring costs for subsequent years (£, 2014/15)
IFN β-1a 30 µg IM once weekly (Avonex)	190.73	10.78
IFN β-1a 44 or 22 µg SC three times weekly (Rebif)	203.25	10.78
IFN β-1b 250 µg SC every other day (Betaferon/Extavia)	190.73	10.78
Pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy)	191.92	10.78
GA 20 mg SC daily or 40 mg SC three times weekly (Copaxone)	175.75	10.78

14.1.12 Health state/EDSS costs

Health state costs (payers' perspective) by EDSS level and type (RRMS/SPMS) are presented in Table 40. These costs were related to MS management (expected/unexpected visits to healthcare providers). The company also identified and presented cost estimates from other sources (Karampampa et al., 2012)[264] and the burden of illness (BOI) study). Costs obtained from Karampampa et al. were inflated using the hospital and community health services (HCHS) index, and these seemed to be correctly derived. These costs estimated were used in sensitivity analyses. Costs were presented from the payer, government and societal perspectives. It appears, that these cost estimates by EDSS states vary between studies. For the cost estimates derived in the submission and the BOI study, there appears to be a gradual increase in management costs for EDSS 0 to 6, then increases beyond EDSS 6. However, in the Karampampa study, management costs seemed to increase gradually from EDSS 0 to 10.

Table 40: Mean unit costs in the model from payers' perspective, Biogen model

EDSS state	RRMS (£, 2014/15)			SPMS (£, 2014/15)		
	Biogen	Karampampa et al., 2012	BOI study	Biogen	Karampampa et al., 2012	BOI study
0	937	1179	4301	1263	1470	4301
1	974	1399	4783	1301	1745	4783
1.5-2	714	1674	8666	1040	2088	8666
2.5-3	3906	2006	7720	4232	2502	7720
3.5-4	1892	2393	7159	2218	2985	7159
4.5-5	3210	2837	9147	3537	3538	9147
5.5-6	4285	3337	12,830	4611	4161	12,830
6.5-7	11,279	3892	17,971	11,605	4854	17,971
7.5-8	27,472	4503	29,915	27,798	5616	29,915
8.5-9.5	21,982	5170	37,656	22,309	6449	37,656
10	0	0	0	0	0	0

14.1.13 Cost of relapse

In the main report of the company's submission, the costs of a relapse was obtained from the ScHARR model[257] (£2697) and subsequently inflated to current prices (£4265) using the Hospital and Community Health Services pay and price index 2014/15.[260] Using costs from a dated source, suggests that the management and resource use for treating relapses have not change post-2009. The assessment group considered this to be a strong assumption..

In critiquing the economic model submitted (and stated in the appendices), the assessment group noted that the cost of relapse used were obtained from the Hawton and Green (2015) study,[111] then subsequently inflated to current prices using the Hospital and Community Health Services (HCHS) pay and price index 2014/15.[260] The cost represents an average cost regardless of the severity of the relapse. Costs were derived for relapses not requiring (£568) and those requiring hospitalisation (£3651). The assessment group noted that these costs were the same in all arms (interventions and comparator) of the model. These costs appear to have been correctly derived. However, the company did not elaborate on the resource use estimates used to derive the unit cost of a

relapse. Resource use information in the Hawton and Green study was obtained from information collected in the UK South West Impact of Multiple Sclerosis (SWIMS) project.[265] SWIMS is a prospective, longitudinal cohort study of people with MS in Devon and Cornwall, with people followed-up every six months. In this study information was collected on the type of MS, disease severity measured by the EDSS, number of relapses in the previous six months, length of relapse, whether relapses led to hospital admittance, and the treatment received for relapses. Additional information was collected on health or social care use in the previous six months and the frequency of contact with a health care professional. Resource use was valued using the Personal Social Services Unit, NHS Reference costs and the British National Formulary.[24] All costs derived were reported in UK pound sterling using 2012 prices. The ERG considers this study to be methodologically robust. However, these costs represented people with various types of MS (RRMS, PPMS, SPMS, Benign or combination or not known) who experienced relapses over a six month period. Resource use and costs were not reported by type of MS in the Hawton and Green study.[111] The assessment group considers these costs used in the model to be an underestimate of the cost of a relapse.

14.1.14 Adverse events and cost of adverse events

The model included costs for adverse events as a result of disease modifying treatment. In Appendix K of the company's submission, estimates on resource use were presented. Healthcare resource use for each adverse event was validated by a Delphi panel conducted by the company in December 2013. The company provided the percentages of people who developed these adverse events by DMTs. Table 41 shows the annual costs of treatment for adverse events used in the model by DMT. These annual costs for treatment of adverse events appear to be correctly derived.

Table 41: Annual cost of treatment for adverse events by DMT, Biogen model

DMT	Unit cost (£, 2014/15)
IM IFN β-1a 30 µg once weekly (Avonex)	154.97
SC pegylated IFN β-1a 125 µg every two weeks (Plegridy)	76.95
SC IFN β-1a 22 µg three times weekly (Rebif)	127.33
SC IFN β-1a 44 µg three times weekly (Rebif)	140.89
SC IFN β-1b 250 µg every other day (Betaferon)	104.12
SC IFN β-1b 250 µg every other day (Extavia)	104.12
GA 20 mg SC once daily (Copaxone)	74.78
GA 40 mg SC once daily (Copaxone)	74.78

14.1.15 Health state utility values

Utilities were derived by EDSS level and MS type (RRMS and SPMS). In the base case, these were derived by combining information from the placebo arm of the ADVANCE trial[211] (EDSS 0-5) with information from the UK MS survey (EDSS ≥6). Utility values for EDSS 6 were derived by adding the utility value from EDSS 5 (taken from ADVANCE study) to the difference between EDSS 6 and 5 from the UK MS Survey. The same method was used to derive utility values for EDSS scores ≥7 to 9). Utility values used in the model are presented in Table 42. The company also included disutilities associated with relapses experienced in an RRMS health state (-0.071) and those in a SPMS health state (-0.045). These disutilities were applied across all EDSS levels by MS type (RRMS and SPMS). Disutilities were obtained from the Orme study.[105] An analysis was

undertaken which included carers' disutilities by EDSS state. Table 42 shows the disutility values used in the model. Due to the lack of information, carers' burdens associated with caring for people with either RRMS and SPMS were assumed to be the same.

Table 42: Mean utility values used, Biogen model

EDSS state	Utility value		Carer's disutility	
	RRMS	SPMS	RRMS	SPMS
0	0.879	0.834	0.000	0.000
1	0.866	0.821	-0.001	-0.001
1.5-2	0.771	0.726	-0.003	-0.003
2.5-3	0.662	0.617	-0.009	-0.009
3.5-4	0.573	0.528	-0.009	-0.009
4.5-5	0.549	0.504	-0.020	-0.020
5.5-6	0.491	0.446	-0.027	-0.027
6.5-7	0.328	0.283	-0.053	-0.053
7.5-8	-0.018	-0.063	-0.107	-0.107
8.5-9.5	-0.164	-0.209	-0.140	-0.140
Relapse disutility in the RRMS states				-0.071
Relapse disutility in the SPMS states				-0.045

14.1.16 Adverse event disutility

The disutilities associated with adverse events by DMTs are presented in Table 43.

Table 43: Annual disutility values associated with each DMT, Biogen model

Disease modifying treatments	Annual disutility
IFN β-1a 30 µg IM once weekly (Avonex)	-0.024
Pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy)	-0.016
IFN β-1a 44 µg SC three times weekly (Rebif)	-0.019
IFN β-1b 250 µg SC every other day (Betaferon)	-0.018
IFN β-1b 250 µg SC every other day (Extavia)	-0.018
GA 20 mg SC once daily (Copaxone)	-0.007
GA 40 mg SC once daily (Copaxone)	-0.007

14.1.17 Mortality rate

Mortality was assumed to be equivalent between RRMS and SPMS and dependent on EDSS state. All patients were modelled to be at risk of mortlity from MS and other causes. This was modelled by first estimating standardised mortlity rates using data from the Office of National Statistics, as cited in the Biogen submission, and applying a mortality multiplier to reflect both causes of death. Additional, individuals in EDSS states 7-9, could die from MS-specfic mortlity from transition to EDSS state 10 (death).

14.1.18 Relapse frequency

The annualised relapse rates (ARR) were obtained from the ADVANCE trial[211] up to EDSS 5.5, and supplemented with rates derived from the Patzold et al. (2008), as cited in the manufacturer submission, and the

ADVANCE trial. Table 44 shows the relapse rates by EDSS level used in the base case and other relapse rates used in scenario analyses.

Table 44: Relapse frequency by EDSS state and type of MS (RRMS and SPMS) for BSC, Biogen model

EDSS	ADVACE placebo		Patzold 1982 and UK MS survey (TA254, TA320 methods)		Patzold 1982 and UK MS survey (TA303, TA312 methods)	
	RRMS	SPMS	RRMS	SPMS	RRMS	SPMS
0	0.260	0.000	0.709	0.000	0.725	0.000
1	0.237	0.000	0.729	0.000	0.743	0.000
1.5-2	0.460	0.315	0.676	0.465	0.690	0.447
2.5-3	0.495	0.602	0.720	0.875	0.723	0.788
3.5-4	0.670	0.515	0.705	0.545	0.707	0.567
4.5-5	0.181	0.160	0.591	0.524	0.599	0.517
5.5-6	0.150	0.139	0.490	0.453	0.508	0.445
6.5-7	0.156	0.104	0.508	0.340	0.504	0.312
7.5-8	0.156	0.104	0.508	0.340	0.504	0.312
8.5-9.5	0.156	0.104	0.508	0.340	0.504	0.312
10	0	0	0	0	0	0

Relapse rates per person per year for EDSS levels >5.5 were derived based on the relative increase in ARR reported in the Patzold study (Patzold et al., 1982).[266] Patzold reported ARR based on the year of diagnosis of RRMS. ARR by year were converted to ARR by EDSS level by taking the mean number of relapses per year for each health state from the UK MS survey and multiplying by the relative relapse rates per person reported by Patzold.

14.1.19 Treatment discontinuation

In the model, people who progressed to a SPMS health state discontinued treatment. However, treatment was assumed not to discontinue due to reaching a particular EDSS level. This is in accordance to current ABN guidelines.[262] Annual discontinuation rates used in the model are presented in Table 45.

Table 45: Annual discontinuation by DMT, Biogen model

Disease modifying treatments	Annual withdrawal (%)
IM IFN β-1a 30µg once weekly (Avonex)	7.9
Pegylated IFN β-1a SC 125 µg every two weeks (Plegridy)	10.4
IFN β-1a 22 µg SC three times weekly (Rebif)	6.0
IFN β-1a 44 µg SC three times weekly (Rebif)	12.3
IFN β-1b 250 µg SC every other day (Betaferon)	5.7
IFN β-1b 250 µg SC every other day (Extavia)	5.7
GA 20 mg once daily (Copaxone)	7.2
GA 40 mg once daily (Copaxone)	7.2
GA, glatiramer acetate; IM, intramuscular; SC, subcutaneous	

14.1.20 Analysis (cycle length, time horizon and perspective)

The analysis was undertaken from the National Health Service (NHS) and Personal Social Services (PSS) perspective. The outcome measure used in the analysis was quality-adjusted life-years gained, over a 50-year time horizon with annual cycle lengths. The starting age of the population was 36 years. Results were presented

as an incremental cost-effectiveness ratio (ICER) and expressed as cost per quality-adjusted life-years (QALYs) gained. Both costs and benefits were discounted at 3.5% per annum.

14.1.21 Assumptions

In order to have a workable model, the company made the following assumptions:

1. The probability of transitioning to a health state in the next cycle depends only on the health state of the present cycle
2. Transition from RRMS to SPMS is accompanied by an increase in EDSS scale of 1.0
3. The population at baseline in ADVANCE is representative of the RRMS population in clinical practice
4. Each year, EDSS score can remain the same, increase or decrease
5. In the base case, treatments affect EDSS progression but not EDSS regression
6. Treatment effects on relapse and EDSS progression are independent
7. In the base case, treatments have the same effect on progression in each EDSS state
8. In the base case, treatment efficacy is constant over time
9. Treatments do not directly impact transitions to SPMS, but impact patients' EDSS state, which influences transition to SPMS
10. Treatment discontinuation is constant for all years
11. It is assumed that mortality rates for age>100 is same as age=100
12. The annualised adverse event risks are applied every year - this may overestimate the incidence of adverse events since patients who have adverse events may discontinue in the initial years on treatment
13. RRMS patients in all EDSS states may receive treatments depending upon the maximum EDSS limit selected on sheet ‘Settings’
14. SPMS patients receive BSC only
15. Patient access schemes, where publicly available, are considered in the base case

14.1.22 Summary of Biogen submission results

Base-case results showed that treatment with pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy) resulted in the highest mean life-years gained (20.658) and mean QALYs (9.642) compared to all other interventions included in the analysis. Pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy) compared to best supportive care had a mean incremental cost of approximately £25,200 with corresponding incremental 0.810 QALYs, which equated to an ICER of approximately £31,000 per QALY.

Results from the sensitivity analyses showed that the base-case results were robust to univariate changes made to key input parameters except the hazard ratio for the confirmed disability progression, which had the greatest impact. The probabilistic sensitivity analysis suggested that at a willingness to pay threshold of £30,000/QALY, pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy) had a <0.4 probability of being cost-effective when compared to best supportive care.

14.2 **Teva UK Limited**

14.2.1 Background

This section focuses on the economic evidence submitted by Teva UK Ltd. on glatiramer acetate (Copaxone). This section is set out as for the previous copmpnay submission follows: first, we present an overview/summary then a critique of the economic model submitted by Teva UK Ltd. This section describes in detail the evidence (e.g. natural history information, effectiveness of interventions included in the analysis, resource use and costs, mortality and health-related quality of life) used to parameterise the models.

The economic submission to NICE included:

- A description of an economic model from Teva UK Ltd. which assesses the cost-effectiveness of disease modifying drugs for the treatment of RRMS; this includes details on the intervention and comparators, study population, resource use and costs, the modelling methodology, and assumptions.
- Appendices with details of the evidence used to inform the model, and a description of a network meta-analysis carried out to generate alternative estimates of efficacy which are used in sensitivity analysis.

14.2.2 Overview

In the Teva UK Ltd. model, an economic analysis was conducted to assess the cost-effectiveness of disease modifying treatments—IFN β-1a 30 µg IM once weekly (Avonex), IFN β-1a 44 or 22 µg SC three times weekly (Rebif), IFN β-1b 250 µg SC every other day (Betaferon/Extavia), pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy) and GA 20 mg SC daily or 40 mg SC three times weekly (Copaxone), as well as fingolimod, nataliumab and dimethyl fumarate—compared with best supportive care for people with RRMS.

In the analysis, a Markov model was used to depict the natural history of people with RRMS through progression to secondary progressive multiple sclerosis (SPMS). The model includes 21 health states, defined by EDSS score and disease stage (RRMS or SPMS). Only integer EDSS values were allowed, and fractional values were rounded down. Disease progression rates during RRMS on best supportive care were based on the British Columbia multiple sclerosis database, as in the RSS.[151] Transition rates to SPMS were estimated using hazard rates observed in the London Ontario dataset,[84] following assumptions made in the ScHARR model.[257] The Teva UK model assumes that progression to SPMS increases EDSS scores by 1. Progression between EDSS scores for SPMSS were calculated using the same transition probabilities as for RRMS. Treatment was assumed to continue until patients progressed to SPMS, or reached an EDSS score of 7 or greater, and was not reinitiated.

The analysis was undertaken from the payer perspective, although sensitivity analyses were included from a societal perspective. The outcome measure used in the analysis was QALYs gained, over a 50-year time horizon. Treatment effects were assumed to delay the progression of the disease and reduce the frequency of relapses. The assumed hazard ratio (applied to all forward transitions) of glatiramer acetate (Copaxone) vs. best supportive care was [redacted] in the base case, based on the subset of patients in the RSS who received this DMT. Utilities for RRMS by EDSS level were based on pooling data from the MS Trust and Orme et al.,[105] following the RSS. Utility values for SPMS by EDSS level were assumed to be the same as for RRMS. Carers' disutilities

were based on information obtained from the manufacturer's submission to NICE for TA127.[263] Utility values for adverse events associated with each DMT were taken from a range of sources, including the NICE appraisal of alemtuzumab, and Maruszczak et al.[267]

Information on resource use and unit costs were obtained from various sources (British National Formulary,[24] PSSRU, NHS reference costs). The results were presented as an ICER and expressed as cost per life years gained (LYG) and cost per QALYs gained. Both costs and benefits were discounted at 3.5% per annum. Authors undertook a number of sensitivity analyses (societal perspective, patient baseline characteristics, transition probabilities, treatment efficacy, relapse rates, discontinuation rates, utility values, mortality multipliers, patients' out-of-pocket costs, carers' costs, loss of productivity for people with MS and adverse events) and probabilistic sensitivity analysis to determine the robustness of the base-case results. Base-case results showed that treatment with glatiramer acetate (Copaxone) resulted in a mean gain per patient of [redacted] life years or [redacted] QALY, at a net discounted cost of [redacted], giving an ICER [redacted] per QALY. The probability of cost-effectiveness for glatiramer acetate (Ccopaxone) relative to best supportive care was [redacted] at £20,000 per QALY and [redacted] at £30,000 per QALY. Results from deterministic sensitivity analyses showed that the base-case results were robust to univariate changes made to key input parameters except the hazard ratio for the confirmed disability progression, which had the greatest impact, and EDSS score related costs, which did influence whether glatiramer acetate (Copaxone) was cost-effective relative to best supportive care (see below).

14.2.3 Evidence used to parameterise the Risk Sharing Scheme (RSS) multiple sclerosis model

Natural history of relapsing-remitting multiple sclerosis

Two key sources informed the analysis of natural history of RRMS; the London Ontario dataset[84] for transition to SPMS, and the British Columbia[151] dataset for EDSS progression. Table 46 and Table 47 show the natural history transition matrices from the British Columbia dataset.

Table 46: Natural history transition matrix based on information from the British Columbia dataset (below median age)

EDSS from/to		EDSS state (to)										
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
EDSS state (from)	**0**	0.68701	0.21104	0.07196	0.02236	0.00434	0.00136	0.00176	0.00012	0.00003	0.00000	0.00000
	1	0.06122	0.67867	0.16643	0.06463	0.01698	0.00474	0.00667	0.00052	0.00014	0.00001	0.00000
	2	0.01692	0.12654	0.59552	0.17292	0.04538	0.01842	0.02190	0.00182	0.00054	0.00005	0.00000
	3	0.00620	0.05215	0.11649	0.54385	0.09451	0.05729	0.11479	0.01070	0.00366	0.00035	0.00000
	4	0.00176	0.02251	0.06617	0.12104	0.48739	0.10090	0.16645	0.02622	0.00689	0.00067	0.00000
	5	0.00055	0.00562	0.02915	0.05935	0.09154	0.47268	0.28098	0.03961	0.01909	0.00143	0.00000
	6	0.00012	0.00141	0.00447	0.02516	0.03209	0.04241	0.72834	0.11509	0.04566	0.00525	0.00000
	7	0.00001	0.00016	0.00052	0.00260	0.00730	0.00419	0.12198	0.68147	0.16283	0.01895	0.00000
	8	0.00000	0.00001	0.00004	0.00030	0.00057	0.00053	0.01885	0.05747	0.86099	0.06124	0.00000
	9	0.00000	0.00000	0.00000	0.00002	0.00004	0.00004	0.00178	0.00596	0.17091	0.82124	0.00000
	10	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	1.00000

Table 47: Natural history transition matrix based on information from the British Columbia dataset (above median age)

EDSS from/to		EDSS state (to)										
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
EDSS state (from)	**0**	0.69537	0.20294	0.07251	0.02170	0.00422	0.00137	0.00175	0.00011	0.00003	0.00000	0.00000
	1	0.05826	0.69503	0.15781	0.06087	0.01638	0.00458	0.00643	0.00048	0.00013	0.00001	0.00000
	2	0.01586	0.12135	0.60786	0.16796	0.04458	0.01849	0.02160	0.00174	0.00052	0.00004	0.00000
	3	0.00594	0.04961	0.12008	0.54421	0.09107	0.05844	0.11651	0.01029	0.00355	0.00030	0.00000
	4	0.00165	0.02214	0.06660	0.11518	0.48936	0.10387	0.16812	0.02580	0.00671	0.00056	0.00000
	5	0.00052	0.00533	0.02942	0.05866	0.08738	0.48692	0.27312	0.03880	0.01883	0.00102	0.00000
	6	0.00012	0.00133	0.00444	0.02497	0.03069	0.04080	0.74072	0.10894	0.04377	0.00423	0.00000
	7	0.00001	0.00015	0.00052	0.00247	0.00727	0.00385	0.11683	0.69268	0.16063	0.01559	0.00000
	8	0.00000	0.00001	0.00004	0.00029	0.00055	0.00050	0.01880	0.05573	0.90340	0.02067	0.00000
	9	0.00000	0.00000	0.00000	0.00002	0.00004	0.00003	0.00176	0.00568	0.17414	0.81832	0.00000
	10	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	1.00000

14.2.4 Types of multiple sclerosis

The model includes people who commenced in an RRMS health state and progressed to SPMS. People with CIS, primary progressive multiple sclerosis or benign disease were not included in the analysis.

14.2.5 Interventions

The interventions considered in the economic analyses are presented in Table 48. The interventions included IFN β-1a 30 µg IM once weekly (Avonex), IFN β-1a 44 or 22 µg SC three times weekly (Rebif), IFN β-1b 250 µg SC every other day (Betaferon/Extavia), pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy) and GA 20 mg SC daily or 40 mg SC three times weekly (Copaxone), as well as fingolimod (Gilenya), natalizumab (Tysabri) and dimethyl fumarate (Tecifdera) as second-line therapies. It is assumed that the split between these second-line therapies will be 50%, 30% and 20% respectively, based on expert opinion. The interventions are compared against best supportive care treatment for people with RRMS.

Table 48: Interventions included in the economic analysis, Teva model

Brand	Drug	Dose regime	Route of administration	Label indications
Avonex	IFN β-1a	30 µg once a week	Intramuscular	RRMS
Rebif		RRMS: 22 or 44 µg three times per week	Subcutaneous	RRMS
Betaferon/Extavia	IFN β-1b	300µg every other day		RRMS
Plegridy	Pegylated IFN β-1a	250µg every 2 weeks		RRMS
Copaxone	Glatiramer acetate	20mg once daily	Oral	RRMS
Gilenya	Fingolimod	500mg once daily	Oral	RRMS
Tysabri	Natalizumab	300mg once every 4 weeks	IVI	RRMS
Tecfidera	Dimethyl fumarate	240mg twice daily	oral	RRMS
IFN, interferon; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; IVI, Intravenous infusion.				

14.2.6 Model structure

The illustrative Markov model structure submitted by the company was based on the original ScHARR model[257] with developments to include other interventions. The company used a cohort-based Markov model to depict the natural history of people with RRMS. The model simulated the disability progression, progression from RRMS to SPMS, and the relapsing nature of the disease. People with RRMS were able to occupy one of the EDSS health states, which ranged from 0 to 10, and in increments of 0.5. The model allowed for people to progress, regress or stay in the same EDSS health state, or progress from EDSS to SPMS. When people progress to SPMS, they can progress, regress or remain in the same EDSS state.

In the model, people incurred costs and accrued benefits depending on the EDSS state for RRMS and SPMS. Benefits were measured using quality-adjusted life years, whereby each model cycle a utility is assigned to people occupying a specific health state.

14.2.7 Population

The population included in the economic analysis was similar to the population for the RSS dataset (i.e. [redacted] of females with a starting age of 30 years with relapsing-remitting multiple sclerosis). The initial distribution of people in each EDSS state is presented in Table 49.

Table 49: Baseline distribution of people by EDSS score, Teva model

EDSS	Distribution (%)
0	3%
1	16%
2	26%
3	23%
4	16%
5	10%
6	6%
7	0%
8	0%
9	0%
10	0%

14.2.8 Resource use and costs

All costs included in the analysis were those directly related to the NHS and PSS perspective, and were reported in pounds sterling in 2015/16 prices. The model included the following resource use and costs in order to conduct their analyses:

- Drug acquisition costs
- Administration costs
- Monitoring costs
- Health state/EDSS costs
- Cost of relapse
- Treatment-related adverse event costs

14.2.9 Drug acquisition costs

Treatment costs for glatiramer acetate (Copaxone) along with the other DMTs are presented in Table 50. Annual costs were presented for the list and net price for each DMT that was available at the time of the RSS. From the Excel model submitted, cost of treatments were based on the dosage (per week and year), price per packet, and the annual costs for each drug was derived.

Table 50: Annual treatment costs, Teva model

DMT	Annual acquisition costs (list price: £, 2014/15 prices)	Annual acquisition costs (net price: £, 2014/15 prices)
Glatiramer acetate (Copaxone)	6,704.29	[redacted]
IFN β-1a 30 µg IM weekly (Avonex)	8,531.20	8,501.98
IFN β-1b 250 µg SC every other day (Betaferon)	7,264.82	7,259.34

IFN β-1a 44 µg SC three times weekly (Rebif)	10,608.43	[redacted]
IFN β-1a 22 µg SC three times weekly (Rebif)	8,003.67	[redacted]
Fingolimod (Gilenya)	19,175.63	19,175.63
Natalizumab (Tysabri)	14,740.45	14,740.45
Dimethly fumarate (Tecfidera)	17,910.29	[redacted]
Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy)	8,531.20	8,531.20

Where no net prices for DMTs were available because of treatments not being included in the RSS, the list price of these drugs were used in the analysis.

14.2.10 Administration costs

Annual administration costs included costs associated with training/teaching people self-administration. The administration costs are presented in Table 51.

Table 51: DMT administration costs, Teva model

DMT	Annual administration cost for Year one (£, 2014/15)	Resource use	Annual administration cost for subsequent years (£, 2014/15)	Resource use
Glatiramer acetate (Copaxone)	174.00	3 hours of nurse's time to teach self-administration	0.00	None
IFN β-1a 30 µg IM weekly (Avonex)				
IFN β-1b 250 µg SC every other day (Betaferon/Extavia)				
IFN β-1a 44 µg SC three times weekly (Rebif)				
IFN β-1a 22 µg SC three times weekly (Rebif)				
Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy)				
Fingolimod (Gilenya)	144.99	Continuous electrocardiogram and blood presume monitoring for six hours following first dose	0.00	None
Natalizumab (Tysabri)	5,199.02	Thirteen infusions per year with 1g Methylprednisolone per infusion	5,199.02	Thirteen infusions per year with 1g Methylprednisolone per infusion
Dimethyl fumarate (Tecfidera)	0	None	0	None

14.2.11 Monitoring costs

Annual monitoring costs for each treatment were presented in Appendix 6 of the main report. The company clearly outlined the resource use, used to derive monitoring costs. Monitoring costs were presented for Year one and for subsequent years. The monitoring costs for all interventions are presented in Table 52. These annual monitoring costs appeared to be derived and used in the model correctly. The monitoring costs for second line therapies are not presented in appendix 6 of the submission.

Table 52: Annual monitoring costs for each DMT, Teva model

DMT	Monitoring costs for Year 1 (£, 2014/15)	Monitoring costs for subsequent years (£, 2014/15)
Glatiramer acetate (Copaxone)	414.00	414.00
IFN β-1a 30 µg IM weekly (Avonex)	521.08	512.54
IFN β-1a 22 µg SC three times weekly (Rebif)	521.08	512.54
IFN β-1a 44 µg SC three times weekly (Rebif)	521.08	512.54
Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy)	521.08	512.54
IFN β-1b 250 µg SC every other day (Betaferon/Extavia)	521.08	512.54

14.2.12 Health state/EDSS costs

Health state costs (payers' perspective) by EDSS level and type (RRMS/SPMS) are presented in Table 53. These costs were related to MS management (expected/unexpected visits to healthcare providers). The costs were taken from the ScHARR model and inflated to 2015 prices. Sensitivity analyses were carried out using health state costs sourced from Tyas et al.[268] and from Karampampa et al.[264] The former involve lower costs for high EDSS scores, and increase the ICER for glatiramer acetate (Copaxone) to [redacted].

Table 53: Mean unit costs from payers' perspectives, Teva model

EDSS State	0	1	2	3	4	5	6	7	8	9
Cost (£)	1,195	1,195	1,195	2,204	2,284	8,049	8,978	27,398	42,541	54,080

14.2.13 Cost of relapse

The cost of a mild relapse was estimated at £870, and the cost of a severe relapse requiring hospitalisation was £5,580. The submission states that these costs were sourced from the manufacturer submission for NICE TA312[269] (alemtuzumab for treating RRMS), which took these costs from a budget impact analysis in the republic of Ireland (Dee 2012).[270]. This raises questions about the robustness of the estimate, and its relevance for a UK setting. The assessment group for TA312 conducted their own sensitivity analysis in which the cost of

a severe relapse was assumed to be lower (£3039). A justification for this was not presented in the report, but it implies that the assessment group at the time thought the higher figure might be an overestimate.

14.2.14 Cost of adverse events

The model included costs for adverse events as a result of disease modifying treatment. In Appendix 6 of the company's submission, estimates on resource use have been presented. Table 54 shows the annual costs of treatment for adverse events used in the model by DMT. Unit costs for resources used to manage adverse events were sourced from the PSSRU,[260] national reference costs and the manufacturer submission for TA312[269], although insufficient detail is presented for the accuracy of the costs assumed for adverse events to be fully verified.

Table 54: Annual cost of treatment for adverse events by DMT, Teva model

DMT	Unit cost (£, 2014/15)	Unit cost (£, 2014/15)
	Year 1	Year 2
Glatiramer acetate (Copaxone)	44.61	44.61
IFN β-1a 30 µg IM weekly (Avonex)	32.81	32.81
IFN β-1a 22 µg SC three times weekly (Rebif)	20.59	20.59
IFN β-1a 44 µg SC three times weekly (Rebif)	26.90	26.90
Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy)	13.64	22.66
IFN β-1b 250 µg SC every other day (Betaferon/Extavia)	30.75	30.75
IFN, interferon; IM, intramuscular; SC, subcutaneous		

14.2.15 Health state utility values

Utilities were derived by EDSS level and assumed to be independent of MS type (RRMS and SPMS). In the base case, these were derived from the same sources as the RSS model. Utility values used in the model are presented in Table 55.

Table 55: Utility values by health state, Teva model

EDSS State	0	1	2	3	4	5	6	7	8	9
Utility	0.925	0.761	0.674	0.564	0.564	0.491	0.445	0.269	0.008	-0.230
Carer's disutilities	0.002	0.002	0.002	0.002	0.045	0.142	0.167	0.063	0.095	0.095

14.2.16 Carer's disutility

An analysis was undertaken which included carers' disutilities by EDSS state. Table 55 shows the disutility values used in the model.

14.2.17 Mortality rate

An EDSS-dependent mortality multiplier was used to estimate mortality from UK general population rates (sourced from ONS data for 2012-2014). These multipliers were taken from the Teriflunomide manufacturer submission to NICE (which were themselves adapted from Pokorski et al. (1997).[271, 272] This raises concerns around the robustness of assumed mortality, and questions around whether a more up to date source could be identified.

14.2.18 Adverse event disutility

The assumed annual disutilities due to adverse events are given in Table 56. These were calculated from adverse event rates derived from clinical trials of the treatments included in the submission. Disutilities for adverse events were obtained from Maruszczak et al.[267] and from manufacturer submissions to NICE for alemtuzumab, teriflunomide, dimethyl fumarate, and IFN β-1a 44 µg SC three times weekly (Rebif).

Table 56: Disutilities associated with adverse events, Teva model

Disease modifying treatment	Annual adverse event disutility	
	Year 1	Year 2+
Glatiramer acetate (Copaxone)	-0.0043	-0.0043
IFN β-1a 30 µg IM weekly (Avonex)	-0.0009	-0.0009
IFN β-1a 22 µg SC three times weekly (Rebif)	-0.0027	-0.0027
IFN β-1a 44 µg SC three times weekly (Rebif)	-0.0034	-0.0034
Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy)	-0.0043	-0.0037
IFN β-1b 250 µg SC every other day (Betaferon/Extavia)	-0.0028	-0.0028

14.2.19 Relapse

The disutility per relapse was assumed to be 0.058 QALYs if the relapse was severe, and 0.009 otherwise. The lower utility was based on the study by Orme et al.[105] The manufacturer was unable to identify a UK source for estimating disutility associated with severe relapse. Estimates for a US population were identified, but the manufacturer argues that these over-estimate the equivalent for a UK population. They therefore downweighted this utility by the ratio of UK to US disutilities for non-severe relapse (0.071/0.091), which resulted in a reduction of the severe disutility from 0.302 to 0.236. This was combined with an assumed duration of 90 days to give the 0.058 estimate.

14.2.20 Treatment discontinuation

In the Teva model, people who progressed to an SPMS health state discontinued treatment. Accordingly, treatment was assumed to discontinue at EDSS state 7, in agreement with ABN guidelines.[262]

14.2.21 Analysis (cycle length, time horizon and perspective)

The analysis was undertaken from the NHS and Personal Social Services (PSS) perspective. The outcome measure used in the analysis was QALYs gained, over a 50-year time horizon with annual cycle lengths. The starting age of the population was 30 years. Results were presented as an incremental cost-effectiveness ratio (ICER) and expressed as cost per QALYs gained. Both costs and benefits were discounted at 3.5% per annum.

14.2.22 Summary of model assumptions

In summary, the Teva model made the following assumptions:

1. The probability of transitioning to a health state in the subsequent cycle depends only on the health state in the present cycle
2. Transition from RRMS to SPMS is accompanied by an increase in EDSS scale of 1
3. Each year, EDSS score can remain the same, increase or decrease
4. In the base case, treatments affect EDSS progression but not EDSS regression
5. Treatment effects on relapse and EDSS progression are independent
6. In the base case, treatments have the same effect on progression in each EDSS state
7. In the base case, treatment efficacy is constant over time
8. Treatments do not directly impact transitions to SPMS, but impact patients' EDSS state, which influences transition to SPMS
9. Treatment discontinuation is constant for all years
10. The annualised adverse event risks are applied every year - this may overestimate the incidence of adverse events since patients who have adverse events may discontinue in the initial years on treatment
11. Patients who discontinue move on to one of three second-line treatments – Gilenya (50%), Tysabri (30%) and Tecfidera (20%)
12. SPMS patients receive BSC only
13. Patient access schemes for which data are publicly available are considered in the base case

14.2.23 Summary of results

Base-case results showed that treatment with glatiramer acetate (Copaxone) resulted in a mean gain per patient of [redacted] life years or [redacted], at a net discounted cost of [redacted], giving an ICER of [redacted] per QALY. The probability of cost-effectiveness for glatiramer acetate (Copaxone) copaxone relative to best supportive care was [redacted] at £20,000 per QALY and [redacted] at £30,000 per QALY.

14.3 **Merck**

14.3.1 Background

This section of the report focuses on the economic evidence submitted by Merck Biopharma on IFN β-1a 44 µg/22 µg SC three times weekly (Rebif). In the section, we will provide a summary of the economic analysis presented by Merck, and then critically appraise their analysis and findings. Merck have provided NICE with their economic model and analysis of IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) for the treatment of RRMS, SPMS and CIS; this includes details on the intervention and comparators, study population, resource use and costs, the modelling methodology, and assumptions.

In the Merck IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) model, an economic analysis was conducted to assess the costs-effectiveness of this DMT compared with best supportive care for people with RRMS, SPMS and CIS. Merck initially conducted a systematic review of the cost-effectiveness literature relating to MS and identified four studies that meet their inclusion criteria, two of these studies examined DMTs in CIS. In addition, they reviewed cost-effectiveness analysis undertaken as part of health technology assessments for

NICE (4 publications) and CADTH (1 publication). The concluded that majority of studies used a comparable approach to the ScHARR analysis[257] undertaken for TA32. In addition, they highlight that they adopted a commonly used approach to modelling mortality for MS patients, although they have not specified which studies from their review used this approach.

14.3.2 Merck IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) RRMS model

For the RRMS model analysis, a Markov model was used to depict the natural history of people with RRMS. The analysis was undertaken from the UK National Health Service (NHS) and Personal and Social Services (PSS) perspective. The outcome measure used in the analysis was quality-adjusted life-years (QALYs). The model was run over a 50-year time horizon with one-year cycles and half-cycle correction was applied. A 3.5% discount rate was applied to all future costs and health outcomes.

The model used EDSS scores, increasing increments of one, to model disability progression with and without DMDs. The model does not have separate health states for SPMS and assumes all patients stop DMTs upon reaching EDSS 7. The British Columbia natural history model[151] was used to model disease progression in people with RRMS. For those not on treatment, disability could improve (backward transition in EDSS scores). The model included information from both doses of the drug; thus they estimated outcomes for patients given both doses, based on numbers given the respective doses in the RSS cohort, and then pooled the outcomes. Of note, the model used dose specific parameters to populate their models (e.g. costs, treatment effects etc.)

In their analysis, the initial distribution of EDSS scores were based on what was observed in the RSS IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) treated dataset. Treatment effects were assumed to delay the progression of the disease and reduce the frequency of relapses. For progression, they used the hazard ratios from the 10-year RSS data provided by DH to model the impact of DMTs on disability progression (worsening EDSS scores). They also incorporated the 'waning effect' of DMTs on disability progression hazards. For relapse rates, they used findings from the PRISMS study.[187] In their base case analysis, they modelled mortality in the same way as the ScHARR model[257] by applying a SMR of 2.0 to life table mortality estimates, and an additional MS-specific mortality risk applied to those whose EDSS scores reaches 6.

Health outcomes were measured in QALYs. For this they assigned utility weights to the EDSS health states and included utility decrements for caregivers, relapses and adverse drug reactions. Utility estimates were derived by pooling data from the UK MS Trust postal survey, as cited in the company submission, and the Heron dataset.[105] The data were pooled using sample size weighted averages, and undertaken by IMS Health for the MS trust. They assumed the duration of the utility decrement from a relapse to be 46 days, and approximately 5% per annum would experience utility decrement from an adverse event. Healthcare resource use and cost estimates used in the model were derived from the DH/ScHARR estimates[257] and adjusted accordingly. The costs were assigned to EDSS health states, and for relapses. The cost of DMTs was based on the annual per-patient NHS acquisition cost.

Merck undertook a number of sensitivity analyses to investigate the impact of discounting, shorter time horizons, alternative approaches to deriving mortality rates and hazard ratios, alternative sources for utility and

costs, alternative assumptions regarding adverse events and discontinuation rates. In addition, they undertook probabilistic sensitivity analysis to determine the robustness of the base-case results.

In their base case analysis, they estimated that treatment of RRMS with IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) would result in an additional [redacted] QALYs gained at an additional cost of [redacted] over a 50-year time horizon. They estimated the ICER to be [redacted]/QALY gained. The ICER estimated from the PSA was [redacted]/QALY gained. In their sensitivity analysis, they found the base-case results were robust to univariate changes made to key input parameters. The majority of their sensitivity analyses resulted in the ICERs being lower. The ICERs were higher when they used different approaches to estimate EDSS health state costs.

14.3.3 Merck IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) SPMS model

Merck also undertook an economic analysis of providing IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) (Rebif) to patients with SPMS. The used the same model structure and modelling techniques as before, and populated the model with patient characteristics and treatment effects for treatment with IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) in SPMS patients. As highlighted before, the model does not include separate health states for SPMS and assumed all patients stop DMTs upon reaching EDSS 7. For the characteristics of the population modelled they used observed data from the SPECTRIMS study,[222] and assumed 64% female, mean age 43 years and patients had EDSS score 5 or 6 at baseline. Additional assumptions they made included the constant relapse rate independent of EDSS level.

In their base-case deterministic analysis, they estimated that treatment of SPMS with IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) would result in an additional [redacted] QALYs gained at an additional cost of [redacted] over a 50-year time horizon. They estimated the ICER to be [redacted]/QALY gained. The ICER estimated from the PSA was [redacted]/QALY gained. In their sensitivity analysis, they found the base-case results were robust to univariate changes made to key input parameters. The majority of their sensitivity analyses resulted in comparable ICER estimates (Appendix 17 of company submission).

14.3.4 Merck IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) CIS model

Merck also undertook an economic analysis of providing IFN beta-1a (Rebif) to patients with CIS. They estimated the ICERs for starting DMDs in CIS patients, to providing best supportive care for CIS patients with DMDs when patients progress to RRMS. The used the same model structure and modelling techniques as before, and populated the model with patient characteristics and treatment effects for treatment with IFN beta-1a (Rebif) in CIS patients. The characteristics of population modelled were based on participants of the REFLEX study.[173] The relative risks for conversion from CIS to RRMS for the first and second year on DMTs, and relative risk of relapse were extracted from the REFLEX study. In addition, they assumed there was no treatment effect of DMTs on risk of progression to RRMS after two years. For delayed therapy we considered that the rate of conversion and relapse were also based on the placebo arm of the REFLEX study, although this is not clear from thr submission. They also assumed that for CIS patients EDSS scores remained constant till conversion to RRMS, at which point the EDSS score was based on the EDSS score whilst in the CIS state.

In their base-case deterministic analysis, they estimated that early treatment of CIS with IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) would result in an additional [redacted] QALYs gained at an additional cost of [redacted] over a 50-year time horizon. They estimated the ICER to be [redacted]/QALY gained. The ICER estimated from the PSA was [redacted]/QALY gained. In their sensitivity analysis, they found the base-case results were robust to univariate changes made to key input parameters. The majority of their sensitivity analyses resulted in comparable ICER estimates (Appendix 17 of company submission).

14.3.5 Evaluation of Merck's IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) submission

Types of multiple sclerosis

Merck undertook economic analysis of IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) for treatment of RRMS, SPMS and CIS. The base case analysis examined costs and health outcomes for MS patients aged<30.

Model structure

The illustrative Markov model structure submitted by the company was based on the original School of Health and Related Research (ScHARR) model.[257] The company used a cohort-based Markov model to depict the natural history of people with RRMS. The model simulated the disability progression, progression from RRMS to SPMS, and the relapsing nature of the disease. People with RRMS/SPSS were able to occupy one of the EDSS health states, which ranged from 0 to 9, and in increments of 1.0. The model allowed for people to progress, regress or stay in the same EDSS health state, or progress from EDSS to SPMS. For those on DMDs no backward transition in EDSS score was permitted.

They used the same model structure for the economic analysis of DMTs for treatment of SPMS, and parameterised the model with patient characteristics and treatment effects for treatment with IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) in SPMS patients. The CIS model had an additional 5 on treatment and 5 off treatment health states defined by EDSS score (0-5, increments of one) for CIS. In addition, for the CIS model they assumed that EDSS scores remained constant till conversion to RRMS, at which point the EDSS score was based on the EDSS score whilst in the CIS state.

Interventions

The interventions considered in the economic analyses are presented in Table 57. For RRMS they compared IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) to best supportive care, for SPMS they compared IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) to best supportive care, and for CIS they compared IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) to best supportive care for CIS with DMTs started on progression to RRMS. For all those started on DMTs, treatment was discontinued once EDSS score ≥7 and 5% per annum discontinued treatment due to adverse reactions. For DMT treatment strategy, the model aggregated the observed RSS data across both doses of the drug.

Table 57: Interventions included in the economic analysis, Merck model

Brand	Drug	Dose	Route of Administration	Type of MS
Rebif	IFNβ-1a	44 µg or 22 µg	Subcutaneous	RRMS

	IFNβ-1a	44 µg or 22 µg	Subcutaneous	SPMS
	IFNβ-1a	44 µg or 22 µg	Subcutaneous	CIS
CIS, clinically isolated syndrome; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis				

Population

For their RRMS model, the population included in the economic analysis was similar to the population who started IFN beta-1a (Rebif) in the RSS cohort. In their base case RRMS analysis they examined the costs and health outcomes for MS patients aged<30. In addition, they examined costs and health outcomes for MS patients aged ≥30. For their SPMS model, the population included in the economic analysis was similar to the population included in the SPECTRIMS study,[222] and for CIS, the population included in the REFLEX study.[173] The initial distribution of people in each EDSS state is presented in Table 58. Of note, the distribution of initial EDSS scores for the RRMS population below were taken from the Excel file and are not the same as that presented in the company's final written summary.

Table 58: Baseline distribution of people in the base case analysis, Merck model

	Population	EDSS score						
		0	1	2	3	4	5	6
RRMS: 44µg < 30 years	[redacted] Female Mean age of onset: 30 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RRMS: 22µg < 30 years		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SPMS (all)	64.0% Female Mean age of onset: 43 years	0%	0%	0%	0%	0%	50%	50%
CIS	67.0% Female Mean age of onset: 31 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CIS, clinically isolated syndrome; EDSS, expanded disability scale score; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis								

Mortality rate

In their base-case analysis, the company modelled mortality in the same way as the ScHARR model by applying an SMR of 2.0 to life table mortality estimates, and an additional MS-specific mortality risk applied to those whose EDSS scores reaches 6. In their sensitivity analyses they used an alternative approach to modelling mortality. Briefly, this approach resulted in lower mortality rates assigned to early EDSS health states, and higher mortality rates from those with more advanced disability. Whilst this approach may be valid, the data used to derive these values is from about 20 years ago, when best supportive care is likely to have been less optimal than current provision, especially for those with more advanced disability.

Treatment effects of disease modifying treatments

Merck followed the same approach used in the DH RSS model analysis in modelling the impact of DMTs on disability progression. The British Columbia natural history model[151] was used to model disease progression in people with RRMS, allowing for improvements in disability (backward transition in EDSS scores).

For their RRMS model, the DMT strategy utilised the IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) specific hazard ratios supplied by the DH from the year 10 RSS data. These hazard ratios were applied to the natural history model to model the on treatment impact. Of note, they individually modelled the treatment impact for the two different dosages of the drug, and pooled the final costs and health outcomes to estimate the ICERs. They also assumed that there would be no improvement in disability (backward transition in EDSS score) for those on DMTs. In their models they assumed that IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) would be stopped when disability progressed to EDSS level ≥7. In addition, they assumed that 5% of patients stopped treatment for other reasons (i.e. drop out) every year. They also incorporated the 'waning effect' of DMTs on disability progression hazards. For relapse rates they used findings from the PRISMS study.

In the CIS model, progression to RRMS in the delayed treatment strategy (DMTs once progressed to RRMS), and the rate of conversion and relapse were based on the outcomes of placebo arm of the REFLEX study.[173] For the DMT CIS treatment strategy the relative risks for conversion from CIS to RRMS for the first and second year on DMTs, and relative risk of relapse were extracted from the REFLEX study. The company assumed that there was no treatment effect of DMTs on risk of progression to RRMS after two years. They also assumed that for CIS patients EDSS scores remained constant till conversion to RRMS, at which point the EDSS score was based on the EDSS score whilst in the CIS state.

Resource use and costs

All costs included in the analysis were those directly related to the NHS and PSS perspective, and were reported in 2015 UK pounds sterling, with future costs discounted at a rate of 3.5% per annum. The model included the following resource use and costs in order to conduct their analyses:

- Drug acquisition costs
- Health state/EDSS costs
- Cost of relapse
- Adverse event costs

Drug acquisition costs

In their model, the drug acquisition costs represents the annual per-patient NHS acquisition cost [redacted]. The drug acquisition costs for the two dosages of IFN β-1a SC three times weekly (Rebif), 44 µg and 22 µg, were [redacted] and [redacted] respectively. In their model they utilized the observed numbers on the two different dosages in the RSS cohort and assigned costs accordingly. Hence the true-modeled cost of the drugs will be an RSS sample weighted average. The costs of administering the drugs and monitoring response to treatment have not been included.

Health state/EDSS costs

Resource use/costs were assigned to each EDSS health state. In the base case analysis they utilised the same costs as previously used in the ScHARR analysis[257] with adjustment to 2015 UK pounds. This is the same approach used in the DoH RSS model analysis. In their sensitivity analysis they did estimate the ICER using

costs reported by Tyas et al (2007)[268] and Karampampa et al (2012),[264] again with adjustment to 2015 UK pounds.

Cost of relapse

In the base-case analysis the company utilised the same costs as previously used in the ScHARR analysis with adjustment to 2015 UK pounds. This is the same approach used in the DoH RSS model analysis.

Adverse event costs

In the base-case analysis the company did not include costs incurred as a result of adverse reactions, in accordance with the DoH RSS model analysis. They undertook sensitivity analysis and incorporated costs incurred as a result from adverse events. For this they used data on adverse events reported in the PRISMS study.[187]

Health state utility values

Health outcomes were measured in QALYs and future health outcomes were discounted at a rate of 3.5% per annum. Utility weights were assigned to the EDSS health states, including utility decrements for caregivers, relapses and adverse drug reactions. Utility estimates were derived by pooling data from the UK MS Trust postal survey and the Heron dataset. The data was pooled using sample size weighted averages, and undertaken by IMS Health for the MS trust. They assumed the duration of the utility decrement from a relapse to be 46 days, and approximately 5% per annum would experience utility decrement from an adverse event.

Table 59 shows the utility weights used in their base-case analysis. Of note, the pooled values do not take into account differences between the two samples in terms of age, sex and other variables that may be independently associated with HRQoL. The pooled utility values are the ones that were used in the DH RSS model analysis, including the impact on caregivers. They state that as the pooled values were not provided with standard errors for the PSA, they therefore used the standard errors reported in one of the two datasets that were pooled (Orme et al).[105] For this they extracted the standard errors from the multivariable regression analysis, and therefore represent the standard errors for the adjusted coefficients.

In their sensitivity analysis they estimated the ICERs utilising different utility weights. They estimated the ICER using utility values derived from an unpublished study by Boggild, and using utility values derived from pooling all three datasets (unpublished data from UK MS Trust postal survey; Heron dataset;[105] unpublished data from Boggild et al.). The utility values assigned to health states in their sensitivity analysis were lower (poorer HRQoL).

Table 59: Summary of utility values for the base case analysis, Merck model

State	Utility value: mean (standard error)	
	Patient health states	Caregiver decrements
EDSS 0	0.925 (0.045)	-0.002 (0.053)
EDSS 1	0.761 (0.048)	-0.002 (0.053)
EDSS 2	0.674 (0.048)	-0.045 (0.057)

EDSS 3	0.564 (0.052)	-0.045 (0.057)
EDSS 4	0.564 (0.048)	-0.142 (0.062)
EDSS 5	0.491 (0.047)	-0.16 (0.055)
EDSS 6	0.445 (0.047)	-0.173 (0.054)
EDSS 7	0.269 (0.049)	-0.03 (0.038)
EDSS 8	0.008 (0.050)	-0.095 (0.075)
EDSS 9	-0.23 (0.074)	0
Relapse	-0.22 (0.089) for 46 (10) days	
Adverse effect	-0.321 (0.051) in 5.1% (8.6%) patients	

14.3.6 Analysis (cycle length, time horizon and perspective)

The analysis was undertaken from the National Health Service (NHS) and Personal Social Services (PSS) perspective. The outcome measure used in the analysis was quality-adjusted life-years gained, over a 50-year time horizon with annual cycle lengths. Results were presented as an incremental cost-effectiveness ratio (ICER) and expressed as cost per quality-adjusted life-years (QALYs) gained. Both costs and benefits were discounted at 3.5% per annum

14.3.7 Assumptions

Merck made a range of assumption in the model analysis. For their RRMS model they assumed:

1. The Year 10 RSS dataset reflects the future MS population characteristics, initial EDSS level on starting DMTs, dosage of IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) and treatment impact on disability progression.
2. Age of MS diagnosis was assumed to be 30 years.
3. Natural history progression of MS, resource use, HRQoL, waning effect of DMTs, and mortality rates were the same as that used by the UK Department of Health in their RSS model analysis.
4. Uncertainty around the hazard ratios characterising treatment impact of DMTs was assumed to have as an upper limit 1.0 in the PSA.
5. DMTs were discontinued once EDSS level reached 7.
6. 5% of patients discontinue DMTs for other reasons (dropout).

The model included additional assumptions relating to SPMS.

1. Starting EDSS 5 and 6 (50% each)
2. Untreated relapse rate set at 1.08 per patient year.
3. Hazard ratios for progression and relative risks for relapse were used per the SPECTRIMS[222] relapsing population.

Finally, the model included several assumptions relating to CIS.

1. Patients' baseline EDSS is as in REFLEX.[173]
2. Conversion from CIS is as in REFLEX for delayed treatment, with relative risks for years one and two calculated from REFLEX.
3. No treatment effect is applied beyond year two, though patients are assumed to remain on treatment for up to 5 years with CIS.
4. Patients are assumed to remain in the starting EDSS during and upon conversion to McDonald MS.

14.3.8 Summary of results

In their base-case analysis, Merck estimated that treatment of RRMS with IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) would result in an additional [redacted] QALYs gained at an additional cost of [redacted] over a 50-year time horizon. They estimated the ICER to be [redacted] QALY gained. The ICER estimated from the PSA was [redacted]/QALY gained.

Table 60: Summary of economic evaluations undertaken by companies

Parameter	Company and drug		
	Biogen: IFN β-1a 30 µg IM once weekly (Avonex), pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy)	**Merck: IFN β-1a 44 or 22 µg SC three times weekly (Rebif)**	**Teva: Glatiramer acetate 20 mg SC daily or 40 mg three times weekly (Copaxone)**
Natural history cohort	Natural history cohort based on extrapolating the ADVANCE placebo arm data with British Columbia cohort	Natural history cohort based on British Colombia natural history model.	Natural history cohort based on London Ontario natural history cohort
Population	Adults (≥ 18 years) with RRMS	RRMS Adults: Mean age 30 years; [redacted] female. Based on RSS data SPMS Adults: Mean age 43 years; 64% female. Based on SPECTRIMS CIS Adults: Mean age 31 years; 67% female. Based on REFLEX	Adults (≥ 18 years) with RRMS
Intervention	**Avonex** IM IFN β-1a 30µg IM once weekly **Plegridy** Pegylated INFβ-1a 125µg SC every two weeks **Rebif** IFN β-1a 44µg SC three times weekly **Betaferon** SC INFβ-1b 250µg every other day **Extavia** SC INFβ-1b 250µg every other day **Copaxone** GA 20mg once daily **Copaxone**	**Rebif** SC INFβ-1a 44µg or 22µg three times weekly.	**Copaxone** GA 20mg once daily **Avonex** IM IFNβ-1a 30µg once weekly **Plegridy** SC pegINFβ-1a 250µg every two weeks **Rebif** SC INFβ-1a 22µg three times weekly **Rebif** SC INFβ-1a 44µg three times weekly **Betaferon** SC INFβ-1b 300µg every other day **Gilenya**

	GA 40mg once daily		500mg once daily **Tysabri** 300mg once every 4 weeks **Tecfidera** 240mg twice daily
Comparator	Best supportive care	CIS: Best supportive care for CIS and DMDs for RRMS RRMS: Best supportive care SPMS: Best supportive care	Best supportive care
Type of model and health states	Cohort based Markov model with 21 health states (10 for RRMS, 10 for SPMS and dead the dead state) characterised by EDSS levels, which ranged from 0-10 with increments of 0.5	CIS Cohort based Markov model with an additional 5 on treatment and 5 off treatment health states for CIS defined by EDSS score (0-5, increments of one) for CIS. Otherwise includes same health states as for RRMS model RRMS + SPMS Cohort based Markov model with 21 health states: 10 EDSS not on treatment states; 10 EDSS on treatment states; absorbing death state. EDSS health states 0-9, with increments of 1.0	Cohort based Markov model with 21 health states (10 for RRMS, 10 for SPMS and one for the dead state) characterised by EDSS levels, which ranged from 0-10 with increments of 1
Hazard ratio	Hazard ratios based on confirmed disability progression. The year 10 implied hazard ratio of [redacted] for IM IFNβ-1a 30µg was used in the company's model	CIS Conversion rate for CIS to RRMS based on REFLEX study RRMS Hazard ratios for sustained disability progression supplied to Merck by the DH based on	Hazard ratios for Copaxone of [redacted] for disability progression and [redacted] derived from 10 year RSS. Sensitivity analysis based on manuf NWMA assuming [redacted] HR for progression vs BSC.

		analysis of year 10 RSS data. **Progression** [redacted] **Relapse** HR (44µg): 0.67 HR (22µg): 0.71 SPSMS Relapse rate for SPMS not on treatment based on placebo arm of SPECTRIMS. HR for treatment derived from SPECTRIM, but utilised HR for 44 µg dosage as lack of confidence intervals for 22µg dosage. **Progression** HR (44µg): [redacted] **Relapse** HR (44µg): 0.62 HR (22µg): 0.53	
Resource use and costs	Drug acquisition costs, monitoring costs, administration costs, relapse costs (including a percentage requiring hospitalization as a proxy for severity), health state costs, treatment-related adverse event costs	RRMS Based on DH/ScHARR resource use and costs, adjusted to 2015. Costs include grug acquisition costs, monitoring costs, administration costs, relapse costs, health state costs, treatment-related adverse event costs SPMS and CIS Based on RRMS model approach	Drug acquisition costs, monitoring costs, administration costs, relapse costs (including a percentage requiring hospitalization as a proxy for severity), health state costs, treatment-related adverse event costs
Health-related quality of life	Utility values by EDSS level were based on information from the ADVANCE trial and	Utility values by EDSS score Utility values derived by pooling	Utility values by EDSS level were based on information from Orme et al., 2007, which was derived from utility values from

	Orme et al., 2007, which were derived from utility values from the UK MS survey Carers' disutilities were derived based on information obtained from the manufacturer's submission to NICE for TA127.	data from a UK MS Trust postal survey and the Heron dataset. Data pooled using sample size weighted averages, and undertaken by IMS Health for the MS trust.	the UK MS survey. A sensitivity analysis was performed using smoothed data from three RSS datasets. Carers' disutilities were derived based on information obtained from the manufacturer's submission to NICE for TA127.
Discontinuation of treatment	Only people who progressed to secondary progressive multiple sclerosis discontinued disease modifying treatment	Treatment is stopped when EDSS score reaches 7. In addition, 5% stop treatment irrespective of EDSS levels. Derived from observed drop-out rate from the 8-year RSS data.	Withdrawal rate of 5% per year as per RSS model. Treatment also discontinued for EDSS 7+
Relapse	Relative risk of a relapse per person in the RRMS health states has been estimated from the ADVANCE study for EDSS levels up to 5.5. ARR for EDSS > 5.5 were based on the relative increases in ARR as reported in the Patzold study (Patzold et al., 1982).	CIS RRMS SPMS	Relative risks of relapse were estimated from RSS data. A distinction was made between moderate and severe relapse. ARR was applied to the proportion of relapses that were severe. For Copaxone this was 0.796 (source, COMI 2000 European Canadian). For other DMTs this ranged from 0.495 (PegINFβ-1a) to 1.282 (Tecfidera).
Adverse events	Annualised risks for adverse events were considered for all treatments. AEs for people in the BSC arm were not considered. Annualised risks for each treatment were qualitatively analysed. Adverse events reported from the ADVANCE study which were >5% for any DMT or >3% for all treatments were included in the economic analysis	5.1% experience adverse events every year on DMDs. Adverse events associated with utility decrement of 0.02	The nature and rate of adverse events were derived from pooled clinical trial data. The assumed probability of an adverse event on Copaxone was 0.481 (1st and 2nd year). For other DMTs, the probabilities ranged from 0.32 (Tecfidera) to 0.752 (pegIFNβ-1a). The disutility of an AE was 0.004 QALYs for Copaxone, and ranged from 0.000 (Gilenya, Tecfidera) to 0.004 QALYs (Copaxone, pegIFNβ-1a)
Mortality	Mortality was assumed to be equivalent between RRMS and SPMS, and dependent on the EDSS level	Utilised DH/RSS approach for base-case analysis. This involved applying a SMR of 2.0 to life table estimates and a MS specific mortality rate for those with EDSS score 6 or higher.	An EDSS-dependent mortality multiplier was used to estimate mortality from UK general population rates (sourced from ONS data for 2012-2014). These multipliers were taken from the Teriflunomide manuf submission to NICE (which were adapted from Pokorski et al 1997)
Time horizon	50-year time horizon	50-year time horizon	50-year time horizon
Base-case	SC pegINFβ-1a 125µg compared to best	CIS	Copaxone incremental cost-effectiveness ratio (ICER) of

analysis results	supportive care had an ICER of approximately £31,000 per QALY	ICER: [redacted] gained RRMS ICER: [redacted] gained SPMS ICER: [redacted] gained	[redacted] per quality-adjusted life year (QALY) vs best supportive care [redacted] when excluding support for nursing/infrastructure costs) in the DoH agreed analysis. De novo model [redacted] per QALY for Copaxone vs best supportive care. Copaxone was [redacted]
Sensitivity analysis (and PSA) results	All base-case results except the hazard ratio for the confirmed disability progression were robust to sensitivity analysis. At a willingness-to-pay threshold for a QALY, SC pegINFβ-1a 125µg had a <0.4 probability of being cost-effective when compared to best supportive care	CIS ICER: [redacted] gained RRMS ICER: [redacted] gained SPMS ICER : [redacted] gained	[redacted] of cost-effectiveness at £20,000 vs best supportive care. The cost-effective results were most sensitive to the choice of data informing the hazard ratio for progression
ARR, annualised relapse rate; DoH, Department of Health; EDSS, expanded disability status scale; ICER, incremental cost-effectiveness ratio; MS, multiple sclerosis; NICE, National Institute for Health and Care Excellence; ONS, Office National Statistics; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-years; RRMS, relapsing-remitting multiple sclerosis; RSS, Risk Sharing Scheme; SC, subcutaneous; ScHARR, School of Health and Related Research; SPMS, secondary progressive multiple sclerosis			

14.4 *Summary and critique of the companies' submissions*

14.4.1 Overview of company submissions

This section provides an overview of the economic evidence submitted by the three companies: (1) Biogen Idec ltd; (2) Teva UK Limited; and (3) Merck Biopharma. We provide a summary of the company submissions and an assessment of how they compare to the NICE reference case, and of how they differ to each other and to the DH RSS model analysis.

Biogen Idec ltd undertook an economic analysis to assess the costs-effectiveness of their disease modifying treatments, IFN β-1a 30 µg IM once weekly (Avonex) and pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy), and other DMTs on the market, including IFN β-1a 44 or 22 µg SC three times weekly (Rebif), IFN β-1b 250 µg SC every other day (Betaferon/Extavia), and GA 20 mg SC daily or 40 mg SC three times weekly (Copaxone). Teva UK Ltd. undertook a comparable economic analysis of their DMT, GA 20 mg SC daily or 40 mg SC three times weekly (Copaxone), and others on the market, including IFN β-1a 30 µg IM once weekly (Avonex), pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy), IFN β-1a 44 or 22 µg SC three times weekly (Rebif), IFN β-1b 250 µg SC every other day (Betaferon/Extavia), fingolimod (Gilenya), natalizumab (Tysabri), and dimethyl fumarate (Tecfidera), whilst Merck Biopharma undertook an economic analysis of only their disease modifying treatment, IFN β-1a 44 or 22 µg SC three times weekly (Rebif).

In the primary analysis, all three companies undertook an economic analysis of DMTs compared with best supportive care for people with relapsing-remitting multiple sclerosis (RRMS). The three companies clearly state their decision problem, which is consistent with NICE's scope for the appraisal.

14.4.2 Type of multiple sclerosis

Biogen and Teva only undertook a cost-effectiveness analysis of DMTs for those with RRMS. Merck also evaluated the cost-effectiveness of their DMT in patients presenting with SPMS and with CIS.

14.4.3 Analysis (cycle length, time horizon, perspective)

All three companies followed the same approach with regards to the model analysis, perspectives, outcome measures and time horizon for analysis. They all undertook a cost utility analysis from the National Health Service (NHS) and Personal Social Services (PSS) perspective. The outcome measure used in the analysis was quality-adjusted life-years gained, over a 50-year time horizon with annual cycle lengths. Results were presented as an ICER and expressed as cost per QALYs gained. Both costs and benefits were discounted at 3.5% per annum.

The perspectives used in the three company submissions, in terms of costs and health outcomes, are in accordance to the NICE reference case. All three companies undertook cost-utility analysis and measured health outcomes in QALYs, and present the ICER estimates, as advocated in the NICE reference case. In their base-case analysis all three companies evaluated the decision over a 50-year time horizon, with the starting age for the population modelled aged >=30 years. The time horizon on the analysis should be sufficiently long to reflect differences in costs and outcomes.

14.4.4 Model structure

All three company submissions utilised a Markov cohort model, based on the original ScHARR model[257] to undertake their cost-effectiveness analysis. Broadly all the company submissions used EDSS scores to define RRMS and SPMS health states, with 10 mutually exclusive EDSS defined health states. In all the models, people with RRMS could progress, regress (improve) or stay in the same EDSS health state, or progress from RRMS to SPMS. People could not move from SPMS to RRMS, and once progressed to SPMS, individuals' EDSS scores could not improve.

There were some differences between the company submissions regarding when DMTs were stopped in the model analysis. In the Biogen company submission, DMTs were assumed to be stopped once patients progressed to SPMS. Teva discontinued DMTs once EDSS score ≥7, or when patients had progressed to SPMS. Merck discontinued DMTs once EDSS score ≥7, irrespective of whether patients had progressed to SPMS. In all three company submissions, DMTs were stopped if patients experienced adverse drug reactions. When DMTs are stopped is likely to impact on the modelled lifetime costs, and therefore the ICER estimate.

14.4.5 Interventions evaluated

All three company submissions compared the treatment of RRMS with DMTs to providing best supportive care. For SPMS Merck compared IFN β-1a 44 or 22 µg SC three times weekly (Rebif) to best supportive care, and for CIS they also compared IFN β-1a 44 or 22 µg SC three times weekly (Rebif) to best supportive care with DMTs started once progressed to RRMS.

14.4.6 Population modelled

There were differences between the three company submissions in how they determined the population to be modelled. Teva and Merck used the population characteristics (age; sex distribution; starting EDSS scores) observed in the RSS cohort data, whilst Biogen used the baseline characteristics observed in the ADVANCE trial.[211] Major differences include the mean age of onset of RRMS. In the Biogen model this was 36 years, whilst in the Teva and Merck models, this was 30 years. Also in the Biogen model approximately 32% of the cohort modelled started with a EDSS score <=1, whilst in the Teva and Merck models between 19% and 23% of the cohort modelled started with a EDSS score <=1. The age of the population is likely to impact on modelled lifetime costs and lifetime quality adjusted years. For example, modelling cost-effectiveness of DMTs in an older population will likely result in lower total lifetime costs and lower total lifetime quality adjusted years, but how this impacts on the ICER estimate may be complex. In addition, the initial distribution of EDSS scores in the population modelled will also have an impact on lifetime costs and quality-adjusted years, especially as higher EDSS health states are associated with higher costs and poorer utility weights than lower EDSS health states. Again how this impacts on the ICER is complex. The assessment group cosnider that the age, sex and EDSS scores amongst those in the RSS dataset better reflect the UK RRMS population than participants recruited into a clinical trial.

14.4.7 Transition probabilities: disease progression, relapse and mortality

The company submissions used different approaches to model disease progression for those on best supportive care (BSC). Biogen derived transition probabilities using disability progression observed amongst the placebo arm of the ADVANCE trial[211] supplemented with information from the British Columbia dataset.[151] Teva used the London Ontario data[84] to derive the majority of their transition probabilities to model progression, whilst Merck used the British Columbia dataset. The data sources used to model disease progression for the BSC strategy is likely to impact on the ICER. Whilst it may be difficult to argue which of the London Ontario or British Columbia data sets provide the optimal representation of disease progression in MS patients not receiving DMTs, it would seem unorthodox to use patients recruited into the placebo arm of a clinical trial to represent this.

For relapse rates (annualised relapse rate) there were some differences in the data used by each company. All three company submissions applied EDSS health state specific relapse rates. Biogen estimated relapse rates using data obtained from the ADVANCE trial up to EDSS 5.5, and supplemented with rates derived from the Patzold et al. (2008) and the ADVANCE trial. Teva and Merck both followed the DH RSS model approach, and used the same relapse rates as in the previous ScHARR model.[257] The relapse rates (for BSC) used by Biogen tended to be lower, translating into fewer episodes and lower modelled lifetime costs and lifetime quality-adjusted years for those on BSC. How this impacts on the ICER estimate will also depend on the relapse rates assigned for the DMT strategy.

All three company submissions followed comparable approaches to modelling mortality. As with the RSS model, background all-cause mortality was derived from age and gender-specific mortality rates. In addition, an MS-specific mortality rate was included through mortality multipliers assigned to each EDSS health state.

Transition probabilities: treatment effect

All three company submissions followed comparable approaches to modelling the treatment effect of DMTs, however, there were some differences in the data sources used. Treatment effects included the impact of DMTs on disease progression and on relapses. A hazard ratio was applied to the natural history progression matrices to determine disease progression for those on DMTs. Biogen and Teva state they undertook a network meta-analysis to estimate the hazard ratios for disability progression. Of note, implied hazard ratios for pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy) are not available from the year-10 RSS dataset. However Merck state that they used the implied hazard ratio for disability progression from the 10-year RSS data provided by DH. Of note, the implied hazard ratios from the RSS datasets tended to be higher than those obtained from the network meta-analysis. A higher hazard ratio for disability progression will result in higher ICER estimates.

For relapse rates on DMTs, Biogen and Teva undertook a network meta-analysis whilst Merck extracted the value from the previous ScHARR model. As previously mentioned the Biogen used a different data source for relapse rates for BSC than the other two companies, with the relapse rates they used for BSC being lower. The relapse rates on DMTs obtained from the network meta-analysis tended to be lower that that obtained from the 10-year RSS datasets. Untangling the impact on the final ICER is complex, especially in the case of Biogen's

company submission. However, a greater effect of DMTs on reducing relapse rates will lead to smaller ICER estimates.

There were minor differences in how treatment discontinuation was modelled in the three company submissions. Biogen reported that they used the discontinuation rates observed in clinical trials of the DMTs. Teva and Merck followed the DH RSS model and assumed 5% would discontinue treatment per annum. The discontinuation rates used by Biogen were generally higher than 5% per annum for the DMTs they evaluated. A higher discontinuation rate will lead to lower lifetime costs but also lower quality adjusted years on DMTs. This may potentially impact on the ICER estimate.

There were significant differences in how treatment waning effect was modelled in the three company submissions. Biogen assumed that there would be no treatment waning effect in their base case analysis, and assumed that the efficacy of DMTs would be maintained. Teva and Merck followed the approach taken in the RSS model and assumed that after 10 years on DMTs, efficacy would be lower. Not including a waning effect will not impact on lifetime costs on DMTs but will increase quality-adjusted years on DMTs, and likely result in lower ICER estimates.

Although the NICE reference case highlights that systematic reviews should be undertaken to obtain evidence on outcomes, the RSS cohort long-term outcome data may be a more valid data source.

14.4.8 Resource use and costs

In all three company submissions, costs included in the analysis were those directly related to the NHS and PSS perspectives, with costs inflated to 2015 UK Sterling. There were some differences in the costs included by the three company submissions. All three companies included:

- Drug acquisition costs
- Administration costs
- Monitoring costs
- Health state/EDSS costs
- Cost of relapse
- Treatment-related adverse event costs

There were some differences in how the cost of providing DMTs (acquisition, administration and monitoring) was estimated and/or described. Biogen and Teva provide a detailed breakdown of the costs included, broken down by the cost for drug acquisition, administration and monitoring. Merck provided a single total cost for treatment with DMTs. It is unclear whether this estimate includes the cost of administering and/or monitoring treatment on DMTs. Additionally, the estimate used in the model analysis was classified as commercial in confidence material, and may not represent the list price for the drug. The total cost involved in providing DMTs to patients will be an important driver of cost-effectiveness. It does not seem that any of the three companies included the infrastructure costs (e.g nursing infrastructure) in the drug treatment costs.

Teva and Merck used previously reported resource use data in the ScHARR model to determine the costs to assign to EDSS defined health states. The costs assigned by Teva and Merck, adjusted to 2015 UK Sterling,

were approximately the same. Biogen reported that they used cost data reported in the UK MS Survey, and assigned different costs depending on both EDSS state and whether patients had RRMS or SPMS. The costs assigned to the EDSS states in Biogen's company submission tended to be lower than that used by Teva and Merck. This is likely to result in lower lifetime costs, but will affect both DMT and BSC strategies.

For the cost of relapse, the three companies followed the same approach. A proportion of those experiencing relapses would experience mild relapses (not requiring hospitalisation) whilst others would experience severe relapses (requiring hospitalisation). The costs of each type of relapse differed, so an average cost of relapse is estimated (based on proportions). The sources of the data differed, with Biogen using data from a recent study[111] whilst Teva and Merck inflated costs reported in the ScHARR model. The cost estimates used in Biogen's model were lower than those used in the Teva and Merck models.

Merck did not include the cost of treatment-related adverse events in the primary analysis, but included them their sensitivity analysis. Biogen and Teva included the costs of adverse events. Biogen undertook their own study with specialists (a Delphi panel) to estimate resource use for adverse events and consequently the unit costs. Teva derived the unit costs for adverse events using a combination of information from the PSSRU, national reference costs and the manufacturer submission for TA312.[269]

14.4.9 Health state utility values

There were some differences in the company submissions in the source of health state utility weights, and how they were assigned to the health states. In the company submissions by Teva and Merck, health state utilities for EDSS health states were derived by pooling data from the MS Trust and the Heron datasets (Orme et al., 2007). [105] Both assumed that the current EDSS score determined the utility scores for both the RRMS and SPMS health states. This was the approach used in the RSS model. Biogen derived utility weights differently in their model analysis. They used a combination of utility data from the ADVANCE study[211] and the UK MS survey, and their approach to pooling the data was driven by the data availability and not by standard methodological approaches to pooling data. In addition, Biogen assigned different utility weights for the EDSS health states by whether or not a patient had RRMS or SPMS. As the EDSS provides an assessment of disability, it may not be appropriate to apply a lower utility weight for the same EDSS score if patients had SPMS.

All three company submissions used different approaches to quantify the disutility from relapses. Teva and Merck assigned a disutility weight for a relapse and assumed the disutility from a relapse would last for duration between 46 to 90 days, with Teva further stratifying relapse disutility by the severity of the relapse (mild v severe). Although it is not clear, it seems that Biogen assumed the disutility from a relapse would persist and assigned an additional disutility to all EDSS health states (by subtracting the EDSS assigned utility by the relapse disutility) for those who had a relapse.

The above two issues highlight major differences in the utility weights assigned to the EDSS health states by Biogen, as compared to those assigned by Teva and Merck. The way in which this impacts on the ICER estimate is multifactorial and complex. There is a potential that this may lead to more favourable ICERs (greater QALY gain from DMTs) as one of the benefits of DMTs is to reduce relapses, and delay progression to SPMS.

There were also some minor differences in the data sources for quantifying carer's disutility in the company submissions. Teva and Merck followed the approach used in the RSS model by using data reported by Acaster et al. (2013),[261] but Biogen used data from the Orme study.[105] Overall this translated to Biogen assigning predominantly lower disutility weights for lower EDSS health states, and higher disutility weights for the two highest EDSS health states.

There were some minor differences in how disutilitiesfrom adverse drug reactions were modelled. All three companies assigned an average disutility, as was done in the RSS model. The average disutility was based on the proportion experiencing adverse events and the disutility weight attached to adverse drug reactions. Overall the values were not too dissimilar and are unlikely to impact on ICER estimates.

14.4.10 Summary

The assessment group reviewed the three company submissions from Biogen, Teva and Merck. Overall the methodological approaches used by the three companies are in accordance with the NICE reference case (see Table 61). There were however significant differences in the modelling approach and data sources used by each of the three companies, and this is likely to explain differences in the estimated ICERs. Importantly, there were significant differences between the approaches used by the companies to the approach used in the DH RSS model analysis. Biogen's submission differed most from the DH RSS model analysis, whilst Merck's company submission differed least.

Table 61: Company analyses against the NICE reference case

Element of health technology assessment	Biogen Idec	Teva UK Ltd	Merck Biopharma	Reference case
Defining the decision problem	✓	✓	✓	The scope developed by NICE
Comparator(s)	✓	✓	✓	As listed in the scope developed by NICE
Perspective on outcomes	✓	✓	✓	All direct health effects, whether for patients or, when relevant, carers
Perspective on costs	✓	✓	✓	NHS and PSS
Type of economic evaluation	✓	✓	✓	Cost–utility analysis with fully incremental analysis
Time horizon	✓	✓	✓	Long enough to reflect all important differences in costs or outcomes between the technologies being compared
Synthesis of evidence on health effects	✓	✓	✓	Based on a systematic review
Measuring and valuing health effects	✓	✓	✓	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults

Source of data for measurement of health-related quality of life	✓	✓	✓	Reported directly by patients and/or carers
Source of preference data for valuation of changes in health-related quality of life	✓	✓	✓	Representative sample of the UK population
Equity considerations	✓	✓	✓	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit
Evidence on resource use and costs	✓	✓	✓	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS
Discounting	✓	✓	✓	The same annual rate for both costs and health effects (currently 3.5%)

14.5 ***Impact on the results based on the assumptions made by companies***

In order to understand the consequences of company assumptions, we have calculated results using company submitted treatment effects and list prices, but otherwise using RSS assumptions.

In these analyses, we retained the majority of the assumptions made in the RSS model but have made the following changes:

1. We excluded carers' disutilities,
2. We used the hazard ratios on the disability progression submitted by each company, and
3. We used the list price of disease modifying treatments.

Using the RSS base run and the time-varying models, we estimated the cost-effectiveness of DMTs (IFN β-1a 30 µg IM weekly (Avonex), IFN β-1a 44 µg SC three times weekly (Rebif), and glatiramer acetate 20 mg (Copaxone)) included in the RSS and with company submissions compared to best supportive care for people with RRMS. We present results in terms of total mean costs and total mean QALYs, and incremental cost-effectiveness ratio based on the cost per QALY gained. We report results based on a pairwise comparison (each DMT compared with best supportive care) and based on an incremental analysis. In the incremental analysis the strategies are ranked in ascending order on mean costs. We eliminated strategies where one strategy was cheaper and more effective (dominance). If there was a linear combination of two other strategies that were more costly and less effective (extended dominance), these were eliminated. For the remaining strategies we derived an incremental cost per QALY gained.

1.1.1.3 Results in terms of QALYs gained

At a 50-year time horizon, the results from the base run model showed that the best supportive care arm had expected mean costs of approximately £344,900 with a corresponding 8.451 QALYs. IFN β-1a 30 µg IM once weekly (Avonex) had mean costs of approximately [redacted] and corresponding [redacted] mean QALYs. Mean costs for IFN β-1a 44 µg SC three times weekly (Rebif) and glatiramer acetate 20 mg (Copaxone) were

approximately [redacted], with corresponding mean QALYs of [redacted], respectively. Results from the incremental analysis (see Table 62) showed that [redacted]. Excluding strategies that were dominated resulted in the comparison between best supportive care and [redacted]. Our pairwise analysis (see Table 63) showed that ICERs for each drug compared to best supportive care were different between the company submission and our estimates from the RSS model.

Table 62: Results based on the RSS model with individual company submission hazard ratios (incremental analysis)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	344,900	-	8.451	-	-
Glatiramer acetate 20 mg SC daily (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 30 µg IM weekly (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 44 µg SC three times weekly (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 63: Comparison between incremental costs and QALYs submitted by each company and those derived using the RSS model (pairwise analysis)

Disease modifying treatment, company	Company's incremental costs	Incremental costs based on RSS model	Company's incremental QALYs	Incremental QALYs based on RSS model	Company's ICERs (£)	ICER (£) based on RSS model
IFN β-1a 30 µg SC once weekly (Avonex) (Biogen)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 44 µg SC three times weekly (Rebif) (Merck)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg SC once daily (Copaxone) (Teva UK limited)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14.5.1 Discussion and conclusion

In this analysis, we compared DMTs with best supportive care, and report the incremental costs and QALYs for each company and those derived from using the RSS model. Of note we had concerns about the total quality adjusted life years estimated in the companies' submissions. The RSS model and our own cost-effectiveness model analysis estimated that for best supportive care in the base case analysis the mean quality adjusted life years to be approximately 8.5 QALYs, whilst Teva's model estimated it to be approximately [redacted] QALYs and Merck to be approximately [redacted] QALYs. When we adapted the RSS model to use disability progression from Teva and Merck, the mean quality adjusted life years approximated to 8.5 QALYs. We looked at a range of parameters that may affect this estimation: natural history cohort, utility values, mortality rates and starting EDSS distributions. Teva used the London Ontario dataset in order to model disease progression and this may explain why their estimate might have been different. We could not explain this difference between the findings from the RSS model and Merck's submission. All other aforementioned parameters were comparable between the models.

15 HEALTH ECONOMIC ASSESSMENT (RRMS)

15.1 *Objectives and methods*

15.1.1 Objectives

In Chapter 13, the assessment group outlined some limitations of the RSS model. We undertook several sensitivity analyses to address these concerns and to use alternative information sources and assumptions. We present these additional analyses undertaken by the assessment group below.

To assess the impact of disease modifying treatments used to treat people who were diagnosed with relapsing remitting multiple sclerosis, we developed a decision-analytical modelling framework which uses longitudinal data from natural history cohorts to provide information on the progression of RRMS. The objective of the model is to estimate the cost-effectiveness of disease modifying treatments within their marketing authorisation for treating people diagnosed with RRMS. In the model, health outcomes were measured in quality adjusted life years (QALYs), and we present results in terms of incremental cost per QALY gained. In the UK, an incremental cost-effectiveness ratio (ICER) below £20,000- £30,000 per QALY is considered cost-effective by decision-makers[273].

15.1.2 Methods: Developing the model structure

To estimate the cost-effectiveness of disease modifying treatments for treating people with RRMS, we used, rebuilt and developed the model structure for the RSS scheme submitted by the Department of Health. Details of the RSS model are outlined elsewhere in this report (see Chapter 13). Briefly, the RSS model is a cohort based Markov model. The model cycled yearly, with a starting age of 30 years and estimated the mean costs and effects associated with treatment compared with no treatment (best supportive care) over a 50-year time horizon. The analysis was conducted from the NHS and Personal Social Services (PSS) perspective and the results reported in terms of an incremental cost-effectiveness ratio, expressed as cost per QALYs gained. Both costs and benefits were discounted at 3.5% per annum. Health states for people with RRMS or secondary progressive multiple sclerosis (SPMS) were characterised by EDSS levels ranging from 0-10. In the model, transition matrices are applied to show how people move through the model. People are able to progress to more severe EDSS levels, regress to less severe EDSS levels, or there is a probability of dying from MS-related or other causes.

15.1.3 Methods: Model assumptions and characteristics changed from the RSS model in our analyses

The assessment group has assessed the impact of the following changes to the RSS model, which we discuss further below:

1. Use of discontinuation rates obtained from our clinical effectiveness review
2. Use of alternative estimates of treatment effectiveness (annualised relapse rates and hazard ratios for disability progression) derived from our clinical effectiveness review
3. Changes to mortality assumptions

4. Use of list prices for disease modifying treatments
5. Exclusion of carers' disutilities
6. Impact of varying key model input parameters
7. Implementation of probabilistic sensitivity analysis

15.1.4 Methods: Changes made to the RSS model

Discontinuation rates

In the treatment arm of the economic model it was assumed that every year 5% of people discontinued treatment as a result of adverse events. However, it was unclear whether this assumption was based on empirical evidence. We undertook further analyses to derive a combined discontinuation rate based on all the drugs used in the RSS and a discontinuation rate based on each individual drug used in the RSS model. These proportions were derived from the RRMS studies included in our clinical review. Studies reported the instantaneous rate of people who discontinued treatment as a result of disease modifying treatments. We converted this rate to an annual probability using the equation (probability = 1 – exp (-rt)), where r is rate and t is time.

Table 64: Annual proportion of people discontinuing treatment following adverse events

Parameter	Reported in RSS model	Derived from assessment group clinical review	Reported by each company	Derived from assessment group clinical review
IFN β-1a 30 µg IM once a week (Avonex)	0.0500	0.0229	0.0790	0.0150
IFNβ-1a pegylated 125 µg SC every 2 weeks (Plegridy)			0.1040	0.0150[a]
IFN β-1a 44/22 µg SC three times per week (Rebif)			0.0500	0.0263
IFN β-1b 250 µg SC every other day (Betaferon)			Not submitted	0.0219
Glatiramer acetate 20 mg SC daily or 40 mg SC three times a week (Copaxone)			0.0500	0.0263

DMT; disease modifying treatment; IFN, interferon
[a]We assumed that the discontinuation was the same as IFN β-1a 30 µg once a week (Avonex)

Table 64 shows the annual discontinuation rates for each disease modifying treatment, as well as the annual discontinuation rate for all disease modifying treatment combined. Our combined annual probability of 2.29% is lower than the discontinuation rate assumed in the RSS model. Using this value in the model would lead to more people remaining on treatment. Discontinuation rates reported by each company, tended to be lower than those derived from our clinical review.

Treatment effectiveness: annualised relapse rates

In the RSS model the annualised relapse rate for those treated with disease modifying agents as compared to those not treated was 0.72. We undertook further analyses to derive the annualised relapse rate based on the studies identified in our clinical effectiveness review to see how this compares with the value reported in the

RSS model, and with those reported in the companies' submissions. From our meta-analysis we derived a combined annualised relapse rate of 0.6494 (95% CI [0.5572, 0.7567]). Our annualised relapse rate is lower than the annualised relapse rate presented in the RSS model. The combined treatment effect from our network meta-analysis of the published studies suggests that there is a discrepancy in the assessment of the effectiveness of disease modifying therapies depending on the data source used. RCT evidence appears to show that disease-modifying therapies are more effective than is suggested by the RSS (see Table 65). In addition, we compared the annualised relapse rates for each individual disease modifying treatment derived from our network meta-analysis with the annualised relapse rates reported by each company. These two annualised rates appear to be very similar.

Table 65: Annualised relapse rates by DMT

Parameter	Reported by RSS (95% CI)	Derived from assessment group clinical review (95% CI)	Reported by each company (95% CI)	Derived from assessment group clinical review (95% CI)
IFN β-1a 30 µg IM once a week (Avonex)	0.72 (not reported)	0.6494 (0.5572, 0.7567)	[redacted]	0.80 (0.72, 0.88)
IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy)			0.6420 (0.4070, 1.0380)	0.64 (0.50, 0.83)
IFN β-1a 44 µg three times per week (Rebif)			0.670 (0.57, 0.79)	0.68 (0.61, 0.76)
IFN β-1b 250 µg every other day (Betaferon)			Not submitted	0.69 (0.62, 0.76)
Glatiramer acetate 40 mg three times a week with at least 48 hours apart (Copaxone)			[redacted]	0.66 (0.54, 0.80)
Glatiramer acetate 20 mg SC daily (Copaxone)			[redacted]	0.66 (0.59, 0.72)

DMT; disease modifying treatment; IFN, interferon

Treatment effectiveness: time to disability progression

We used both pooled and DMT-specific estimates of disability progression relative to best supportive care from our network meta-analyses and compared them to other relevant inputs.

First, we estimated a combined treatment effect of disease modifying treatments by pooling relevant active vs. placebo trials for on-scheme DMTs. Results showed a reduced hazard of sustained confirmed disability progression for people treated with disease modifying treatment compared to best supportive care. The HR was 0.6955 (95% CI [0.5530, 0.8747]). In contrast, the RSS model reported a reduced risk of sustained disease progression of HR 0.7913 (0.7705, 0.8122).

Second, we compared the estimates on disease progression reported by each company with the estimates derived from our analysis. Again, our results demonstrate a discrepancy between the effect sizes generated by the different sources of data (the RSS, the pooled RCT evidence, the effects reported by the companies and the DMT-specific effects estimated in our network meta-analyses). Table 66 shows the treatment effects on

disability progression, with assessment group values for disability progression confirmed at 3 months. We additionally considered disability progression confirmed at 6 months (see Table 67).

Table 66: Treatment effects on disability progression

Parameter	Reported by RSS model	Derived from assessment group clinical review	Reported by each company	Derived from assessment group clinical review
IFN β-1a 30 µg IM once a week (Avonex)	0.7913 (0.7705, 0.8122)	0.6955 (0.5530, 0.8747)	[redacted]	0.7300 (0.5300, 1.0000)
IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy)			0.620 (0.2090, 1.8150)	0.6200 (0.4000, 0.9700)
IFN β-1a 44 µg three times per week (Rebif)			[redacted]	0.6300 (0.4600, 0.8600)
IFN β-1b 250 µg every other day (Betaferon)			Not submitted	0.7800 (0.5900, 1.0200)
Glatiramer acetate 40 mg SC three times a week (Copaxone)			[redacted]	Not derived
Glatiramer acetate 20 mg SC daily (Copaxone)				0.7600 (0.6000, 0.9700)

DMT; disease modifying treatment; IFN, interferon

Table 67: Time to disability progression confirmed at 6 months

Parameter	Derived from assessment group clinical review
IFN β-1a 30 µg IM once a week (Avonex)	0.68 (0.49, 0.94)
IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy)	0.46 (0.26, 0.81)
IFN β-1a 44 µg three times per week (Rebif)	0.47 (0.24, 0.93)
IFN β-1b 250 µg every other day (Betaferon)	0.34 (0.18, 0.63)
Glatiramer acetate 40 mg SC three times a week (Copaxone)	Not reported
Glatiramer acetate 20 mg SC daily (Copaxone)	0.82 (0.53, 1.26)

DMT; disease modifying treatment; IFN, interferon

Mortality

The assessment group previously highlighted concerns regarding overestimation of MS-related mortality. In the RSS model we noted that individuals were subject to MS-related mortality (modelled as twice the standardised mortlity rate from other causes), in addition to mortality from transition to EDSS 10 (MS-related death). We highlighted that this would theorectically lead to double-counting of MS-related deaths in the model, and that results would therefore show a reduction in life years and QALYs gained. Hence, we changed the risk of MS-related death to the same as that for the general population, since the risk of MS-related death is already captured in the transition matrices. An alternative approach that we did not explore in these analyses would have been to to consider using mortality multipliers for lower EDSS levels to capture the increased risk of mortality for those with MS compared to the general popualtion.

Resource use and costs

The costs of disease modifying treatments were obtained from the British National Formulary 2016.[24] The annual cost of £8502 for treatment with IFN β-1a (Avonex) was derived based on the recommended dosage of 30 µg once a week. The annual cost of £10,572 for treatment with IFN β-1a (Rebif) was derived based on a dosage of 44 µg three times per week. We derived annual costs of £7264 and £6681 (£6724) for treatment with IFN β-1b 250 µg every other day (Betaferon) and glatiramer acetate (Copaxone) 40 mg SC three times weekly or 20 mg SC daily, respectively. Table 68 presents the costs for each disease modifying treatment. Of note, we have not specifically taken into account that those on IFN β-1a (Rebif) 44µg three times per week may subsequently have their dosage reduced to 22µg three times per week.

Table 68: Costs of disease modifying treatments

Disease modifying treatment	Cost (£, 2015)	Reference
IFNβ-1a (30 µg once a week)	8502	British National Formulary 2015[24]
IFNβ-1a pegylated (125 mcg every 2 weeks)	8502	
IFNβ-1a (44 µg three times per week)	10,572	
IFNβ-1b (250 µg every other day)	7264	
Glatiramer acetate (20 mg three times a week with at least 48 hours apart	6704	
Glatiramer acetate (40 mg three times a week with at least 48 hours apart	6681	

Utility values, including carers' disutilities

The assessment group considered the utility values used in the RSS analyses to be appropriate. However, we identified through literature searching other sources of utility estimates. In sensitivity analyses, we explored the impact of using these other sources of utility values.

Disutilities associated with caring for people with multiple sclerosis were included in the RSS analyses. However, it appears that carers included in the analysis represent informal/unpaid carers. The NICE reference case suggests that the perspective should be all direct health effects, whether for patients or other people. Hence, the assessment group has excluded carers' disutilities from the main analysis. We present analyses with the carer disutilities in Appendix 9.

15.1.5 Methods: Base case cost effectiveness analysis

The Markov model was developed and programmed to choose the base case model inputs in order to assess the cost-effectiveness of disease modifying treatments for the management of people with RRMS. The model estimated the mean costs and health benefits associated with each DMT, and assumed that the starting age of the population was 30 years old. **We consider the RSS model base case with changes made to avoid double counting of mortality and removal of carer disutilities to be our base case.** The analysis was undertaken from an NHS and PSS perspective in a specialist MS care setting and outcomes were reported as ICERs, expressed in terms of cost per QALY gained. All costs and outcomes were discounted at 3.5% per annum.

15.1.6 Methods: Sensitivity analysis

Multiway sensitivity analyses were undertaken, and these are summarised below:

1. **SA 1 Pooled on-scheme DMTs from assessment group review.** In this analysis, we used inputs from our review of the evidence pooled across all on-scheme DMTs. We used the aggregated hazard ratio for disability progression confirmed at 3 months, the aggregated annualised relapse rate, and the aggregated discontinuation rate.
2. **SA 2 Individual drugs from AG review**
    a. **Individual drugs from AG review, progression confirmed at 3 months.** Using the hazard ratio for disability progression confirmed at 3 months derived from our clinical effectiveness review, with the rate ratio for annualised relapse rate derived from our clinical effectiveness review, as well as relevant discontinuation rates and list prices
    b. **Individual drugs from AG review, progression confirmed at 6 months.** Using the hazard ratio for disability progression confirmed at 6 months derived from our clinical effectiveness review, with the rate ratio on annualised relapse rate derived from our clinical effectiveness review, as well as relevant discontinuation rates and list prices
3. **SA 3 Hazard ratios from company submissions.** Using the hazard ratios (confirmed disease progression) reported by each company with the annualised relapse rates reported by each company, as well as relevant discontinuation rates and list prices
4. **SA 4 Time horizon changed.** Individual drugs from AG review, progression confirmed at 3 months and relapse rate from clinical effectiveness review, relevant discontinuation rates and list prices, with time horizon changed from 50 years to 20 years or 30 years.
5. **SA 5 Parameter uncertainty analysis for the base case and SA 1.** We varied the hazard ratio for disability progression, the rate ratio for annualised relapse rates, cost of disease modifying treatments, and the annual discontinuation rate by ±10% for the base case and SA 1.

15.1.7 Methods: Probabilistic sensitivity analysis

We undertook probabilistic sensitivity analyses on the base case and SA 1 models to determine the uncertainty of the key model input parameters.

In the probabilistic sensitivity analysis, we varied the following parameters: hazard ratio for disability progression, rate ratio for annualised relapse rate, utility values for each EDSS state, disutility associated with relapses, management costs by EDSS state and costs of relapses, and assigned a distribution, which reflected the amount and pattern of its variation.

Standard errors for the annualised relapse rate reported in the RSS model were not available. Thus, we used standard errors derived from the pooled analysis of on-scheme DMTs to represent this uncertainty.

Cost-effectiveness results were calculated by simultaneously selecting random values from each distribution. The process was repeated 1000 times in a Monte Carlo simulation of the model to give an indication of how

variation in the model parameters lead to variation in the ICERs for a given treatment combination (e.g. disease modifying treatment compared with best supportive care).

In Table 69 we present the point estimates and the appropriate distribution for the input parameters. This type of analysis allows all parameter uncertainties to be incorporated into the analysis. Sampling parameter values from probability distributions, rather than from a simple range defined by the upper and lower bounds, places greater weight on the likely combinations of parameter values, and simulation results quantify the impact of uncertainties on the model in terms of the confidence that can be placed in the analysis results.

In Table 70, we summarise sensitivity analyses 1 through 4 with respect to key model parameters.

Table 69: Input parameters for RRMS economic assessment

Variable	Base-case value	95% confidence intervals	Distribution	Reference(s)
Baseline distribution of people in RSS				
EDSS 0	135	-	Fixed	Base case values obtained from the RSS model
EDSS 1	689	-	Fixed	
EDSS 2	1088	-	Fixed	
EDSS 3	970	-	Fixed	
EDSS 4	652	-	Fixed	
EDSS 5	441	-	Fixed	
EDSS 6	242	-	Fixed	
EDSS 7	0	-	Fixed	
EDSS 8	0	-	Fixed	
EDSS 9	0	-	Fixed	
EDSS 10	0	-	Fixed	
RRMS: relapse frequency (% of RRMS patients)				
EDSS 0	0.8895 (1.000)	-	Fixed	Base case values obtained from the RSS model
EDSS 1	0.7885 (0.861)	-	Fixed	
EDSS 2	0.6478 (0.861)	-	Fixed	
EDSS 3	0.6155 (0.806)	-	Fixed	
EDSS 4	0.5532 (0.545)	-	Fixed	
EDSS 5	0.5249 (0.343)	-	Fixed	
EDSS 6	0.5146 (0.270)	-	Fixed	
EDSS 7	0.4482 (0.053)	-	Fixed	
EDSS 8	0.3665 (0.000)	-	Fixed	
EDSS 9	0.2964 (0.000)	-	Fixed	
EDSS 10	0.0000 (0.000)	-	Fixed	
SPMS: relapse frequency (% of SPMS patients)				
EDSS 0	0.0000 (0.000)	-	Fixed	Base case values obtained from the RSS model
EDSS 1	0.0000	-	Fixed	

Variable	Base-case value	95% confidence intervals	Distribution	Reference(s)
	(0.139)			
EDSS 2	0.6049 (0.139)	-	Fixed	
EDSS 3	0.5154 (0.194)	-	Fixed	
EDSS 4	0.4867 (0.455)	-	Fixed	
EDSS 5	0.4226 (0.657)	-	Fixed	
EDSS 6	0.3595 (0.730)	-	Fixed	
EDSS 7	0.3025 (0.947)	-	Fixed	
EDSS 8	0.2510 (1.000)	-	Fixed	
EDSS 9	0.2172 (1.000)	-	Fixed	
EDSS 10	0.0000 (1.000)	-	Fixed	
Hazard ratio				
Disability progression in RSS model	0.7913	0.7705, 0.8122	Lognormal	Derived from assessment group analysis
Disability progression in assessment group model	0.6955	0.5530, 0.8747	Lognormal	
Rate ratio				
Annualised relapse rate in the RSS model	0.7200	0.5262, 0.7623	Lognormal	Base case valued obtained from RSS model, and confidence intervals derived from assessment group analysis
Annualised relapse rate in assessment group model	0.6494	0.5572, 0.7567	Lognormal	Derived from assessment group analysis
Management costs by EDSS				
EDSS 0	£1164	Assumed to lognormally distributed with standard error of 10% of the mean value	Lognormal	Base case values obtained from the RSS model
EDSS 1	£1164		Lognormal	
EDSS 2	£1164		Lognormal	
EDSS 3	£2147		Lognormal	
EDSS 4	£2225		Lognormal	
EDSS 5	£7840		Lognormal	
EDSS 6	£8746		Lognormal	
EDSS 7	£26,688		Lognormal	
EDSS 8	£41,439		Lognormal	
EDSS 9	£52,679		Lognormal	
EDSS 10	0		Fixed	
Management of relapse				
Cost of relapse	£4263	Assumed to lognormally distributed with standard error of 10% of the mean value	Lognormal	Base case values obtained from the RSS model

Variable	Base-case value	95% confidence intervals	Distribution	Reference(s)
Utility values				
EDSS 0	0.9248	-	Beta (5.30, 1.33)	Base case values obtained from the RSS model, and ScHARR model
EDSS 1	0.7614	-	Beta (5.30, 1.33)	
EDSS 2	0.6741	-	Beta (5.30, 1.33)	
EDSS 3	0.5643	-	Beta (10.99, 3.21)	
EDSS 4	0.5643	-	Beta (64.35, 19.31)	
EDSS 5	0.4906	-	Beta (33.54, 10.35)	
EDSS 6	0.4453	-	Beta (6.43, 2.37)	
EDSS 7	0.2686	-	Beta (2.24, 2.28)	
EDSS 8	0.0076	-	Beta (1.27, 5.55)	
EDSS 9	-0.2304	-	Beta (0.38, 2.18)	
Dead	0	-	Fixed	By definition
Other				
Mortality (age-specific death rates)	Life tables	-	Fixed	ONS 2014, as cited in the Biogen submission
Discount rate per annum (costs and QALYs)	3.5%	-	Fixed	

EDSS, expanded disability status scale; ONS, office of National Statistics; QALYs, quality adjusted life years gained; RRMS, relapsing remitting multiple sclerosis; RSS, risk sharing scheme; SPMS, secondary progressive multiple sclerosis

Table 70: Summary of parameters across sensitivity analyses

Parameter	Base case analysis	SA1: Pooled on-scheme DMTs from assessment group review	SA 2a: Individual drugs from AG review, progression confirmed at 3 months	SA2b: Individual drugs from AG review, progression confirmed at 6 months	SA 3: Hazard ratios from company submissions	SA 4: Time horizon changed
Cost of disease modifying treatment	£7300	£7300	IFN β-1a 30 µg IM once a week (Avonex): £8502 IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): £8502 IFN β-1a 44 µg SC three times per week (Rebif): £10,572 IFN β-1b 250 µg every other day (Betaferon/Extavia): £7264 Glatiramer acetate 20 mg SC daily (Copaxone): £6704	IFN β-1a 30 µg IM once a week (Avonex): £8502 IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): £8502 IFN β-1a 44 µg SC three times per week (Rebif): £10,572 IFN β-1b 250 µg every other day (Betaferon/Extavia): £7264 Glatiramer acetate 20 mg SC daily (Copaxone): £6704	IFN β-1a 30 µg IM once a week (Avonex): £8502 IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): £8502 IFN β-1a 44 µg SC three times per week (Rebif): £10,572 IFN β-1b 250 µg every other day (Betaferon/Extavia): £7264 Glatiramer acetate 20 mg SC daily (Copaxone): £6704	IFN β-1a 30 µg IM once a week (Avonex): £8502 IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): £8502 IFN β-1a 44 SC µg three times per week (Rebif): £10,572 IFN β-1b 250 µg every other day (Betaferon/Extavia): £7264 Glatiramer acetate 20 mg SC daily (Copaxone): £6704
Pooled on-scheme DMTs on disability progression	0.7913	0.6955 (0.5530, 0.8747)	Not applicable	Not applicable	Not applicable	Not applicable
Individual drug time to disability progression	Not applicable	Not applicable	IFN β-1a 30 µg IM once a week (Avonex): 0.73 (0.53, 1.00) IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): 0.62 (0.40, 0.97)	IFN β-1a 30 µg IM once a week (Avonex): 0.68 (0.49, 0.94) IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): 0.46 (0.26,	IFN β-1a 30 µg IM once a week (Avonex): [redacted] IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): 0.620 (0.21, 1.82)	IFN β-1a 30 µg IM once a week (Avonex): 0.73 (0.53, 1.00) IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): 0.62 (0.40, 0.97)

Parameter	Base case analysis	SA1: Pooled on-scheme DMTs from assessment group review	SA 2a: Individual drugs from AG review, progression confirmed at 3 months	SA2b: Individual drugs from AG review, progression confirmed at 6 months	SA 3: Hazard ratios from company submissions	SA 4: Time horizon changed
				0.81)		
			IFN β-1a 44 µg SC three times per week (Rebif): 0.63 (0.46, 0.86)	IFN β-1a 44 µg SC three times per week (Rebif): 0.47 (0.24, 0.93)	IFN β-1a 44 µg SC three times per week (Rebif): [redacted]	IFN β-1a 44 µg SC three times per week (Rebif): 0.63 (0.46, 0.86)
			IFN β-1b 250 µg every other day (Betaferon/Extavia): 0.78 (0.59, 1.0)	IFN β-1b 250 µg every other day (Betaferon/Extavia): 0.34 (0.18, 0.63)	IFN β-1b 250 µg every other day (Betaferon/Extavia): NS	IFN β-1b 250 µg every other day (Betaferon/Extavia): 0.78 (0.59, 1.0)
			Glatiramer acetate 20 mg SC daily (Copaxone): 0.76 (0.60, 0.97)	Glatiramer acetate 20 mg SC daily (Copaxone): 0.82 (0.53, 1.26)	Glatiramer acetate 20 mg SC daily (Copaxone): [redacted]	Glatiramer acetate 20 mg SC daily (Copaxone): 0.76 (0.60, 0.97)
Aggregated annualised relapse rate	0.72	0.6494 (0.5572, 0.7567)	Not applicable	Not applicable	Not applicable	Not applicable
Individual drug annualised relapse rate	Not applicable	Not applicable	IFN β-1a 30 µg IM once a week (Avonex): 0.80 (0.72,0.88)	IFN β-1a 30 µg IM once a week (Avonex): 0.80 (0.72,0.88)	IFN β-1a 30 µg IM once a week (Avonex): 0.7870 (0.5990, 0.9790)	IFN β-1a 30 µg IM once a week (Avonex): 0.80 (0.72,0.88)
			IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): 0.64 (0.50,0.83)	IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): 0.64 (0.50,0.83)	IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): 0.6420 (0.4070, 1.0380)	IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): 0.64 (0.50,0.83)
			IFN β-1a 44 µg three times per week (Rebif): 0.68 (0.61, 0.76)	IFN β-1a 44 µg three times per week (Rebif): 0.68 (0.61, 0.76)	IFN β-1a 44 µg three times per week (Rebif): [redacted]	IFN β-1a 44 µg three times per week (Rebif): 0.68 (0.61, 0.76)
			IFN β-1b 250 µg every other day	IFN β-1b 250 µg every other day	IFN β-1b 250 µg every other day (Betaferon/Extavia): NR	IFN β-1b 250 µg every

Parameter	Base case analysis	SA1: Pooled on-scheme DMTs from assessment group review	SA 2a: Individual drugs from AG review, progression confirmed at 3 months	SA2b: Individual drugs from AG review, progression confirmed at 6 months	SA 3: Hazard ratios from company submissions	SA 4: Time horizon changed
			(Betaferon/Extavia): 0.69 (0.62, 0.76) Glatiramer acetate 20 mg SC daily (Copaxone): 0.66 (0.59, 0.72)	(Betaferon/Extavia): 0.69 (0.62, 0.76) Glatiramer acetate 20 mg SC daily (Copaxone): 0.66 (0.59, 0.72)	Glatiramer acetate 20 mg SC daily (Copaxone): [redacted]	other day (Betaferon/Extavia): 0.69 (0.62, 0.76) Glatiramer acetate 20 mg SC daily (Copaxone): 0.66 (0.59, 0.72)
Annual discontinuation of treatment rate	0.05	0.0229	IFN β-1a 30 µg IM once a week (Avonex): 0.0150 IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): 0.0150 IFN β-1a 44 µg SC three times per week (Rebif): 0.0263 IFN β-1b 250 µg every other day (Betaferon/Extavia): 0.0219 Glatiramer acetate 20 mg SC daily (Copaxone): 0.0263	IFN β-1a 30 µg IM once a week (Avonex): 0.0150 IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): 0.0150 IFN β-1a 44 µg SC three times per week (Rebif): 0.0263 IFN β-1b 250 µg every other day (Betaferon/Extavia): 0.0219 Glatiramer acetate 20 mg SC daily (Copaxone): 0.0263	IFN β-1a 30 µg IM once a week (Avonex): 0.0790 IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): 0.1040 IFN β-1a 44 µg SC three times per week (Rebif): 0.0500 IFN β-1b 250 µg every other day (Betaferon/Extavia): NS Glatiramer acetate 20 mg SC daily (Copaxone): 0.0500	IFN β-1a 30 µg IM once a week (Avonex): 0.0150 IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): 0.0150 IFN β-1a 44 µg SC three times per week (Rebif): 0.0263 IFN β-1b 250 µg every other day (Betaferon/Extavia): 0.0219 Glatiramer acetate 20 mg SC daily (Copaxone): 0.0263
Time horizon	50 years	50 years	50 years	50 years	50 years	20 years, then at 30 years
AG, assessment group; DMTs, disease modifying treatments; IM, intramuscular; NS, not submitted; SA, sensitivity analysis; SC, subcutaneous						

15.2 ***Results of cost-effectiveness analysis***

We present analyses below relating to the base run model. Further results relating to the time-varying model can be found in Appendix 9.

15.2.1 Cost-effectiveness analysis results: base case and sensitivity analyses

Base Case

In Table 71, we present the findings from our base case analysis, taking into account the concerns described in above. The results showed that at a 50-year time horizon the DMT strategy was more costly and more effective than best supportive care. The expected mean costs per person for the disease modifying treatment strategy were approximately £25,600 more costly than the best supportive care strategy and produced 0.943 more QALYs with an ICER of approximately £27,200 per QALY.

Table 71: Base case results based cost per QALY

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
Disease modifying treatments	387,800	25,600	9.607	0.943	27,200
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

SA 1: Pooled on-scheme DMTs from assessment group review

We used two key estimates of treatment effectiveness from our clinical effectiveness review: the aggregated hazard ratio for disability progression confirmed at 3 months and the aggregated annualised relapse rate.

In Table 72, the results are presented in terms of cost per QALY. The results show that disease modifying treatment strategy was more costly and more effective than best supportive care alone. The disease modifying treatment strategy was approximately £14,800 more costly than best supportive care and produced 1.822 more QALYs, which equated to an ICER of approximately £8100 per QALY. This indicates that for every additional QALY from DMTs there is an incremental cost of £8100.

Table 72: Cost per QALY, SA 1

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
Disease modifying treatments	376,900	14,800	10.486	1.822	8100
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

SA 2a Individual drugs from AG review, progression confirmed at 3 months (preferred analysis)

In this model, we used the hazard ratios (DMT vs. placebo) for disability progression confirmed at three months (Table 66) and annualised relapse rates (Table 65) derived from our clinical effectiveness review applied to the individual DMTs.

Table 73: Cost per QALY, SA 2a (assessment group estimates, progression confirmed at 3 months)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
IFN β-1a 125µg (Plegridy)	379,900	17,800	11.223	2.559	7000
Glatiramer acetate 20mg (Copaxone)	381,400	1500	10.012	-1.211	Dominated
IFN β-1b 250µg every other day (Betaferon)	393,400	13,500	9.934	-1.289	Dominated
INF β-1a 44µg SC (Rebif)	404,800	24,900	10.867	-0.356	Dominated
IFNβ-1a 30µg IM (Avonex)	406,400	26,500	10.348	-0.875	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

Results from this sensitivity analysis (see Table 73) show that best supportive care was the least expensive strategy and IFN β-1a 30µg IM once weekly (Avonex) the most expensive. In terms of QALYs, best supportive care is expected to result in the least QALYs (8.664) and IFN β-1a 125 µg SC every two weeks (Plegridy) expected to yield the most QALYs (11.223). IFN β-1a 125 µg (Plegridy) dominated all other disease modifying treatment strategies being less costly and more effective. When compared to best supportive care, IFN β-1a 125 µg (Plegridy) was approximately £17,800 more costly and was more effective by expected mean gains of 2.559 QALYs, with an ICER of £7000 per QALY.

SA 2b: Individual drugs from AG review, progression confirmed at 6 months

In this sensitivity analysis, we used hazard ratios for disability progression confirmed at 6 months derived from our clinical effectiveness review, findings showed that IFN β-1a 125 µg SC every two weeks (Plegridy) was the least costly and most effective treatment strategy, dominating other treatment strategies included in this analysis (see Table 74). We did not include IFN β-1b 250µg every other day (Betaferon) in this analysis as its value for progression confirmed at 6 months was a) extreme, b) derived from indirect evidence, and c) driven by one open-label trial using an imputed hazard ratio.

Table 74: Cost per QALY, SA 2b (assessment group estimates, disability progression confirmed at 6 months)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
IFN β-1a 125 µg SC every two weeks	347,000	-	12.583	-	-

(Plegridy)					
Best supportive care	362,100	15,100	8.664	-3.919	Dominated
IFN β-1a 44 µg SC three times a week (Rebif)	377,600	30,600	12.041	-0.542	Dominated
Glatiramer acetate 20 mg SC daily (Copaxone)	391,800	44,800	9.650	-2.933	Dominated
IFN β-1a 30 µg IM once weekly (Avonex)	397,200	50,200	10.717	-1.866	Dominated
BSC, best supportive care; IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

SA 3: Hazard ratios from company submissions

When we used the estimates for treatment effectiveness (annualised relapse rate and disability progression) reported by each company, results from this sensitivity analysis showed that best supportive care was the least expensive strategy and IFN β-1a 44µg SC three times a week (Rebif) was the most expensive (see Table 75). In terms of QALYs, best supportive care is expected to result in the least QALYs (8.664) and IFN β-1a 125 µg SC every two weeks (Plegridy) expected to yield the most QALYs (9.931). Results also showed that IFN β-1a 125 µg (Plegridy) dominated all other disease modifying treatment strategies. When compared to best supportive care, IFN β-1a 125 µg (Plegridy) demonstrated an ICER of £3300 per QALY.

Table 75: Cost per QALY, SA 3 (company estimates of effectiveness)

Strategy	**Mean cost (£)**	**Incremental costs (£)**	**Mean QALYs**	**Incremental QALYs**	**ICER (£)**
Best supportive care	362,100	-	8.664	-	-
IFN β-1a 125 µg SC every two weeks (Plegridy)	366,300	4200	9.931	1.267	3300
Glatiramer acetate 40 mg SC three times weekly (Copaxone)	387,000	20,700	9.409	-0.522	Dominated
IFN β-1a 30µg IM once weekly (Avonex)	387,600	21,300	9.563	-0.368	Dominated
IFN β-1a 44µg SC three times a week (Rebif)	412,900	46,600	9.719	-0.212	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

SA 4: Time horizon changed from 50 years to 20 and 30 years

Table 76 and Table 77 show the results based on a 20-year and 30-year time horizon, respectively. These results showed that the glatiramer acetate treatment strategy is extendedly dominated by IFN β-1a 125 µg (Plegridy) in both analyses. Additionally, IFN β-1a 125 µg (Plegridy) dominated both IFN β-1a 30 µg IM (Avonex) and IFN β-1a 44µg SC (Rebif) treatment strategies. Excluding all dominated strategies, IFN β-1a 125 µg (Plegridy) when compared to best supportive care had an ICER of approximately £21,200 and £10,600 per QALY for the 20-year and 30-year time horizon, respectively.

Table 76: Cost per QALY, SA 3 (time horizon changed to 20 years)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	196,900	-	6.644	-	-
Glatiramer acetate 20mg (Copaxone)	220,900	24,000	7.436	0.792	Extendedly dominated
IFNβ-1a 125µg (Plegridy)	225,800	28,900	8.007	1.363	21,200
IFNβ-1a 30µg IM (Avonex)	242,900	17,100	7.570	-0.437	Dominated
INFβ-1a 44µg SC (Rebif)	245,200	19,400	7.882	-0.125	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; SC, subcutaneous					

Table 77: Cost per QALY, SA 3 (time horizon changed to 30 years)

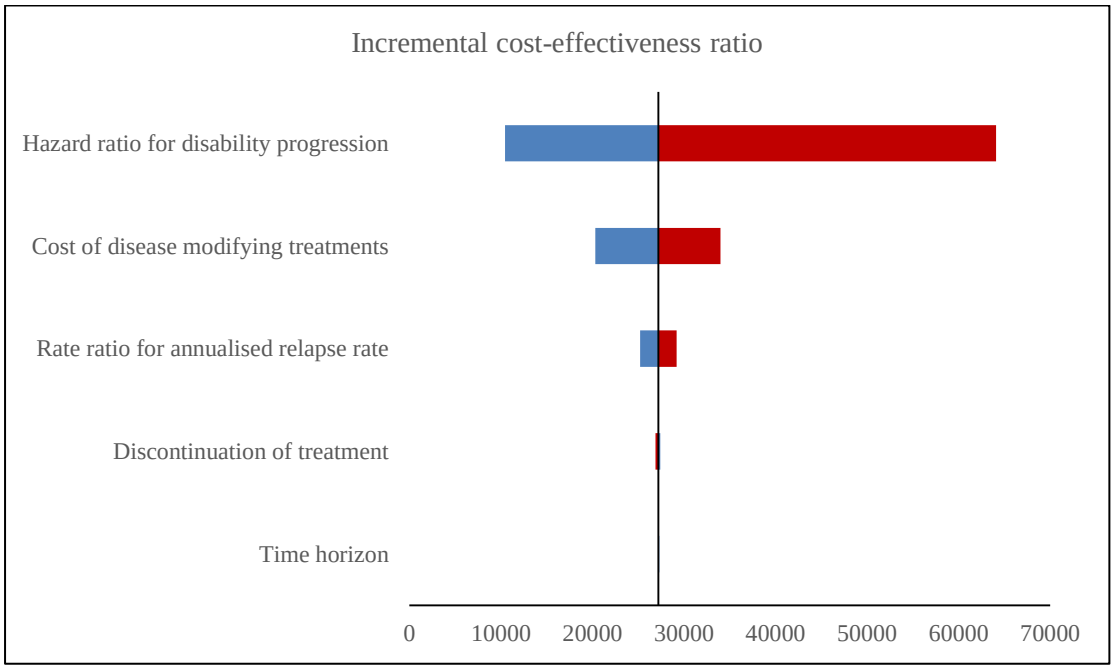
Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	279,400	-	7.774	-	-
Glatiramer acetate 20mg (Copaxone)	299,400	20,000	8.874	1.1	Extendedly dominated
IFNβ-1a 125µg (Plegridy)	300,400	21000	9.756	1.982	10,600
INFβ-1a 44µg SC (Rebif)	322,900	22500	9.532	-0.224	Dominated
IFNβ-1a 30µg IM (Avonex)	323,300	22,900	9.103	-0.653	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; SC, subcutaneous					

SA 5: Parameter uncertainty analysis

Figure 26 shows a graphical representation (also known as a tornado diagram) of the impact **on the base case** of varying key model input parameters. In this analysis, we varied the hazard ratio for disability progression, the rate ratio for annualised relapse rates, cost of disease modifying treatments, and the annual discontinuation rate by ±10%. Additionally, we assessed the impact of the base case results by varying the model time horizon by ±10%. The results show that changes to the hazard ratio for disability progression have the greatest impact on

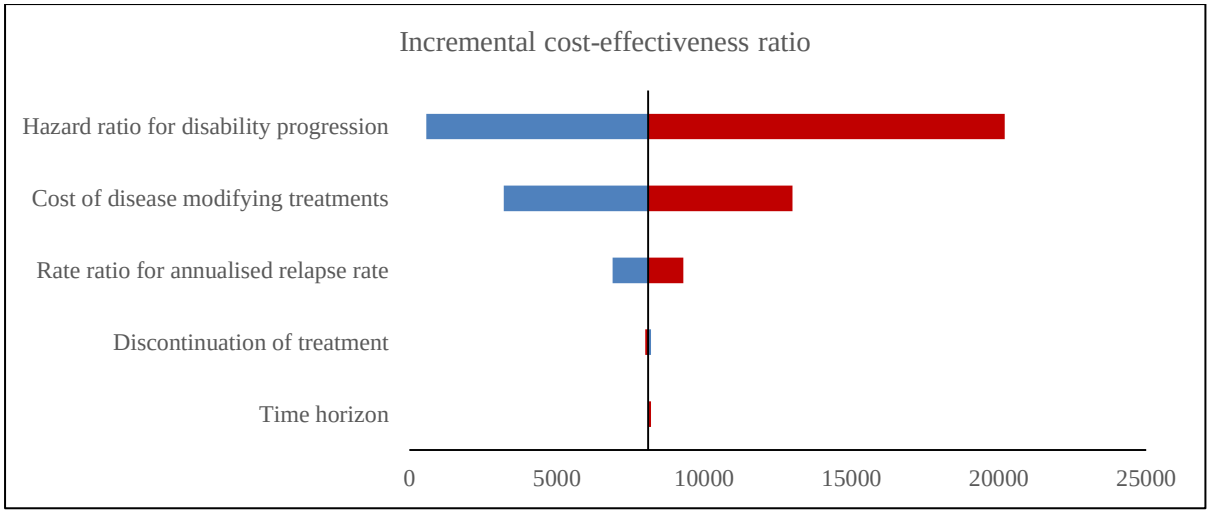
the cost-effectiveness results. A decrease in the treatment effect (increase in the hazard ratio) by 10% resulted in an ICER of approximately £64,000 per QALY gained. An increase in the treatment effect (decrease in the hazard ratio) by 10% resulted in an ICER of approximately £10,400 per QALY gained. The model remained robust to changes to the treatment discontinuation rate and the model time horizon.

Figure 26: Base case tornado diagram for DMTs vs. best supportive care



In Figure 27, we show the impact **on the model estimated in SA 1** of varying model input parameters on the cost-effectiveness results. In SA 1, model input parameters were based on pooled estimates of treatment effectiveness for on-scheme DMTs. To determine the robustness of these results we varied the hazard ratio for disability progression, the rate ratio for annualised relapse rates, cost of disease modifying treatments, the annual discontinuation rate, and the model time horizon. The results show that the model was sensitive to changes to the cost of disease modifying treatment. An increase by 10% in cost of disease modifying treatment led to an increase in the incremental cost-effectiveness ratio by 60%. A decrease by 10% of the cost of DMTs led to a decrease in the ICER by approximately 61%. These results remained robust to changes made to annualised relapse rate, model time horizon and discontinuation of treatment.

Figure 27: SA 1 tornado diagram for DMTs vs. best supportive care



Probabilistic sensitivity analysis conducted on the base case

Table 78 presents the results of the probabilistic sensitivity analysis **conducted on the base case,** that is, when the RSS data were used to estimate the hazard ratio for disability progression and the rate ratio for annualised relapse rates. These results show that the disease modifying treatment strategy was more costly and more effective than best supportive care, with an ICER of approximately £32,000 per QALY gained.

Table 78: Findings from the probabilistic sensitivity analysis conducted on the base case

Strategy	**Mean cost(£)**	**Incremental costs (£)**	**Mean QALYs**	**Incremental QALYs**	**ICER (£)**
Best supportive care	363,900	-	12.65	-	-
Disease modifying treatments	389,200	25,300	13.45	0.79	32,000
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Figure 28 shows the cost-effectiveness plane for the results from the 1000 simulations from the probabilistic sensitivity analysis conducted on the base case, and Figure 29 shows the proportion of these simulations at various willingness-to-pay thresholds in the form of a cost-effectiveness acceptability curve. The cost-effectiveness plane shows that a substantial number of simulations are in the north-east quadrant, where disease modifying treatments are more effective and more costly than best supportive care. We believe that the hazard ratio for disability progression is likely to be one of the key drivers of the economic model. The results from the cost-effectiveness acceptability curve show that at a willingness-to-pay threshold of £20,000 per QALY, disease-modifying treatment when compared to best supportive care, has a probability of being cost-effective of 0.37. It is important to note that the probabilistic sensitivity analysis shows a small but significant number of simulations where best supportive care dominates treatment with disease modifying drugs (north-west quadrant).

Figure 28: Cost-effectiveness plane, probabilistic sensitivity analysis conducted on the base case

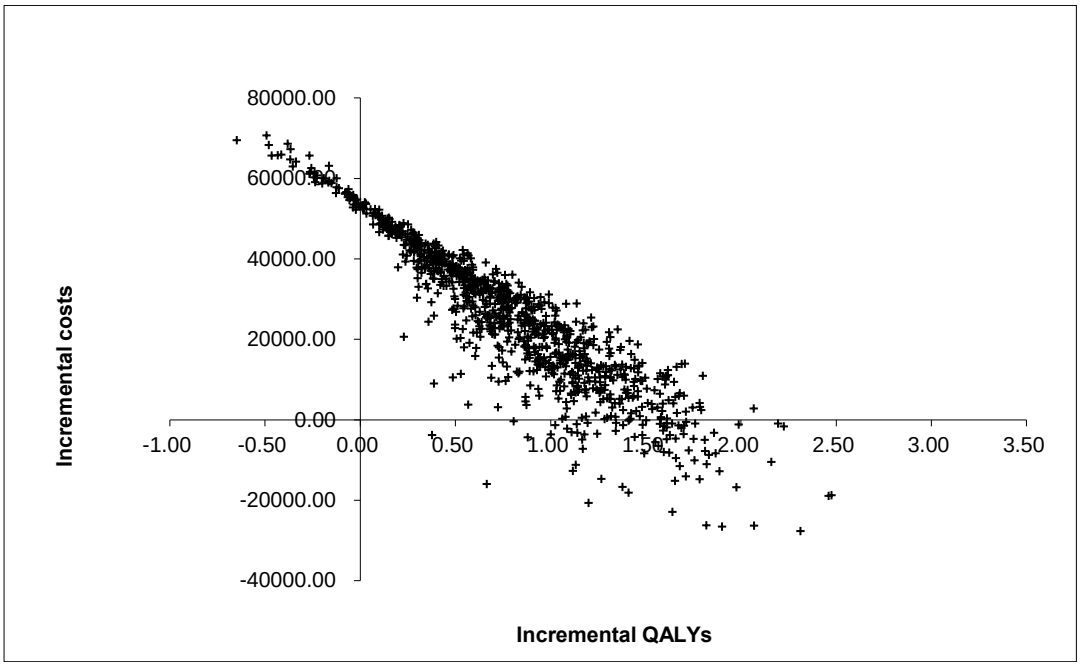
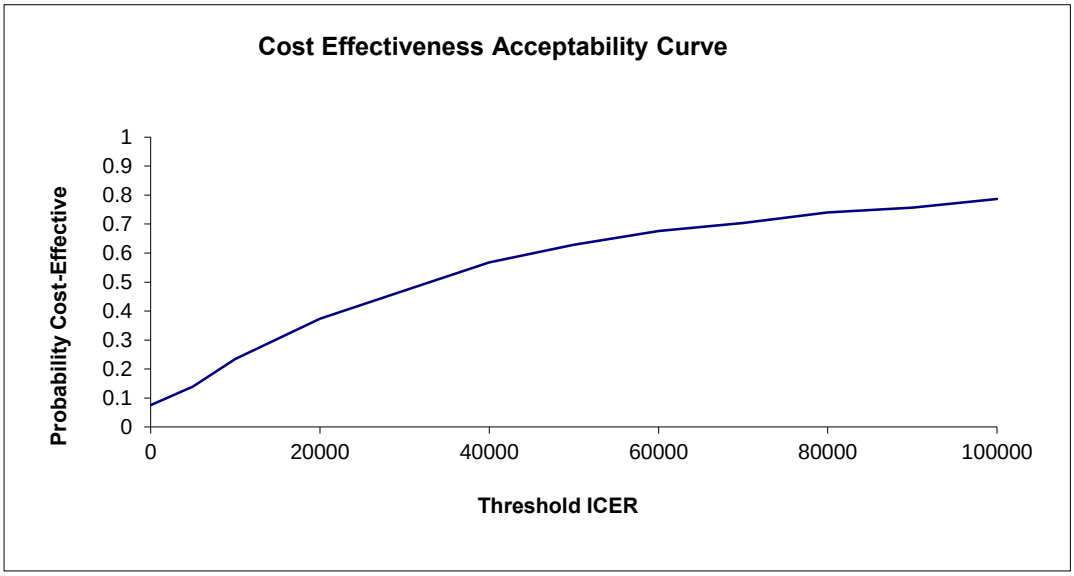


Figure 29: Cost-effectiveness acceptability curve, probabilistic senstivity analysis conducted on the base case



Probabilistic sensitivity analysis conducted on SA 1

Table 79 presents the results of the probabilistic sensitivity analysis when the findings from the assessment group review were used to estimate the pooled hazard ratio for disability progression and the pooled rate ratio for annualised relapse rates. The probabilistic sensitivity analysis shows that the ICER for disease modifying treatments compared to best supportive care was approximately £8000 per QALY gained.

Table 79: Findings from the probabilistic sensitivity analysis conducted on SA 1

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)

Best supportive care	364,400	-	12.70	-	-
Disease modifying treatments	374,100	9700	13.91	1.21	8000
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Results from the simulations are also presented on a cost-effectiveness plane (Figure 30), and cost-effectiveness acceptability curve (Figure 31). Results from 1000 simulations show that a substantial number of points are in the northeast quadrant. Importantly, a significant number of simulations from the PSA were in the southeast quadrant, where disease-modifying treatments could be considered more effective and less costly than best supportive care. The results from the cost-effectiveness acceptability curve show that at a willingness-to-pay threshold of £20,000 per QALY, and when compared to best supportive care, disease-modifying treatment has a probability of being cost-effective of 0.84.

Through visual inspection of the cost-effectiveness plane, it appears that the incremental costs of providing disease modifying treatments is correlated with the incremental effects from receiving treatment. We have undertaken further model simulations (not presented here). We kept the hazard ratio for disability progression constant, and varied other parameters. This resulted in the majority of the plots concentrated in the northeast quadrant and there was no correlation seen. This finding, in addition to the PSA findings presented in Figure 30 and Figure 31, highlight the fact that the hazard ratio for disability progression is likely to be one of the key drivers in the economic model. The more effective DMTs are in slowing disease progression, the more likely they are to be cost-effective.

Figure 30: Cost-effectiveness plane, probabilistic sensitivity analysis conducted on SA 1

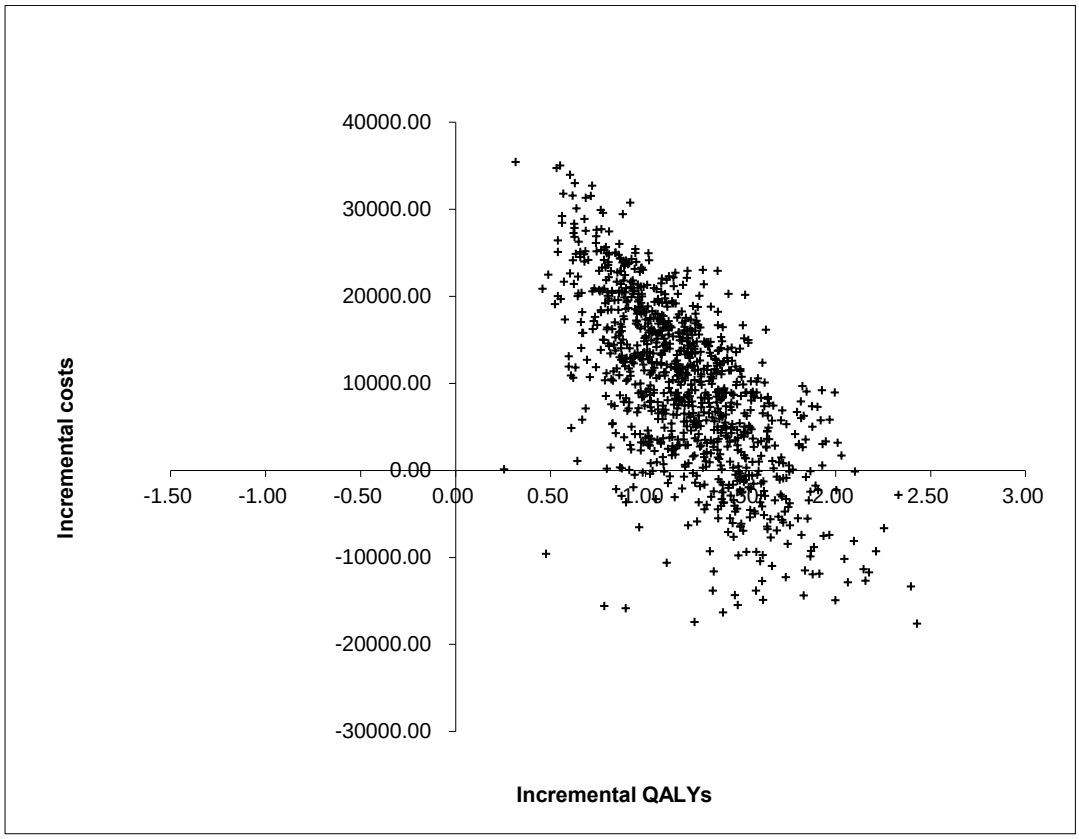
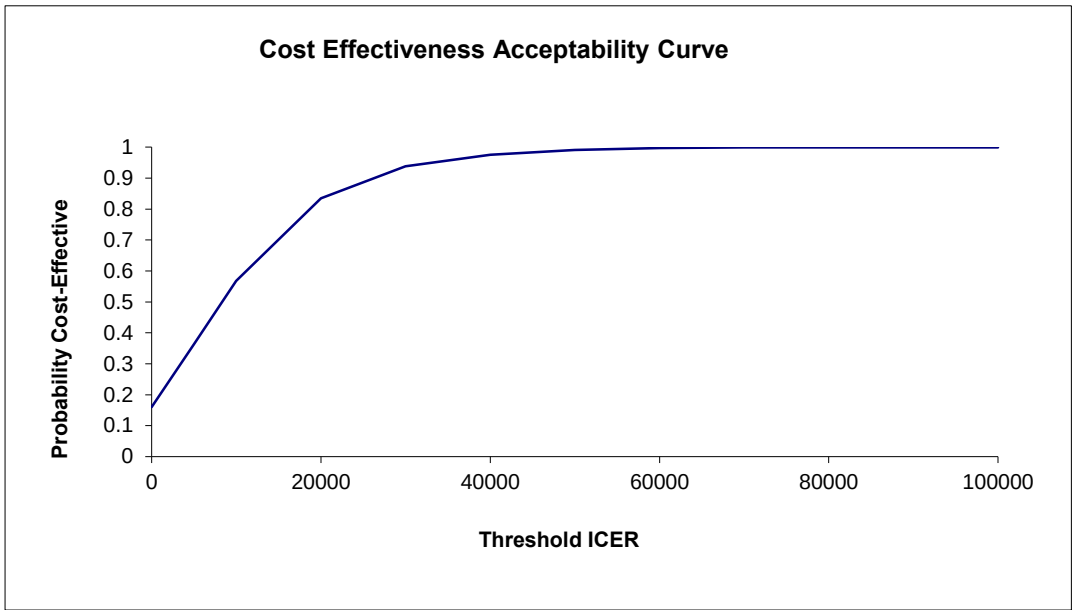


Figure 31: Cost-effectiveness acceptability curve, probabilistic sensitivity analysis conducted on SA 1



15.3 *Discussion of economic assessment of disease modifying treatments for relapsing remitting multiple sclerosis*

15.3.1 Summary of results

In this section, we estimated a variety of sensitivity analyses, in order to address our concerns with the RSS model. In the base case, we drew on the RSS model, and made a number of changes relating to mortality and carers' disutilities. Additionally, we undertook probabilistic sensitivity analyses for our estimates to incorporate uncertainty around input parameters. Deterministic results showed that disease-modifying treatment was more costly and more effective than best supportive care, with an ICER of approximately £27,200 per QALY gained. The PSA results, using the RSS data to estimate the parameters for treatment effectiveness, showed that disease modifying treatment when compared to best supportive care had a probability of 0.37 of being cost-effective at a willingness-to-pay threshold of £20,000 per QALY gained. Even at higher willingness-to-pay thresholds (e.g. £100,000 per QALY), the probability of disease modifying treatments being cost-effective does not reach 1, and some model simulations found best supportive care to dominate the provision of DMTs.

We undertook a number of further sensitivity analyses where we used hazard ratios for disability progression, and rate ratios for annualised relapse rate derived from our network meta-analyses. Deterministic results showed that disease-modifying treatment had an ICER of approximately £8100 per QALY gained when compared to best supportive care. Probabilistic results, using the assessment group data, showed that disease modifying treatment compared to best supportive care had a probability of 0.84 of being cost-effective at a willingness-to-pay threshold of £20,000 per QALY gained.

15.3.2 Strengths and limitations

There were several strengths to our analyses. First and foremost, we assessed the RSS model in detail, and we undertook a number of sensitivity analyses, including probabilistic sensitivity analyses, in order to explore our concerns with the RSS model. Second, we drew on rigorous evidence to estimate a comprehensive set of sensitivity analyses and used probabilistic sensitivity analyses to explore uncertainty. We were able to use clinical inputs from our own rigorous systematic review of the clinical effectiveness evidence, including our network meta-analyses for key treatment effectiveness parameters. This enabled us to compare the implications of different estimates of treatment effectiveness, including the RSS, the pooled on-scheme DMT effect sizes from our clinical effectiveness review, effect sizes for individual DMTs from the network meta-analyses contained in our clinical effectiveness review, and effectiveness estimates supplied by company submissions.

However, there were also limitations to our analyses. Where confidence intervals for input parameters were not provided for probabilistic sensitivity analyses, we had to apply commonly used approaches to model uncertainty. In particular, we did not have a confidence interval for the annualised relapse rate used in the RSS model, so we substituted the standard error from our meta-analysis. The effect of these strategies may be to incorrectly estimate the uncertainty around input parameters, and thus to over-estimate or under-estimate the probability estimate of DMTs being cost-effective at given willingness to pay thresholds. We were unable to include uncertainty around parameters for the natural history cohort used as a comparator in the RSS.

Moreover, any cost-effectiveness analyses undertaken using the estimates from our clinical effectiveness review propagate the major weaknesses identified with that evidence, including sparse networks of evidence, generally short-term follow-up, and differential risk of bias across comparisons. In particular, some estimates of intervention effectiveness, such as for IFN β-1a 125 µg SC every two weeks (Plegridy), relied on few studies; our assessment of Plegridy, in particular, relied on one trial with one year of follow-up connected to evidence networks only via placebo.

Finally, we chose as our base case the RSS model, which draws on observational evidence with a non-contemporaneous, historical control. However, we believed that the long-term follow-up, relevance to the NHS and to current clinical practice, and rigorous methods used in collecting and reporting data made it the best choice as a base case. In contrast, the evidence derived from the clinical effectiveness review had serious limitations discussed at the conclusion of Chapter 10. These limitations led us to believe, on balance, that the RSS was a better choice for the base case.

15.3.3 Conclusion of cost-effectiveness analysis

Based on the model and its inputs, the results of the base case, which draws on the evidence from the RSS, suggest that disease modifying treatment compared to best supportive care had a probability of 0.37 of being cost-effective at a willingness-to-pay threshold of £20,000 per QALY gained. Results from our pooled analysis of randomised controlled trials suggest a probability of 0.84 of disease modifying treatment being cost-effective at a willingness-to-pay threshold of £20,000 per QALY gained. The impact of disease modifying treatment on disability progression was found to be a key driver of cost-effectiveness. In the previous chapters, the clinical effectiveness review highlighted the differences in the estimates of effectiveness of disease modifying treatments, when derived from the RSS data and when derived from the network meta-analysis of clinical trials. The cost-effectiveness analysis in this section highlights how this difference in clinical effectiveness translates into apparent differences in conclusions on cost-effectiveness. However, any analyses undertaken on data from our review of clinical effectiveness propagate the weaknesses in that evidence, including short-term follow-up and sparse data for each comparison.

16 HEALTH ECONOMIC ASSESSMENT (CIS)

16.1 *Health economics methods*

16.1.1 Objective

Our objective was to undertake cost-effectiveness analysis to estimate the incremental cost per quality adjusted life year gained from providing DMTs to patients with clinically isolated syndrome (CIS). We developed a decision-analytical modelling framework, which uses longitudinal data from natural history cohorts and randomised controlled trials to provide information on the progression from CIS to RRMS. The modelling framework was informed by literature searches on model-based economic evaluations of interventions used to treat people with CIS, and longitudinal studies that tracked the progression/conversion of CIS to RRMS. The objective of the model is to estimate the cost-effectiveness of disease modifying treatments within their marketing authorisation for people with CIS. In the model, results are presented in terms of cost per QALY gained.

16.1.2 Developing the model structure

To assess the cost-effectiveness of DMTs for treating CIS, we developed a de novo economic model using TreeAge Pro 2013 software (TreeAge Software Inc., Williamstown, MA, USA).

The model represents, as far as possible, the clinical pathways that people would take while receiving treatment for CIS. Figure 32 shows an illustrative model structure. The model was structured in two stages: treatment of people with CIS and further progression to RRMS, and disease progression whilst in the RRMS health state. In the model we compared six strategies:

1. Best supportive care for people with CIS and RRMS
2. Best supportive care for people with CIS and disease modifying treatment for people converting to RRMS
3. Treatment with IFN β-1a 30 µg IM once weekly (Avonex) for people with CIS, continuing on DMTs after converting to RRMS
4. Treatment with IFN β-1b 250 µg SC every other day (Betaferon) for people with CIS, continuing on DMTs after converting to RRMS
5. Treatment with IFN β-1a 44 µg SC three times weekly (Rebif) for people with CIS, continuing on DMTs after converting to RRMS
6. Treatment with glatiramer acetate 20 mg once daily (Copaxone) for people with CIS, continuing on DMTs after converting to RRMS

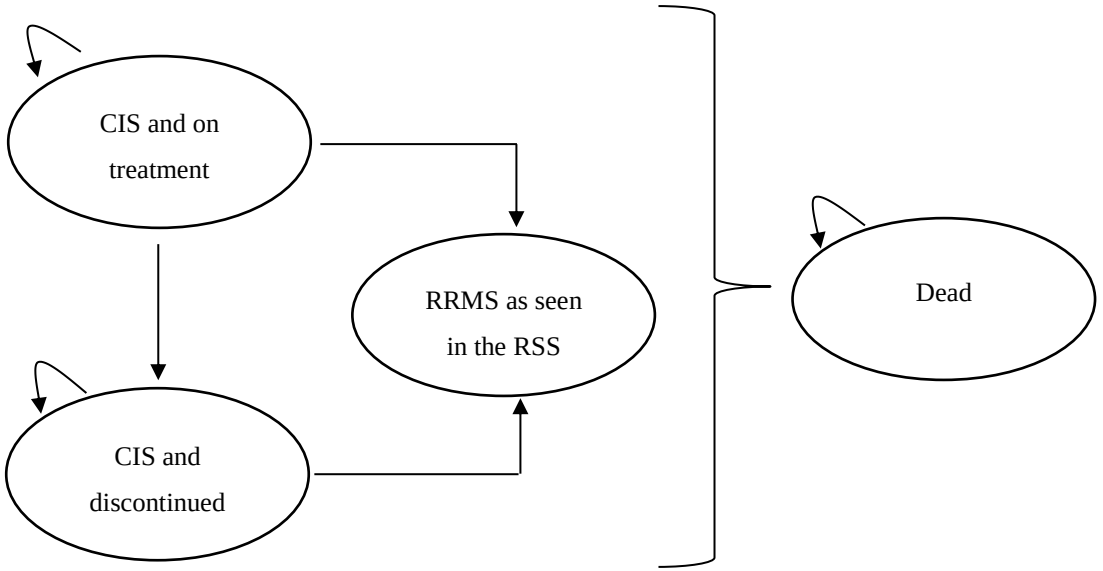


Figure 32: Illustrative model structure

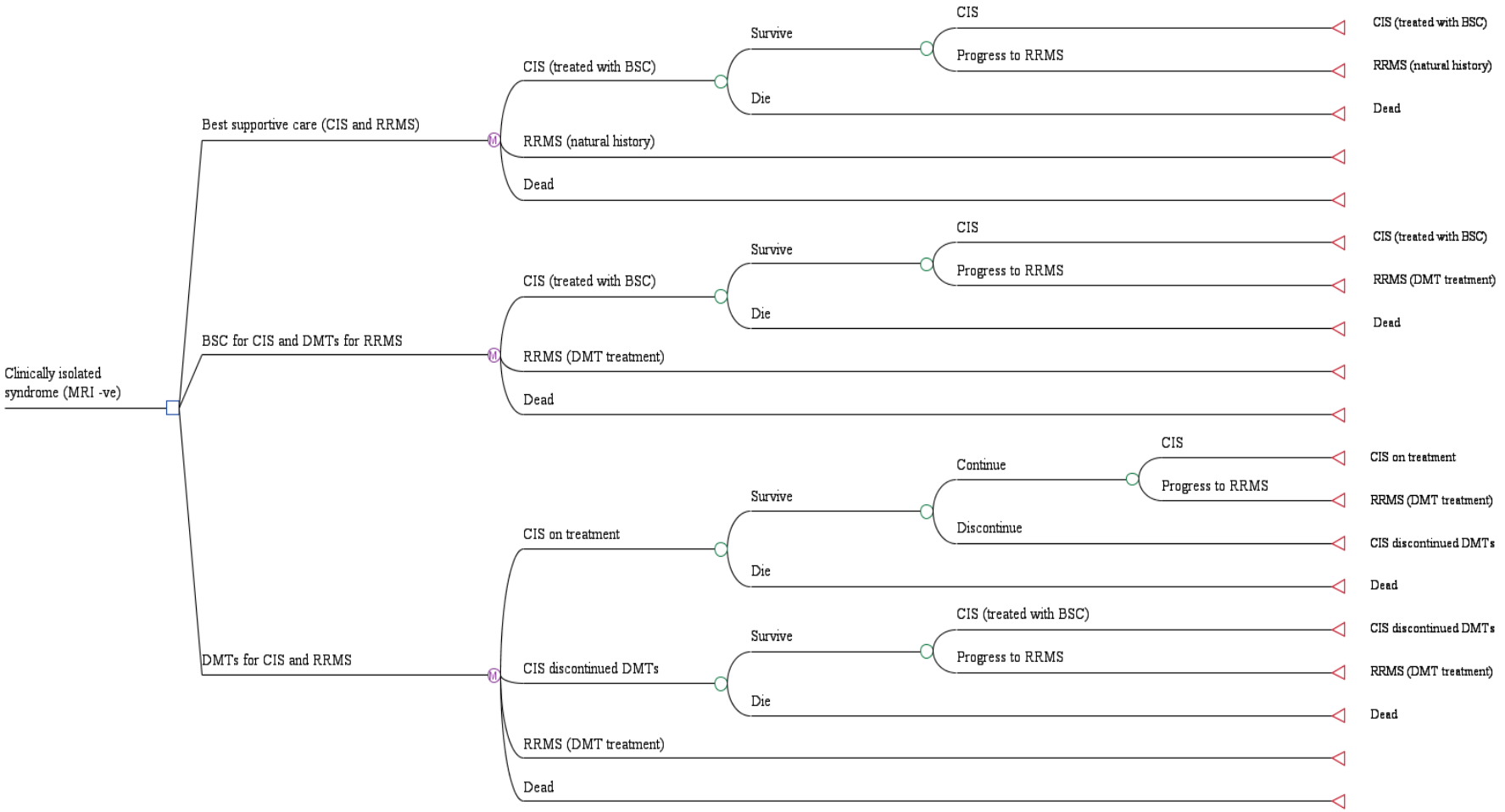


Figure 33: Pathway for the strategies being compared

16.1.3 Overview of strategies

An overview of how these strategies relate to the decision analytical model can be found in Figure 33.

Best supportive care arm for CIS and RRMS

In this strategy, people receive best supportive care as treatment for CIS. People who are alive can remain in this health state or progress to RRMS. People who progress to the RRMS health state are assumed to follow the pathway for people in the natural history cohort of the RSS model.

Best supportive care for CIS and DMTs for people with RRMS

In this strategy, people receive best supportive care as treatment for CIS. People who are alive can remain in this health state or progress to RRMS. People who progress to the RRMS health state are assumed to follow the pathway for people in the DMTs arm of the RSS model.

Disease modifying treatment for CIS and RRMS

People in this strategy receive a DMT for CIS. People can continue receiving treatment or discontinue treatment. People who continue treatment can remain in this health state or progress to the RRMS health state. People who convert to RRMS are assumed to follow the pathway for people in the DMTs arm of the RSS model. People who discontinue CIS treatment can remain in this health state whilst receiving best supportive care treatment or can convert to RRMS. We assumed that people who converted to RRMS follow the pathway for people in the DMTs arm of the RSS model. The pathway for people in the DMTs arm of the RSS model reflects the pooled estimates for all DMTs in the RSS model (e.g. drug acquisition costs), and consequently takes into account that whilst patients with CIS may discontinue the modelled DMT, when they progress to RRMS they may be started on an alternative DMT. The pathways for all DMTs for CIS being compared in the model are the same.

16.1.4 Model assumptions

A number of assumptions were required in order to undertake these analyses:

1. Starting population: People aged 30 years and with CIS, i.e. who had experienced a clinically diagnosed, single demyelinating event in one or several areas of the central nervous system within the last two months, and with no evidence of RRMS on MRI scan;
2. People who have converted to RRMS have no residual treatment benefit based on prior treatment in the CIS health state;
3. People who converted to RRMS are assumed to follow the same pathway as people in the RSS model; and

4. Patients with CIS who discontinue a DMT (e.g. due to adverse events) will be started on an alternative DMT once they progress to RRMS. The risk of patients with RRMS discontinuing a DMT is not dependent on whether or not they had discontinued a DMT whilst they had CIS.

16.1.5 Data required for the model

The model was populated with information identified from the clinical and cost-effectiveness review, and supplemented with information from secondary sources. Information required to parameterise the model included transition probabilities, resource use and costs, and utilities. These are discussed in turn below.

Transition probabilities and proportions

Information was required on the risk of disease progression from clinically isolated syndrome to relapsing remitting multiple sclerosis. Information on progression was required for an untreated cohort and for a treated cohort of people with CIS. For the untreated cohort, progression rates could be derived from a natural history cohort, patient registry or from CIS patients registered on a placebo arm of a trial. In the base case for the best supportive care arm, we identified one study[274] based on a literature review, which provided useful information on time to progression to RRMS for people diagnosed with clinically isolated syndrome with no asymptomatic lesions on magnetic resonance imaging (MRI). We reconstructed the Kaplan-Meier survival curve of time from first-attack to conversion to RRMS based on baseline MRI (no asymptomatic lesion) and fitted with various parametric models. According to the Akaike information criterion (AIC) and Bayesian information criterion (BIC), we found that the Weibull and loglogisitic models provided best fits to the Kerbrat et al.[274] data. Figure 34 shows the reconstructed Kaplan-Meier curve with the Weibull parametric model. From this, annual transition probabilities generated by the Weibull models were used for the best supportive care arm. To derive the transition probabilities on conversion to RRMS for the treatment arms, we applied the hazard ratios derived from our clinical review. Table 80 shows the estimates used to derive transition probabilities for conversion to RRMS in the model.

Figure 34: Reconstructed Kaplan-Meier and Weibull model for time to conversion to RRMS on best supportive care by annual cycles (Kerbrat et al., 2015)[274]

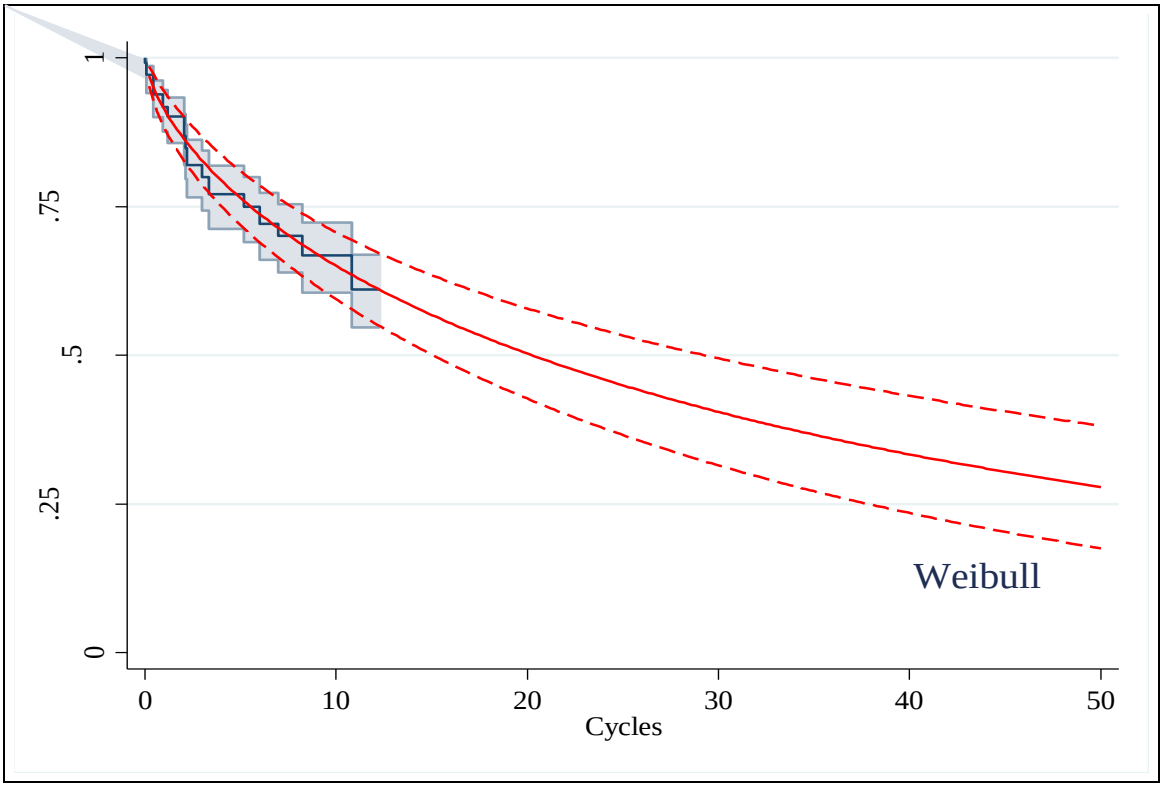


Table 80: Values for progression from CIS to RRMS

Parameter	Base-case value	Hazard ratios 95% CI	Reference(s)
Best supportive care	Weibull (λ = 0.0906; γ = 0.6768)	-	Kerbrat et al., 2015[274] (Reconstructed individual patient data and Weibull model was a good parametric fit); Applied hazard ratios derived from the clinical effectiveness review
IFN β-1a 30 µg IM once a week (Avonex)		0.516 (0.389, 0.684)	
IFN β-1a 44 µg SC three times per week (Rebif)		0.480 (0.314, 0.738)	
IFN β-1b 250 µg every other day (Betaferon)		0.500 (0.36, 0.699)	
Glatiramer acetate 20 mg SC daily (Copaxone)		0.549 (0.397, 0.762)	

Proportion of people discontinuing disease modifying treatment

We have included the annual proportion of people who discontinued DMT as a result of adverse events in the model. These proportions were derived from the CIS and RRMS studies included in our clinical review. Studies reported the instantaneous rate of people who discontinued treatment as a result of DMTs. We converted this to an annual probability using the equation (probability = 1 – exp (-rt), where r is rate and t is time. When discontinuation rates were not available from CIS studies, we used studies following up people with RRMS and assumed that the rates would be applicable to people with CIS. Table 81 shows the proportions obtained from the studies and the annual probability of discontinuation for each DMT used in the base case analysis.

Table 81: Proportion of people discontinuing treatment following adverse events

Parameter	Type of MS	Instantaneous rate	Annual probability	Reference
IFN β-1a 30 µg IM once a week (Avonex)	RRMS	4.4%	0.0222	Derived from Jacobs et al. (2000)[170]
IFN β-1a 44 µg SC three times per week (Rebif)	RRMS	6.0%	0.0330	Derived from Mikol et al. (2008)[190]
IFN β-1b 250 µg SC every other day (Betaferon/Extavia)	CIS	8.2%	0.0419	Derived from Kappos et al. (2006)[169]
Glatiramer acetate 20 mg SC daily (Copaxone)	CIS	5.8%	0.0197	Derived from Comi et al. (2009)

Resource use and costs

The resource use and costs utilised were those that were directly incurred by the National Health Service (NHS) and Personal and Social Services (PSS). Resource use and costs were required for DMTs, drug administration, monitoring costs and health state costs. Unit costs are presented in Table 82, and details on estimates of resource use are provided in Appendix 8.

Costs of disease modifying treatments were obtained from the British National Formulary 2015[24]. The annual cost of £8502 for treatment with IFN β-1a (Avonex) was based on a dosage of 30µg once a week. The annual cost of £10,572 for treatment with IFN β-1a (Rebif) was based on a dosage of 44µg three times per week. We derived annual costs of £7264 and £6704 for treatment with IFN β-1b 250 µg every other day (Betaferon/Extavia) and glatiramer acetate 20 mg SC daily (Copaxone), respectively.

Table 82: Unit costs required for the model

Parameter	Base-case value (£, 2015)	Reference(s)
IFN β-1a 30 µg IM once a week (Avonex)	8,502	British National Formulary (BNF), 2015[24]
IFN β-1a 44 µg SC three times per week (Rebif)	10,572	
IFN β-1b 250 µg SC every other day (Betaferon/Extavia)	7,264	
Glatiramer acetate 20 mg SC daily (Copaxone)	6,704	
Monitoring costs		
IFN β-1a 30 µg IM once a week (Avonex)	553.20	Estimates (see Appendix 8) on resource use from clinical expert and unit costs from BNF 2015[24], NHS reference costs 2014/15[275] and Curtis and Burns 2015[260]
IFN β-1a 44 µg SC three times per week (Rebif)	560.33	
IFN β-1b 250 µg SC every other day (Betaferon/Extavia)	553.20	
Glatiramer acetate 20 mg SC daily (Copaxone)	553.20	
Cost of subsequent monitoring	323.77	
Other costs		
Drug administration	225.00	Assumption on resource use information and unit costs from Curtis and Burns 2015[260]
Health state costs (CIS)		
CIS no treatment	350.49	Assumption on resource use information and unit costs from Curtis and Burns 2015[260] and NHS reference costs 2014/15[275]

CIS; clinically isolated syndrome; IFN, interferon

Costs for monitoring were derived based on clinical expert opinion for resource use and valued using costs from the NHS reference costs[275] and Curtis and Burns[260]. Monitoring costs were derived for initiating treatment, and costs for subsequent monitoring. We derived a cost of £553.20 for monitoring people who received treatment with IFN β-1a 30 µg IM once a week (Avonex), IFN β-1b 250 µg every other day (Betaferon/Extavia) and glatiramer acetate 20 mg SC daily (Copaxone) during the first year of commencing treatment. We assumed that people required visits to a neurologist and an MS nurse, and received a series of blood tests and an MRI scan. For people who commenced treatment with IFN β-1a 44 µg SC three times per week (Rebif), we derived a cost of £560.33. This included the same resources used, as described for the monitoring for other disease modifying treatments, in addition to a cost for a thyroid function test. For subsequent monitoring, we derived a cost of £323.77 for all disease modifying treatments. For this we assumed that people required visits to a neurologist and a MS nurse, and received an annual MRI scan. Further details of the resource use estimates are presented in Table 82.

We calculated an annual cost of administration of £225. For this we assumed a specialist nurse (community), employed on the NHS scale agenda for change Band 6 (£75 per hour of patient-related

work), would spend three hours of contact time to teach people how to self-administer disease modifying treatments.

Utility values

Health outcomes were measured in quality-adjusted life-years (QALYs). In the model, we assigned the same utility values to all the CIS health states. For this we have derived a weighted utility value based on two pooled utility values by EDSS health states (MS Trust survey 2002 and 2005) and weighted by the proportion of individuals at each EDSS health state observed on entry to the RSS cohort. The disutility associated with adverse events from DMTs was based on the estimates from Tappenden et al.[257] This was the approach used in the cost-effectiveness analysis of DMTs in RRMS. Table 83 shows the utility values used in the model.

Table 83: Utility values used in the CIS model

Parameter	Base-case value	Reference(s)
Health state utility values		
CIS	0.6218	Assumption
Disutility associated with AEs		Tappenden et al., 2001[257]
IFN β-1a 30 µg IM once a week (Avonex)	-0.02	
IFN β-1a 44 µg SC three times per week (Rebif)	-0.02	
IFN β-1b 250 µg SC every other day (Betaferon/Extavia)	-0.02	
Glatiramer acetate 20 mg SC daily (Copaxone)	-0.02	

AE, adverse events; CIS, clinically isolated syndrome

16.1.6 Cost-effectiveness analysis

A Markov model was constructed and programmed to choose the base case model inputs in order to assess the cost-effectiveness of various DMTs for the management of people with CIS. The model estimated the mean costs and health benefits associated with each DMT, and assumed that the starting population age of the population was 30 years old. The analysis was undertaken from a NHS and PSS perspective and outcomes were reported as ICERs, expressed in terms of cost per QALY gained. All costs and outcomes were discounted at 3.5% per annum.

16.1.7 Sensitivity analyses

A deterministic sensitivity analysis was undertaken for the base case results for the cost per QALY outcome measures, and these are summarised below:

1. SA 1 Changing the time horizon to 20 years and 30 years
2. SA 2 Assuming 5% of people with CIS would discontinue treatment with DMTs

In addition, we assessed the impact of varying key model input parameters on our base case results.

16.2 *Results of cost-effectiveness analysis*

16.2.1 Base case cost-effectiveness analysis

In Table 84, results for the base case analysis shows that providing best supportive care for people with CIS and continuing best supportive care on conversion to RRMS was the least costly strategy, with a mean cost of approximately £160,600, and the least effective, with a mean 12.78 QALYs gained. The strategy whereby people with CIS receive treatment with glatiramer acetate 20 mg SC daily (Copaxone), then receiving DMT when they convert to RRMS, dominated the IFN β-1a 30 µg IM once weekly (Avonex) and IFN β-1a 44 µg SC three times weekly (Rebif) treatment strategies. Excluding all dominated and extendedly dominated strategies, the optimal strategy was treatment with glatiramer acetate 20 mg SC daily (Copaxone). In comparison to best supportive care, providing glatiramer acetate 20 mg SC once daily (Copaxone) for patients with CIS, and DMTs on progression to RRMS, was associated with an ICER of £12,900 per QALY gained.

Table 84: Base case results, cost per QALY

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
BSC (CIS and RRMS)	136,800	-	12.78	-	-
BSC for CIS and DMTs for RRMS	150700	13900	13.16	0.38	Extendedly dominated
IFN β-1b 250 µg SC every other day (Betaferon/Extavia) for CIS and DMTs for RRMS	196,400	45,700	16.85	3.69	Extendedly dominated
Glatiramer acetate 20 mg SC daily (Copaxone) for CIS and DMTs for RRMS	213,700	76,900	18.73	5.95	12,900
IFN β-1a 30 µg IM once a week (Avonex) for CIS and DMTs for RRMS	231,300	17,900	18.57	-0.16	Dominated
IFN β-1a 44 µg SC three times per week (Rebif) for CIS and DMTs for RRMS	240,300	26,900	17.61	-1.12	Dominated

16.2.2 SA 1: Changing the time horizon to 20 years and 30 years

Table 85 and Table 86 show the findings when the model was run over time horizons of 20 years and 30 years. Over these shorter time horizons, treatment of CIS with IFN β-1b 250 µg SC every other day (Betaferon/Extavia) becomes cost-effective, with an ICER of £16,000/QALY gained and £13,500/QALY gained, for the 20-year and 30-year time horizons, respectively. Treatment with glatiramer acetate 20 mg SC daily (Copaxone) remains cost-effective. Over these shorter time horizons, treatment with IFN β-1a 30

µg IM weekly (Avonex) or IFN β-1a 44 µg SC (Rebif) continues to be dominated by glatiramer acetate 20 mg SC daily (Copaxone).

Table 85: SA 1 results (20-year time horizon)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
BSC (CIS and RRMS)	155,100	-	10.33	-	-
BSC for CIS and DMTs for RRMS	166,400	11,300	10.73	0.40	Extendedly dominated
IFN β-1b 250 µg SC every other day (Betaferon/Extavia) for CIS and DMTs for RRMS	181,600	26,500	11.99	1.66	16,000
Glatiramer acetate 20 mg SC daily (Copaxone) for CIS and DMTs for RRMS	190,400	8800	12.46	0.47	18,700
IFN β-1a 30µg IM weekly (Avonex) for CIS and DMTs for RRMS	204,100	13,900	12.39	-0.07	Dominated
IFN β-1a 44 µg SC three times weekly (Rebif) for CIS and DMTs for RRMS	215,000	24,800	12.15	-0.31	Dominated

Table 86: SA 1 results (30-year time horizon)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
BSC (CIS and RRMS)	173,100	-	12.02	-	-
BSC for CIS and DMTs for RRMS	185,600	12,500	12.46	0.44	Extendedly dominated
IFN β-1b 250 µg SC every other day (Betaferon/Extavia) for CIS and DMTs for RRMS	212,000	38,900	14.89	2.87	13,500
Glatiramer acetate 20 mg SC daily (Copaxone) for CIS and DMTs for RRMS	225,800	13,800	15.88	0.99	13,900
IFN β-1a 30µg IM weekly (Avonex) for CIS and DMTs for RRMS	241,200	15,700	15.78	-0.1	Dominated
IFN β-1a 44 µg SC three times weekly (Rebif) for CIS and DMTs for RRMS	251,000	25,500	15.28	-0.6	Dominated

16.2.3 SA 2 Assuming 5% of people with CIS would discontinue treatment with DMTs

Table 87 shows the findings when we assumed that approximately 5% of those treated with DMTs for CIS discontinue treatment every year. In this scenario, the treatment of CIS with IFN β-1b 250 µg SC every other day was cost-effective, with an ICER of £15,100/QALY gained. Treatment with glatiramer acetate 20

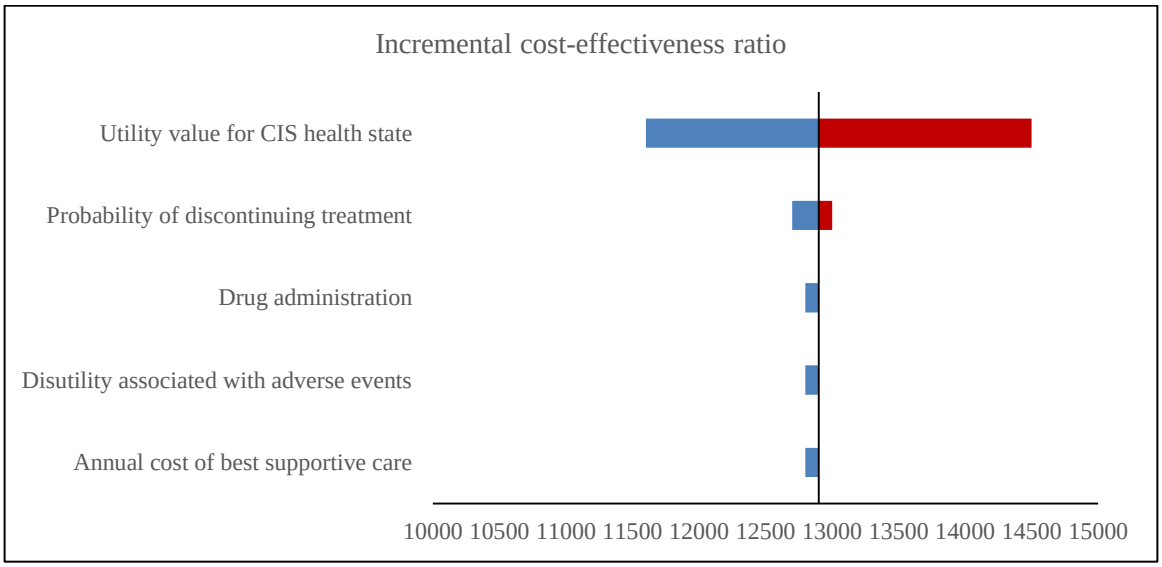
mg SC daily (Copaxone) remains cost-effective. However, treatment with IFN β-1a 30µg IM weekly (Avonex) or IFN β-1a 44 µg SC three times weekly (Rebif) continues to be dominated or associated with an extremely high ICER.

Table 87: SA 2 results (yearly discontinuation rate of 5%)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
BSC (CIS and RRMS)	136,800	-	12.78	-	
BSC for CIS and DMTs for RRMS	150,700	13,900	13.16	0.38	Extendedly dominated
IFN β-1b 250 µg SC every other day (Betaferon/Extavia) for CIS and DMTs for RRMS	188,700	51,900	16.22	3.44	15,100
Glatiramer acetate 20 mg SC daily (Copaxone) for CIS and DMTs for RRMS	191,100	2400	16.36	0.14	17,100
IFN β-1a 30µg IM weekly (Avonex) for CIS and DMTs for RRMS	204,000	12,900	16.31	-0.05	Dominated
IFN β-1a 44 µg SC three times weekly (Rebif) for CIS and DMTs for RRMS	222,200	31,100	16.41	0.05	622,000

In Figure 35, we present graphically the impact of varying model input parameters on the cost-effectiveness results. To determine the robustness of the results, we varied the utlity value for the CIS health state and the probability of treatment discontinuation as well as the mode of drug administration, the disutility associated with adverse events and the annual cost of BSC. The results show that the model was most sensitive to a +/- 10% change in the utility of the CIS health state. A 10% increase in the health state utility of CIS would take the value to 0.6898. However, this would still give an ICER for glatiramer acetate 20 mg (Copaxone) vs. BSC of £14,500, well within the normal expected levels of willingness to pay.

Figure 35: Tornado diagram for glatiramer acetate 20 mg SC daily vs. BSC



16.3 *Discussion of economic assessment of DMTs for CIS*

16.3.1 Summary of results

Having estimated the treatment effect of each DMT on the conversion to RMS, we then assessed the cost-effectiveness of DMTs in people who were diagnosed with CIS in the absence of evidence for RRMS on an MRI scan. We developed a decision analytical model, taking the NHS and PSS perspective, and presented outcomes in terms of cost per QALY gained. We considered six strategies in our analysis, which included treatment with best supportive care in addition to the DMTs available for people with CIS. The base case deterministic results showed that treating people with glatiramer acetate 20 mg (Copaxone) followed by disease modifying treatment on conversion to RRMS dominated the IFN β-1a 30 µg IM once a week (Avonex) and IFN β-1a 44 µg SC three times per week (Rebif) treatment strategies. We found that treatment with IFN β-1b 250 µg SC every other day (Betaferon/Extavia) was extendedly dominated, and although it was cost-effective in comparison to best supportive care, the ICER was higher than that for glatiramer acetate 20 mg SC once daily (Copaxone). Excluding all dominated strategies, the ICER for providing glatiramer acetate 20 mg SC once daily (Copaxone) was approximately £12,900 per QALY gained.

The sensitivity analysis showed that treatment of clinically isolated syndrome with IFN β-1b 250µg SC every other day (Betaferon/Extavia) would also be a cost-effective option if discontinuation rates for all the drug treatments were comparable, or if the decision was evaluated over a short time horizon. The sensitivity analysis did not suggest that treatment with IFN β-1a 30 µg IM once a week (Avonex) or IFN β-1a 44 µg SC three times per week (Rebif) was a cost-effective option in the UK. Results further showed that the

model is likely to be sensitive to the utility associated with the CIS health state and to discontinuation of treatment while in the CIS state.

16.3.2 Strengths and limitations

Our analysis had several strengths. We built a de novo model for CIS, and we were able to incorporate evidence from our systematic review of clinical effectiveness. We also incorporated long-term costs and consequences of progressing to, and receiving disease modifying treatment for RRMS. We also used evidence from the RSS observational cohort to model the effect of conversion to RRMS.

However, our analysis was limited in several important ways. We did not undertake probabilistic sensitivity analysis. Moreover, due to paucity of health related quality of life information in people with CIS, we assumed CIS to be comparable to early phase RRMS. However, we investigated the effect of varying this input parameter on the cost-effectiveness results by 10%, and we found that results still gave ICERs well within expected levels of willingness to pay. Finally, our findings from the clinical effectiveness review relied on a population diagnosed with CIS before the revised 2010 McDonald criteria reclassified many who would have had CIS as in fact having RRMS.

16.3.3 Conclusions

Our cost-effectiveness findings suggest that in people with CIS, it would be cost-effective to start DMTs. We found that of the evaluated DMTs, glatiramer acetate 20 mg SC daily (Copaxone) was the optimal choice. Greater understanding around discontinuation rates of DMTs in CIS patients would be valuable, as it may impact on whether or not IFN β-1b SC 250 µg every other day (Betaferon/Extavia) is also a cost-effective option. These results are presented in the light of some limitations/uncertainty; mainly around the utility values for the clinically isolated syndrome health state, and disutilities associated with adverse events. Our analyses drew on utility values obtained from people with relapsing remitting multiple sclerosis and, due to the complexity of the modeling approach and lack of data, we were unable to quantify this uncertainty by undertaking probabilistic sensitivity analysis. Until more reliable information on utility values become available, these results should be interpreted with caution.

17 DISCUSSION

17.1 *Summary*

17.1.1 Clinical effectiveness

We systematically reviewed and synthesised evidence relating to the effectiveness of interferons and glatiramer acetate within their marketing authorisations for clinically isolated syndrome, relapsing remitting MS and secondary progressive MS. We exhaustively searched databases to update prior high-quality reviews for each of these MS types, and we used standard systematic review methodology to select, appraise and extract data from relevant studies. Our search identified 35 primary studies: five in CIS, 27 in RRMS of which 24 relevant trials reported clinical effectiveness outcomes of interest, and three in SPMS. We synthesised findings from these trials narratively, and where appropriate using pairwise meta-analyses and network meta-analyses. Across MS types, studies were variable in quality. Most studies were manufacturer-sponsored. We also judged that many studies were at high risk of unblinding of participants and personnel due to injection site reactions, with potential implications for blinding of outcome assessors. Many trials, especially of head-to-head comparisons, were open-label.

Clinical effectiveness evidence suggested that IFN and GA were effective for key outcomes and across MS types, and there was little evidence from the NMAs that drugs were superior to others on clinical outcomes. In clinically isolated syndrome, each drug included showed evidence of delaying time to clinically definite MS. In RRMS, drugs showed good evidence of reducing relapse rate, including rate of moderate or severe relapses and in most cases, rate of steroid-treated relapses. Most drugs delayed disability progression confirmed at three months, though findings were less consistent for disability progression confirmed at six months. Finally, in SPMS, all drugs reduced relapse rate, though the network was sparse and relied on three studies. Time to confirmed disability progression at three months was measured in only two studies, which showed variable effects across treatments. We undertook analyses of discontinuation due to AEs in RRMS and SPMS. These analyses, which were intended to be indicative, did not offer evidence that one drug was more likely than another to result in discontinuation due to an AE.

We synthesised findings for additional outcomes in the scope (MS symptoms, health-related quality of life and freedom from disease activity) narratively but were unable to undertake meta-analyses due to heterogeneity, sparsity and poor reporting for these outcomes. Findings suggested a generally beneficial effect on freedom from disease activity, but findings on MS symptoms and health-related quality of life were poorly reported and inconsistent. Additionally, no studies reported discontinuation due to loss of effect attributed to neutralising antibodies.

17.1.2 Cost effectiveness

As part of our assessment of cost effectiveness, we undertook four related work packages. First, we systematically reviewed, appraised and synthesised the recent cost-effectiveness evidence on disease modifying treatments for people with clinically isolated syndrome, and multiple sclerosis. Second, we critically appraised

the Year 10 RSS economic model, including checking the model and reviewing inputs to and assumptions made in the model. Third, we assessed the cost effectiveness of DMTs for the treatment of RRMS. Fourth, we assessed the cost effectiveness of DMTs for the treatment of CIS. We assessed cost effectiveness using a modified RSS model, with clinical effectiveness inputs derived from the Year 10 RSS analyses as the base case. We conducted several additional analyses: 1) using pooled estimates of the effectiveness of on-scheme DMTs from our systematic review of clinical effectiveness, 2) using pooled estimates of the effectiveness of each DMT from our systematic review of clinical effectiveness, and 3) using pooled estimates for the effectiveness of each DMT from company submissions.

We identified ten studies in an RRMS cohort and nine studies in a CIS cohort, which reported evidence on a decision model used to estimate the cost-effectiveness of disease modifying treatment. In general, most studies used appropriate model structures in order to capture/simulate the disease progression. According to best practices for reporting cost-effectiveness analyses, all studies performed satisfactorily in terms of outlining the decision problem, stating the perspective of the analysis, adhering to the scope of the model, and outlining the structural assumptions. However, there were some limitations of these studies. First, we consider the time horizon to be short in some studies, and these analyses may not have captured the full costs and benefits of disease modifying treatments. Second, the choice of model structure in several studies did not accurately reflect disability progression associated with multiple sclerosis. Third, authors did not provide sufficient detail on the meta-analytic methods used to estimate treatment effects of disease modifying treatment or sufficient detail on how treatment effects had been extrapolated beyond trial time horizons.

We considered the RSS model to be appropriate in order to estimate the cost-effectiveness of DMTs compared to best supportive care. The model draws on the best available evidence on disease progression, resource use and costs, and utility values. However, our appraisal highlighted concerns with the RSS model relating to mortality, carers' disutilities, discontinuation rates and how the annualised relapse rate was estimated.

Third, in our base case assessment of cost effectiveness of DMTs for RRMS, our results suggested that it is cost-effective to treat people who have RRMS with DMTs. Using as our base case the RSS model with assumptions relating to mortality and carers' disutilities modified, we found that DMTs were more costly and more effective than best supportive care, with an incremental cost-effectiveness ratio of approximately £27,200 per QALY gained. We also used pooled estimates derived from our clinical effectiveness review for all on-scheme DMTs, which showed that though DMTs were more costly than best supportive care, they also produced more QALYs, and had an incremental cost-effectiveness ratio of approximately £8,100 per QALY. When we compared between each DMT, IFN β-1a SC 125 µg every two weeks (Plegridy) appeared to be the most cost-effective, but clinical effectiveness estimates for this drug were based on one trial with one year of follow-up. Results from the probabilistic sensitivity analysis conducted on the RSS data showed that at a willingness to pay threshold of £20,000/QALY, DMTs had a 37% probability of being cost-effective.

Fourth, we assessed the cost effectiveness of DMTs for CIS. Our base case analysis suggested that treatment with glatiramer acetate 20 mg SC daily was cost-effective relative to best supportive care at £12,900 per QALY gained, and dominated all other strategies in the base case.

17.2 *Strengths and limitations*

17.2.1 In relation to study search, inclusion and exclusion, and selection

We used a rigorous and exhaustive search to locate primary studies, including by updating high-quality systematic reviews. Additionally we used auditable and transparent methods to include and synthesise studies. Where appropriate, we undertook post hoc sensitivity analyses in our clinical effectiveness to check the robustness of our findings.

A limitation of our work, inherent to all systematic reviews, is publication bias. Methods for detecting publication bias in NMAs are still in development, and we did not have enough studies in any one comparison to test for small-study bias. This may be especially relevant since many of the early trials of IFN and GA for MS were small trials.

Another important limitation was the selective and inconsistent reporting of outcomes. For example, one of the reasons we did not undertake a meta-analysis of time to first relapse estimates is that there was inconsistent and often poor reporting, especially across multiple reports of the same study, which prevented imputation of hazard ratios. This was especially a problem with findings relating to MS symptoms and quality of life in individual trials, where findings were often reported as significance thresholds (e.g. $p<0.05$, or $p>0.05$) without effect magnitude.

Finally, we elected to include only studies and arms of studies examining interventions within their marketing authorisations. That is, we did not include study arms examining additional, non-licenced doses of the study drugs. While this meant that our analysis perhaps more closely represents clinical practice today, it does mean that additional information on the effectiveness of these drugs was not included in the analysis. Moreover, because our scope was limited to IFN and GA, we could not include information from additional newer drugs. This was a limitation in that additional trials would have strengthened the resultant study networks analysed (see below).

17.2.2 In relation to synthesis methods and statistical analyses of clinical effectiveness

For most outcomes, we were able to complement narrative syntheses with pairwise and network meta-analyses, but this was not always possible (e.g. magnitude of EDSS change in RRMS, or relapse severity in SPMS).

Our analyses also had several statistical advantages. In examining the effect of IFN and GA on disability progression, we used time to event outcomes and hazard ratios instead of calculating risk ratios or odds ratios at different follow-up points. Thus, trial findings were reported at their fullest 'maturity'[163] and all relevant data

were included. Though hazard ratios are not immune to selection bias, they may be less likely to depend on the time points chosen in the analysis than relative risks.

Related to our decision to use hazard ratios, we were able to use the full complement of methods to estimate effect sizes from available study-level data. This meant that more studies were included in our analyses than would otherwise have been the case. However, this may also be a limitation in that indirect methods (e.g. integrating underneath the survivor function to estimate cumulative hazard) are not preferable to direct estimates of intervention effects.

Our decision to estimate NMAs with effects for relapse rate, relapse severity and time to confirmed disability progression across time points was justified in that rate ratios for relapses account for person-years, and thus under an assumption of a constant rate should not depend on time to follow-up. Similarly, hazard ratios represent 'instantaneous' risk and thus, under a proportional hazards assumption, should not depend on time to follow-up. But this decision is not without its drawbacks. On the one hand, we were unable to verify empirically whether HRs and RRs were time-varying due to few comparisons on every node of the study networks. On the other hand, we judged that stratifying analyses by time to follow-up would have resulted in excessively sparse networks that would have been difficult to interpret collectively. Thus, our decision to pool study estimates across follow-up times for analyses of clinical outcomes was both a strength and a potential limitation. Notably, we did stratify analyses by time to follow-up in NMAs of discontinuations due to AEs, because we judged that the only feasible estimator in these analyses was the risk ratio.

Finally, one issue inherent to the clinical effectiveness evidence was that different sources of bias were spread differentially throughout the networks. Most notably, trials involving active vs. active comparisons in RRMS were frequently open-label in design. Thus, participants were aware of the drugs they were receiving. This might have posed greater risk for unblinding of outcome assessors than in ostensibly double-blinded trials.

17.2.3 In relation to synthesis methods and statistical analyses of cost effectiveness

One strength of our analysis was the considerable effort made to identify the best available evidence on model input parameters and model structure. In addition, several of our analyses were based on estimates derived from our systematic review and NMAs on clinical effectiveness, which were themselves based on rigorous search and analysis. We also appraised the RSS model and were then able modify asssumptions that we found concerning. Our extensive sensitivity analyses, both deterministic and probabilistic, allowed us to explore a variety of data sources. Finally, we were able to develop a de novo model structure for a hypothetical cohort of people with CIS.

However, one limitation of the analyses undertaken with data from the NMAs is that they at times relied on sparse networks with uneven risk of bias throughout the network. For example, analyses relating to pegylated IFN β-1a 125 μg (Plegridy) relied on one trial that was not connected to any other trials except by a placebo comparator. Thus, any issues with the estimates derived from our review of clinical effectiveness would have been propagated through the analysis of cost effectiveness.

Another limitation was the difficulty of estimating uncertainty for key parameters in the RSS model. In conducting our probabilistic sensitivity analysis based on our modified RSS model, we used uncertainty estimates for the annualised relapse rates derived from the clinical effectiveness review rather than from the estimate in the RSS itself.

Additionally, our findings were restricted to IFN and GA. It is possible that other RRMS or CIS treatments may have better cost effectiveness.

17.2.4 In relation to choice of base case for economic analysis

As noted above, we used as our base case a modified version of the RSS model as our base case. While cost-effectiveness estimates derived from the RSS model and from the review of clinical effectiveness evidence have comparative strengths and weaknesses, we decided on balance that estimates from the RSS model provided the best estimate of cost effectiveness. While the RSS model relied on a historical (i.e. non-contemporaneous) comparator and was thus non-randomised evidence likely prone to selection bias, we believed that the long-term follow-up, relevance to the NHS and to current clinical practice, and rigorous methods used in collecting and reporting data made it the best choice as a base case. In contrast, while the estimates from our review of clinical effectiveness were derived from randomised evidence, the predominantly short-term nature of the included trials, the high risk of other biases (including due to manufacturer sponsorship, and due to open-label active vs. active trials), the imbalance of these risks of bias across the networks of evidence, and the sparseness of evidence for some DMTs raised doubts about its value as a base case. While both sources of evidence were at high risk of bias, we believed that the RSS model best represented a relevant base case for MS treatment in the NHS.

17.3 *In relation to the views of patients and carers*

The submission from the Multiple Sclerosis Society supports the use of DMTs for MS including the use of IFN-β and glatiramer acetate based on the results of the RSS, clinical trial data and research on perspectives gathered by the society. These perspectives included several patient case studies reporting that DMTs had significantly reduced or prevented relapses and symptoms, enabling patients to lead more independent active lifestyles. The treatment had improved their mental health by reducing their fear of future relapses and increasing feelings of confidence and control. The MS Society noted that DMTs promote patient choice by allowing individuals to weigh up lower risk moderate efficacy versus higher risk and higher efficacy treatments. The range of treatment options allows for the differential way MS can affect individuals and their differential responses to DMTs.

The current report supports that DMTs are clinically and cost effective for the treatment of both RRMS and CIS, with glatiramer acetate being most effective for annualised relapse rate.

17.4 *In relation to prior research*

Our findings updated prior reviews, though comparability of findings is limited. As compared to Clerico et al. 2008,[154] the key review we used for CIS, we only included trials reporting IFN and GA as used within their marketing authorisation. We included several trials published after their review (Pakdaman 2007,[171] PreCISe 2009,[172] and REFLEX 2012[173]). We were also able to use NMAs for time to clinically definite MS to examine the relative effectiveness of drugs. Our findings substantially update their review and provide additional evidence of the effectiveness of IFN and GA for CIS.

As compared to Tramacere et al. 2015,[155] which broadly examined immunomodulators and immunosuppressants for RRMS, we only included trials examining IFN and GA against each other and against a no-treatment comparator, and only doses and formulations within marketing authorisation. Because they included studies across drugs and because they used risk ratios as the sole outcome estimator, our analyses and theirs are largely incommensurate. However, our analyses for discontinuation due to AEs agreed with theirs in that neither review suggested any one drug had a significant effect on discontinuation due to AEs relative to placebo.

17.5 *Implications for practice*

We did not include formulations outside the recommended usage in the UK. In addition, our study was specifically designed to exclude the clinical and cost-effectiveness of newer MS treatments such as newer monoclonal antibodies (alemtuzumab, daclizumab). This review should be considered in conjunction with newer NICE and other guidance on the clinical and cost-effectiveness of these agents.

Our findings agree with the ABN guidelines[262] in that the guidelines classify IFN-β and GA as drugs of 'moderate efficacy'. Our analysis does suggest that these drugs are effective in controlling relapse rate and disability progression.

17.6 *Protocol variations*

We originally presented our protocol at a Stakeholder Information Meeting and subsequently registered this protocol in PROSPERO. Our methods as conducted differed slightly from the protocol in the following ways.

In our clinical effectiveness systematic reviews, we did not use data from the RSS as a prior distribution in a Bayesian meta-analysis. This was because of the mismatch between the time to follow-up in the trials and the time to follow-up in the year 10 RSS data, and the different analytic methods used between the trials and the RSS analyses. Subsequently, we did not use a Bayesian methodology in our NMA models. We also decided to exclude trials that only examined IFN or GA doses outside their marketing authorisation. Finally, we did not search the database 'Current Clinical Trials', as this would have duplicated searches already covered.

While these were not strictly variations from our protocol, we subsequently refined our definition of several outcomes. We operationalised relapse severity as rate ratios of relapses graded as moderate or severe, or as rate

ratios of relapses requiring steroid treatment. We also took advice from our clinical consultants and examined combined clinical-MRI outcomes for freedom from disease activity.

17.7 *Recommendations for future research*

One key flaw in the assembled clinical effectiveness evidence was the lack of long-term follow-up. The RSS was designed to collect longer-term observational data in this area, however a large-scale, longitudinal randomised trial comparing active first-line agents would contribute meaningfully towards resolving uncertainty about the relative benefits of different IFN or GA formulations. We note that the submission from the MS Society identified a similar research priority. It may be that using blinded adjudicator panels for relapses and disease progression could attenuate the risk of bias accruing to an open-label trial. Because of this lack of long-term follow-up, DMT trials are generally not informative on whether drugs delay progression to SPMS.

There is also a need to reach consensus on the different stages of MS, the distinctiveness of which are open to question. Related to this, there is a need to understand how changing imaging technologies and changes in clinical practice (e.g. changes in the classification of CIS under new diagnostic criteria) impact diagnosis and management. From an epidemiological perspective, a priority for research should be to understand how and under what circumstances MS progresses through different types (e.g. from CIS to RRMS and then SPMS)? We note that the submission from the MS Society identified a similar research priority. Related to this, there is a need to develop outcomes that meaningfully reflect MS symptoms, such as disability progression. Many have enumerated the issues with the EDSS scale, and it is possible that time to progression sustained at 3 months does not reliably capture disability progression, given variable time in recovery from relapses.

Another priority for research is to focus on patients who are not on the lower end of the EDSS scale. This may be of value for populations with MS as survival and advances in support and aids for those with disabilities improve.

Additionally, valuation of health benefits continues to be a vexing area for MS. This was an issue identified in the original guidance resulting from TA32. One possible way to address this issue is through systematic review and metasynthesis of qualitative studies relating to the lived experience of MS, with particular attention to the dominant clinical features, e.g. relapse and disability progression. This could provide a basis for understanding of relefvant health states and benefits, which more closely matches the preferences and experiences of people living with the target condition.

Finally, above and beyond the population average evidence that DMTs reduce relapse rate, there is a need to understand who responds best to DMTs; especially who does not respond to IFN or GA early on, to enable more targeted therapeutic decisions. Though several trials included in our clinical effectiveness review used subgroup analyses based, for example, on presenting lesions or demographic characteristics, a more fine-grained understanding can help patients and clinicians make better-informed decisions.

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19 **Appendix 1: Searches undertaken for systematic reviews of clinical effectiveness**

1.2 Multiple Sclerosis searches

1.2.1 Review articles checked for both included studies and studies excluded with reasons

Cochrane Reviews: Filippini 2013, Tramacere 2015

Other systematic reviews: Tolley 2015

1.2.2 Medline (Ovid), searched 27/01/2016

Exact database: Ovid MEDLINE(R) 1946 to January Week 2 2016

1	exp Multiple Sclerosis/	46764
2	multiple sclerosis.tw.	49799
3	1 or 2	57188
4	randomized controlled trial.pt.	403450
5	controlled clinical trial.pt.	89937
6	clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/	35683
7	(random* or "controlled trial*" or "clinical trial*" or rct).tw.	873696
8	4 or 5 or 6 or 7	1065585
9	Animals/	5743229
10	Humans/	15593111
11	9 not 10	4140900
12	8 not 11	964542
13	3 and 12	4921
14	(metaanalys* or "meta analys*" or "meta-analys*").tw.	69140
15	"systematic* review*".mp.	61461
16	meta analysis.pt.	60117
17	14 or 15 or 16	122687
18	3 and 17	635

19	limit 3 to systematic reviews	1136
20	18 or 19	1233
21	13 or 20	5694
22	limit 21 to yr="2012 -Current"	1545

1.2.3 Medline In-Process & Other Non-Indexed Citations (Ovid), searched 27/01/2016

Actual database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 26, 2016

1	multiple sclerosis.tw.	4892
2	(random* or "controlled trial*" or "clinical trial*" or rct).tw.	108317
3	1 and 2	610
4	(metaanalys* or "meta analys*" or "meta-analys*").tw.	14094
5	"systematic* review*".tw.	15189
6	4 or 5	23570
7	1 and 6	118
8	3 or 7	684
9	limit 8 to yr="2012 -Current"	563

1.2.4 Embase (Ovid), searched 27/01/2016

Actual database: Embase 1974 to 2016 Week 04

1	*multiple sclerosis/	64389
2	multiple sclerosis.tw.	80240
3	1 or 2	87466
4	randomized controlled trial/	392971
5	(random* or "controlled trial*" or "clinical trial*" or rct).tw.	1306964
6	4 or 5	1388801

7	3 and 6	8813
8	meta analysis/	103317
9	(metaanalys* or "meta analys*" or "meta-analys*").tw.	110582
10	"systematic review"/	100520
11	"systematic* review*".tw.	96391
12	8 or 9 or 10 or 11	222654
13	3 and 12	1280
14	7 or 13	9616
15	limit 14 to yr="2012 -Current"	4527
16	limit 15 to (conference abstract or conference paper or conference proceeding)	2363
17	15 not 16	2164

1.2.5 Cochrane Library (Wiley), searched 27/01/2016

ID	Search	Hits
#1	MeSH descriptor: [Multiple Sclerosis] explode all trees	1916
#2	multiple sclerosis:ti,ab,kw (Word variations have been searched)	4921
#3	#1 or #2	4925
#4	#1 or #2 Publication Year from 2012 to 2016	1861

Distribution of results from Cochrane Library search:

- Cochrane Reviews (44)
  - Reviews (39)
  - Protocols (5)
- Other Reviews (DARE) (60)
- Trials (CENTRAL) (1702)
- Methods Studies (0)
- Technology Assessments (HTA Database) (28)
- Economic Evaluations (27)
- Cochrane Groups (0)

1.2.6 Science Citation Index (Web of Knowledge), searched 27/01/2016

# 11	3,248	#9 not #10

		Indexes=SCI-EXPANDED Timespan=All years
# 10	237	(#9) *AND* DOCUMENT TYPES: (Meeting Abstract OR Proceedings Paper) *Indexes=SCI-EXPANDED Timespan=All years*
# 9	3,485	#8 *Indexes=SCI-EXPANDED Timespan=2012-2016*
# 8	9,263	#7 OR #6 *Indexes=SCI-EXPANDED Timespan=All years*
# 7	1,326	#5 AND #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 6	8,425	#2 AND #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 5	216,848	#4 OR #3 *Indexes=SCI-EXPANDED Timespan=All years*
# 4	166,410	TS=(metaanalys* or meta-analys* or (meta NEAR/1 analys*)) *Indexes=SCI-EXPANDED Timespan=All years*
# 3	80,440	TS=(systematic* NEAR/1 review*) *Indexes=SCI-EXPANDED Timespan=All years*
# 2	1,388,789	TS=(random* or (clinical NEAR/1 trial*) or (controlled NEAR/1 trial*) or rct) *Indexes=SCI-EXPANDED Timespan=All years*
# 1	85,913	TS="multiple sclerosis" *Indexes=SCI-EXPANDED Timespan=All years*

1.2.7 UKCRN, searched 27/01/2016

Search:

Keyword: multiple sclerosis

AND

Status: closed

AND

Study Design: Interventional

Total: 41

1.2.8 Cochrane MS group register of trials, searched 26/02/2016

Keywords

(interferon*) OR (interferon beta) OR (beta-1 interferon) OR (beta 1 interferon) OR (interferon beta-1*) OR (rebif) OR (avonex) OR (Betaseron) OR (beta-seron) OR (betaferon) OR (beta-IFN-1*) OR (interferon beta-1*) OR (Interferon-beta*) OR (interferon beta*) OR (recombinant interferon beta-1*) OR (beta-1a interferon) OR (beta 1a interferon) OR (interferon beta-1a) OR (beta 1b interferon) OR (interferon beta1b) OR (IFNb-1b) OR (IFNbeta-1b) OR (interferon beta-1b) OR (copolymer-1) OR (cop-1) OR (copaxone) OR (glatiramer acetate) OR (cpx) OR (cop1) OR (copolymer) OR (glatiramer) OR (polyethylene glycol-interferon-beta-1a) OR (PEG IFN-beta-1a) OR (Pegylated interferon beta-1a) OR (Ocrelizumab)

AND

(relapsing remitting) OR (relapsing-remitting) OR (remitting-relapsing) OR (remitting relapsing) OR (secondary progressive)

Total: 265

1.3 Clinically Isolated Syndrome searches

1.3.1 Review articles checked for included studies and studies excluded with reasons

Cochrane Reviews: Clerico 2008

1.3.2 Medline (Ovid), searched 09/02/2016

Exact database: Ovid MEDLINE(R) 1946 to January Week 4 2016

1	Demyelinating Diseases/	10446
2	Myelitis, Transverse/	1153
3	exp Optic Neuritis/	6737
4	Encephalomyelitis, Acute Disseminated/	1689
5	Demyelinating Autoimmune Diseases, CNS/	316
6	demyelinating disease*.tw.	4725
7	transverse myelitis.tw.	1356
8	neuromyelitis optica.tw.	1735
9	optic neuritis.tw.	3792
10	acute disseminated encephalomyelitis.tw.	1098

11	devic.tw.	107
12	ADEM.tw.	574
13	demyelinating disorder.tw.	335
14	clinically isolated syndrome.tw.	644
15	first demyelinating event.tw.	68
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	24564
17	randomized controlled trial.pt.	404260
18	(random* or "controlled trial*" or "clinical trial*" or rct).tw.	875933
19	17 or 18	975513
20	(metaanalys* or "meta analys*" or "meta-analys*").tw.	69583
21	"systematic* review*".mp.	61879
22	meta analysis.pt.	60490
23	20 or 21 or 22	123386
24	16 and 19	661
25	16 and 23	74
26	24 or 25	713

1.3.3 Medline In-Process & Other Non-Indexed Citations (Ovid), searched 09/02/2016

Actual database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations February 08, 2016

1	demyelinating disease*.tw.	405
2	transverse myelitis.tw.	148
3	neuromyelitis optica.tw.	317
4	optic neuritis.tw.	356
5	acute disseminated encephalomyelitis.tw.	128

6	devic.tw.	6
7	ADEM.tw.	83
8	demyelinating disorder.tw.	55
9	clinically isolated syndrome.tw.	115
10	first demyelinating event.tw.	6
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	1249
12	(random* or "controlled trial*" or "clinical trial*" or rct).tw.	108853
13	(metaanalys* or "meta analys*" or "meta-analys*").tw.	14202
14	"systematic* review*".tw.	15358
15	13 or 14	23763
16	11 and 12	63
17	11 and 15	17
18	16 or 17	73

1.3.4 Embase (Ovid), searched 09/02/2016

Actual database: Embase 1974 to 2016 Week 06

1	demyelinating disease/	12216
2	myelitis/	6771
3	optic neuritis/	6979
4	acute disseminated encephalomyelitis/	1378
5	myelooptic neuropathy/	4897
6	demyelinating disease*.tw.	7443
7	transverse myelitis.tw.	2462
8	neuromyelitis optica.tw.	4162

9	optic neuritis.tw.	6551
10	acute disseminated encephalomyelitis.tw.	1762
11	devic.tw.	229
12	ADEM.tw.	1211
13	demyelinating disorder.tw.	624
14	clinically isolated syndrome.tw.	1758
15	first demyelinating event.tw.	159
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	34739
17	randomized controlled trial/	394252
18	(random* or "controlled trial*" or "clinical trial*" or rct).tw.	1311256
19	17 or 18	1393301
20	meta analysis/	103826
21	(metaanalys* or "meta analys*" or "meta-analys*").tw.	111288
22	"systematic review"/	101172
23	"systematic* review*".tw.	97114
24	20 or 21 or 22 or 23	223913
25	16 and 19	1706
26	16 and 24	322
27	25 or 26	1914
28	limit 27 to (conference abstract or conference paper or conference proceeding or "conference review")	493
29	27 not 28	1421
30	limit 29 to human	1340
31	limit 29 to animals	59
32	31 not 30	59

33	29 not 32	1362

1.3.5 Cochrane Library (Wiley), searched 09/02/2016

ID	Search	Hits
#1	MeSH descriptor: [Multiple Sclerosis] explode all trees	2125
#2	multiple sclerosis:ti,ab,kw (Word variations have been searched)	5081
#3	#1 or #2	5081
#4	first or early or "clinically isolated":ti,ab,kw (Word variations have been searched)	166444
#5	#3 and #4	1037
#6	MeSH descriptor: [Demyelinating Diseases] this term only	71
#7	MeSH descriptor: [Myelitis, Transverse] this term only	6
#8	MeSH descriptor: [Optic Neuritis] explode all trees	95
#9	MeSH descriptor: [Encephalomyelitis, Acute Disseminated] this term only	3
#10	MeSH descriptor: [Demyelinating Autoimmune Diseases, CNS] this term only	2
#11	demyelinating next disease*:ti,ab,kw (Word variations have been searched)	186
#12	transverse myelitis:ti,ab,kw (Word variations have been searched)	14
#13	neuromyelitis optica:ti,ab,kw (Word variations have been searched)	20
#14	optic neuritis:ti,ab,kw (Word variations have been searched)	220
#15	acute disseminated encephalomyelitis:ti,ab,kw (Word variations have been searched)	13
#16	devic:ti,ab,kw (Word variations have been searched)	2
#17	ADEM:ti,ab,kw (Word variations have been searched)	4
#18	demyelinating disorder:ti,ab,kw (Word variations have been searched)	49
#19	clinically isolated syndrome:ti,ab,kw (Word variations have been searched)	114
#20	first demyelinating event:ti,ab,kw (Word variations have been searched)	72
#21	single demyelinating event:ti,ab,kw (Word variations have been searched)	9
#22	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21	1436

Distribution of results from Cochrane Library search:

- Cochrane Reviews (41)

- Other Reviews (8)
- Trials (1369)
- Methods Studies (4)
- Technology Assessments (6)
- Economic Evaluations (8)
- Cochrane Groups (0)

1.3.6 Science Citation Index (Web of Knowledge), searched 10/02/2016

# 19	1,030	#17 NOT #18 Indexes=SCI-EXPANDED Timespan=All years
# 18	93	(#17) AND DOCUMENT TYPES: (Meeting Abstract OR Proceedings Paper) Indexes=SCI-EXPANDED Timespan=All years
# 17	1,123	#16 OR #15 Indexes=SCI-EXPANDED Timespan=All years
# 16	122	#14 AND #10 Indexes=SCI-EXPANDED Timespan=All years
# 15	1,039	#11 AND #10 Indexes=SCI-EXPANDED Timespan=All years
# 14	216,848	#13 OR #12 Indexes=SCI-EXPANDED Timespan=All years
# 13	167,718	TS=(metaanalys* or meta-analys* or (meta NEAR/1 analys*)) Indexes=SCI-EXPANDED Timespan=All years
# 12	80,440	TS=(systematic* NEAR/1 review*) Indexes=SCI-EXPANDED Timespan=All years
# 11	1,393,569	TS=(random* or (clinical NEAR/1 trial*) or (controlled NEAR/1 trial*) or rct) Indexes=SCI-EXPANDED Timespan=All years
# 10	16,869	#9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 Indexes=SCI-EXPANDED Timespan=All years
# 9	96	TS="first demyelinating event" Indexes=SCI-EXPANDED Timespan=All years
# 8	1,195	TS="clinically isolated syndrome" Indexes=SCI-EXPANDED Timespan=All years
# 7	687	TS="ADEM" Indexes=SCI-EXPANDED Timespan=All years
# 6	462	TS="devic" Indexes=SCI-EXPANDED Timespan=All years

# 5	1,596	TS=("acute disseminated" NEAR/1 encephalomyelitis) Indexes=SCI-EXPANDED Timespan=All years
# 4	3,531	TS="neuromyelitis optica" Indexes=SCI-EXPANDED Timespan=All years
# 3	4,584	TS="optic neuritis" Indexes=SCI-EXPANDED Timespan=All years
# 2	1,699	TS=(transverse NEAR/1 myelitis) Indexes=SCI-EXPANDED Timespan=All years
# 1	6,786	TS=(demyelinating NEAR/2 (disease* OR disorder*)) Indexes=SCI-EXPANDED Timespan=All years

1.3.7 Cochrane MS group register of trials, searched 26/02/2016

Keywords for CIS

(interferon*) OR (interferon beta) OR (beta-1 interferon) OR (beta 1 interferon) OR (interferon beta-1*) OR (rebif) OR (avonex) OR (Betaseron) OR (beta-seron) OR (betaferon) OR (beta-IFN-1*) OR (interferon beta-1*) OR (Interferon-beta*) OR (interferon beta*) OR (recombinant interferon beta-1*) OR (beta-1a interferon) OR (beta 1a interferon) OR (interferon beta-1a) OR (beta 1b interferon) OR (interferon beta1b) OR (IFNb-1b) OR (IFNbeta-1b) OR (interferon beta-1b) OR (copolymer-1) OR (cop-1) OR (copaxone) OR (glatiramer acetate) OR (cpx) OR (cop1) OR (copolymer) OR (glatiramer) OR (polyethylene glycol-interferon-beta-1a) OR (PEG IFN-beta-1a) OR (Pegylated interferon beta-1a) OR (Ocrelizumab)

AND

clinically isolated syndrome* OR first demyelinating event* OR first demyelinating episode OR first demyelinating attack OR First event OR first episode OR first clinical episode OR single clinical episodes OR first demyelinating event/* OR clinically isolated syndrome*

Total: 188

1.4 Additional searches for both Multiple Sclerosis and Clinically Isolated Syndrome

1.4.1 ClinicalTrials.gov, searched 03/05/2016

Advanced Search

182 studies found for: Interventional Studies | multiple sclerosis OR clinically isolated syndrome OR CNS demyelinating OR transverse myelitis OR neuromyelitis optica | interferon OR glatiramer OR betaferon OR betaseron OR avonex OR plegridy OR rebif OR extavia OR copaxone | Phase 2, 3, 4

WHO ICTRP, searched 14/07/2016

(Relapsing Remitting Multiple Sclerosis OR RRMS OR clinically isolated syndrome OR CNS demyelinating OR transverse myelitis OR neuromyelitis optica) in the Condition

AND

(interferon OR glatiramer OR betaferon OR betaseron OR avonex OR plegridy OR rebif OR extavia OR copaxone) in the Intervention

588 records for 175 trials found

Websites

	Name (Brand)	**Website address**	**Date searched**
Companies sponsors	Bayer (BETAFERON)	http://www.bayer.co.uk/ http://pharma.bayer.com/	26/04/2016
	Biogen Idec (AVONEX and PLEGRIDY)	https://www.biogen-international.com/ https://www.biogen.uk.com/	28/04/2016
	Merck Serono (REBIF)	http://biopharma.merckgroup.com/en/index.html	
	Novartis (EXTAVIA)	https://www.novartis.com https://www.novartis.co.uk/	28/04/2016
	Teva Pharmaceuticals (COPAXONE)	http://www.tevapharm.com/research_development/ http://www.tevauk.com/	01/05/2016
Patient carer groups	Brain and Spine Foundation	http://www.brainandspine.org.uk	01/05/2016
	Multiple Sclerosis National Therapy Centres	http://www.msntc.org.uk	01/05/2016
	MS UK	http://www.ms-uk.org	01/05/2016
	Multiple Sclerosis Society	https://www.mssociety.org.uk	01/05/2016
	Multiple Sclerosis Trust	https://www.mstrust.org.uk	01/05/2016
	Neurological Alliance	http://www.neural.org.uk	01/05/2016
	The Brain Charity	http://www.thebraincharity.org.uk	01/05/2016

	(formally known as Neurosupport)		
	Sue Ryder	http://www.sueryder.org	01/05/2016
Professional groups	Association of British Neurologists	http://www.theabn.org	01/05/2016
	British Neuropathological Society	http://www.bns.org.uk	01/05/2016
	Institute of Neurology	https://www.ucl.ac.uk/ion https://www.ucl.ac.uk/ion/departments/neuroinflammation http://discovery.ucl.ac.uk	01/05/2016 05/05/2016 10/05/2016
	Primary Care Neurology Society	http://www.p-cns.org.uk	01/05/2016
	Therapists in MS	https://www.mstrust.org.uk/health-professionals/professional-networks/therapists-ms-tims/research	01/05/2016
	United Kingdom Multiple Sclerosis Specialist Nurse Association	http://www.ukmssna.org.uk	01/05/2016
Relevant research groups	Brain Research Trust	http://www.brt.org.uk/research	01/05/2016
	British Neurological Research Trust	http://www.ukscf.org http://www.ukscf.org/about-us/bnrt.html	01/05/2016
	Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System	http://www.cochranelibrary.com http://msrdcns.cochrane.org/our-reviews	01/05/2016
	National Institute for Health Research	http://www.nihr.ac.uk/research/ http://www.nihr.ac.uk/industry/ http://www.nihr.ac.uk/policy-and-standards/	01/05/2016

20 Appendix 2: Sample data extraction sheet for clinical effectiveness reviews

Study acronym/ID:

Name of the reviewer:

Number of publications extracted:

Study details
Study ID (Endnote):
First author surname:
Year of publication:
Country:
Study setting:
Number of centres:
Study period:
Follow up period:
Funding:
Subtypes of MS included:
Definition of CIS used:
Aim of the study
Participants
Inclusion criteria:
Exclusion criteria:
Total number of participants:
Sample attrition/drop out:
Number of participants analysed:
Characteristics of participants
Mean age:
Mean sex:
Race:

EDSS score at baseline: *Relapse rate at baseline:* *Time from diagnosis of MS:* *Other clinical features of MS:*
Intervention (repeat if necessary for multiple intervention arms)
Type of drug: Method of administration: Dose: Frequency: Drug indication as stated:
Best supportive care as described
Outcomes
Primary outcomes: Secondary outcomes: Method of assessing outcomes: If freedom from disease activity is an outcome, how was it defined?: Timing of assessment: Adverse event: Health related quality of life: Yes/No; which measures used?

Number of participants	**Intervention**	**Comparator, if present**
Screened		
Excluded		
Randomised/Included		
Missing participants (people who LTFU during the trial)		
Withdrawals (all who did not complete, including LTFU)		
Patient baseline characteristics	**Intervention:**	**Comparator:**
Age (years)		

Sex		
Race		
EDSS score at baseline		
Relapse rate at baseline		
Time from diagnosis of MS		
Outcome data: relapses, disability	**Intervention**	**Comparator, if present**
Relapse rate		
Severity of relapse		
Disability, including as measured by the Expanded Disability Status Scale		
Freedom from disease activity		
Outcome data: MS symptoms (add rows as necessary)	**Intervention**	**Comparator, if present**
Fatigue		
Visual disturbance		
Cognition		
Outcome data: additional outcomes	**Intervention**	**Comparator, if present**
Mortality		
Health-related quality of life		
Progression to MS (CIS only)		
Discontinuation due to neutralising antibody formation		
Adverse events (add rows as necessary for AEs reported in RCTs)	**Intervention**	**Comparator, if present**

Risk of bias assessment

Random sequence generation	HIGH RISK UNCLEAR LOW RISK
Description in trial	
Allocation concealment	HIGH RISK UNCLEAR LOW RISK
Description in trial	
Blinding of participants and personnel	HIGH RISK UNCLEAR LOW RISK
Description in trial	
Blinding of outcome assessment	HIGH RISK UNCLEAR LOW RISK

Description in trial	
Incomplete outcome data	HIGH RISK UNCLEAR LOW RISK
Description in trial	
Selective reporting	HIGH RISK UNCLEAR LOW RISK
Description in trial	
Other sources of bias	HIGH RISK UNCLEAR LOW RISK
Description in trial	

Authors conclusion
Reviewer's conclusion

21 **Appendix 3: Documentation of excluded studies**

Table 88: Frequency of reasons for study exclusion in the clinical effectiveness review

Reasons	**Number**
Conference abstract	10
DMT used with a non-recommended dose regimen	15
Irrelevant comparator/ intervention	58
Irrelevant comparator/ intervention/outcome	1
Irrelevant comparator/ intervention/population	1
Irrelevant comparator/ intervention/ study type	4
Irrelevant comparator/population	5
Irrelevant comparator/population/study type	1
Irrelevant intervention	7
Irrelevant intervention/population	2
Irrelevant intervention/ study type	8
Irrelevant outcome	13
Irrelevant outcome/study type	2
Irrelevant outcome/study type/population	1
Irrelevant population	11
Irrelevant population/outcomes	1
Irrelevant population/study type	7
Irrelevant study type	24
No results are provided, refers to results from a conference abstract	1
Not a primary research study	3
Not English language	1
Protocol only with no results	15
Systematic reviews that didn’t enable to locate further primary studies	18
Study evaluating a treatment-switch strategy	1
Use of an unlicensed drug formulation	1
Total	**211**

Table 89: Studies excluded from the clinical effectiveness review with reasons

Reference	Reason for exclusion
(2008) "Glatiramer acetate (Copaxone) for a single demyelinating event with an active inflammatory process (Structured abstract)." Health Technology Assessment Database.	Not a primary research study
(2011) "Laquinimod for multiple sclerosis: relapsing-remitting - first or second line (Structured abstract)." Health Technology Assessment Database.	Not a primary research study
(2011) "Teriflunomide for relapsing multiple sclerosis (MS) - first line (Structured abstract)." Health Technology Assessment Database.	Not a primary research study
Above trial (Bayer) NCT 00206648	Study evaluating a treatment-switch strategy
Aggarwal, S., S. Kumar and H. Topaloglu (2015). "Comparison of Network Meta-Analysis and Traditional Meta-Analysis for Prevention of Relapses In Multiple Sclerosis." Value in Health 18(7): A660.	Conference abstract
Agius, M., X. Meng, P. Chin, A. Grinspan and R. Hashmonay (2014). "Fingolimod therapy in early multiple sclerosis: an efficacy analysis of the TRANSFORMS and FREEDOMS studies by time since first symptom." CNS Neuroscience & Therapeutics 20(5): 446-451.	Irrelevant comparator/ intervention
Aivo, J., B. M. Lindsrom and M. Soilu-Hanninen (2012). "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 (no pagination)(802796).	Irrelevant comparator/ intervention
Andersen, O., Elovaara, I., Farkkila, M., Hansen, H. J., Mellgren, S. I., Myhr, K. M., . . . Soelberg Sorensen, P. (2004). Multicentre, randomised, double blind, placebo controlled, phase III study of weekly, low dose, subcutaneous interferon beta-1a in secondary progressive multiple sclerosis. J Neurol Neurosurg Psychiatry, 75(5), 706-710.	DMT used with a non-recommended dose regimen
Andersen, O., I. Elovaara, M. Färkkilä, H. J. Hansen, S. I. Mellgren, K. M. Myhr, M. Sandberg-Wollheim and P. Soelberg Sørensen (2004) "Multicentre, randomised, double blind, placebo controlled, phase III study of weekly, low dose, subcutaneous interferon beta-1a in secondary progressive multiple sclerosis." Journal of neurology, neurosurgery, and psychiatry 75, 706-710.	DMT used with a non-recommended dose regimen
Anderson, G., D. Meyer, C. E. Herrman, C. Sheppard, R. Murray, E. J. Fox, J. Mathena, J. Conner and P. O. Buck (2010) "Tolerability and safety of novel half milliliter formulation of glatiramer acetate for subcutaneous injection: an open-label, multicenter, randomized comparative study." Journal of neurology 257, 1917-1923 DOI: 10.1007/s00415-010-5779-x.	Use of an unlicensed drug formulation
Anonymous (1997). "Visual function 5 years after optic neuritis: experience of the Optic Neuritis Treatment Trial. The Optic Neuritis Study Group." Archives of Ophthalmology 115(12): 1545-1552.	Irrelevant comparator/ intervention
Anonymous (2001). "Early administration of interferon-beta-1a in multiple sclerosis." European Journal of Pediatrics 160(2): 135-136.	Irrelevant study type
Anonymous (2002). "Baseline MRI characteristics of patients at high risk for multiple sclerosis: results from the CHAMPS trial. Controlled High-Risk Subjects Avonex Multiple	Irrelevant outcome

Sclerosis Prevention Study." Multiple Sclerosis 8(4): 330-338.	
Anonymous (2010) "Developing Neuroprotection and Repair Strategies in MS: Phase IIa Randomized, Controlled Trial of Minocycline in Acute Optic Neuritis (ON)." ClinicalTrials Gov, National Institutes of Health [http://www clinicaltrials gov].	Irrelevant intervention
Arnold, D. L., S. Narayanan and S. Antel (2013). "Neuroprotection with glatiramer acetate: evidence from the PreCISe trial." Journal of Neurology 260(7): 1901-1906.	Irrelevant outcome
Ashtari, F., & Savoj, M. R. (2011). Effects of low dose methotrexate on relapsing-remitting multiple sclerosis in comparison to Interferon beta-1alpha: A randomized controlled trial. J Res Med Sci, 16(4), 457-462.	Irrelevant intervention
Balak, D. M., G. J. Hengstman, A. Cakmak and H. B. Thio (2012). "Cutaneous adverse events associated with disease-modifying treatment in multiple sclerosis: a systematic review." Multiple Sclerosis 18(12): 1705-1717.	SRs that didn't enable to locate further primary studies
Balcer, L. J., S. L. Galetta, P. A. Calabresi, C. Confavreux, G. Giovannoni, E. Havrdova, M. Hutchinson, L. Kappos, F. D. Lublin, D. H. Miller, P. W. O'Connor, J. T. Phillips, C. H. Polman, E. W. Radue, R. A. Rudick, W. H. Stuart, A. Wajgt, B. Weinstock-Guttman, D. R. Wynn, F. Lynn, M. A. Panzara, Affirm and S. Investigators (2007). "Natalizumab reduces visual loss in patients with relapsing multiple sclerosis." Neurology 68(16): 1299-1304.	Irrelevant comparator/ intervention
Bandari, D., D. Wynn, T. Miller, B. Singer, S. Wray, R. Bennett, B. Hayward, F. Dangond and L. S. G. RebiQo (2013). "Rebif() 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 2(1): 45-56.	Irrelevant comparator/ intervention
Barkhof, F., C. H. Polman, E. W. Radue, L. Kappos, M. S. Freedman, G. Edan, H. P. Hartung, D. H. Miller, X. Montalban, P. Poppe, M. de Vos, F. Lasri, L. Bauer, S. Dahms, K. Wagner, C. Pohl and R. Sandbrink (2007). "Magnetic resonance imaging effects of interferon beta-1b in the BENEFIT study: integrated 2-year results." Archives of Neurology 64(9): 1292-1298.	Irrelevant outcome
Barkhof, F., M. Rocca, G. Francis, J. H. Van Waesberghe, B. M. Uitdehaag, O. R. Hommes, H. P. Hartung, L. Durelli, G. Edan, O. Fernandez, P. Seeldrayers, P. Sorensen, S. Margrie, M. Rovaris, G. Comi, M. Filippi and G. Early Treatment of Multiple Sclerosis Study (2003). "Validation of diagnostic magnetic resonance imaging criteria for multiple sclerosis and response to interferon beta1a." Annals of Neurology 53(6): 718-724.	DMT used with a non-recommended dose regimen
Beck, R. W. (1995). "The optic neuritis treatment trial: three-year follow-up results." Archives of Ophthalmology 113(2): 136-137.	Irrelevant comparator /intervention/ study type
Beck, R. W. and J. D. Trobe (1995). "The Optic Neuritis Treatment Trial. Putting the results in perspective. The Optic Neuritis Study Group." Journal of Neuro-Ophthalmology 15(3): 131-135.	Irrelevant comparator/ intervention
Berkovich, R., L. Amezcua, D. Subhani and S. Cen (2013) "Pilot study of monthly pulse adrenocorticotropic hormone (ACTH) or methylprednisolone as an add-on therapy to beta-interferons for long-term treatment of multiple sclerosis." Neurology 80, e205-e206.	Irrelevant comparator/ intervention
Bermel, R. A., B. Weinstock-Guttman, D. Bourdette, P. Foulds, X. You and R. A. Rudick (2010) "Intramuscular interferon beta-1a therapy in patients with relapsing-remitting multiple sclerosis: a 15-year follow-up study." Multiple sclerosis (Houndmills, Basingstoke, England) 16, 588-596 DOI: 10.1177/1352458509360549.	Irrelevant comparator/ intervention

Bornstein, M. B., Miller, A., Slagle, S., Weitzman, M., Drexler, E., Keilson, M., . . . et al. (1991). A placebo-controlled, double-blind, randomized, two-center, pilot trial of Cop 1 in chronic progressive multiple sclerosis. Neurology, 41(4), 533-539.	Irrelevant population
Brex, P. A., P. D. Molyneux, P. Smiddy, F. Barkhof, M. Filippi, T. A. Yousry, D. Hahn, Y. Rolland, O. Salonen, C. Pozzilli, C. H. Polman, A. J. Thompson, L. Kappos and D. H. Miller (2001) "The effect of IFNbeta-1b on the evolution of enhancing lesions in secondary progressive MS." Neurology 57, 2185-2190.	Irrelevant outcome
Brunetti, L., M. L. Wagner, M. Maroney and M. Ryan (2013). "Teriflunomide for the treatment of relapsing multiple sclerosis: a review of clinical data." Annals of Pharmacotherapy 47(9): 1153-1160.	Irrelevant intervention/ study type
Calkwood, J., B. Cree, H. Crayton, D. Kantor, B. Steingo, L. Barbato, R. Hashmonay, N. Agashivala, K. McCague, N. Tenenbaum and K. Edwards (2014). "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 14: 220.	Irrelevant comparator/ intervention
Canadian Agency for Drugs and Technologies in Health (2014) "Clinical review report. Teriflunomide (Aubagio - Genzyme Canada) indication: relapsing-remitting multiple sclerosis."	Irrelevant intervention/ study type
Chan, C. K. and D. S. Lam (2004) "Optic neuritis treatment trial:10-year follow-up results." American journal of ophthalmology 138, 695; author reply 695.	Irrelevant study type
Chinea Martinez, A. R., J. Correale, P. K. Coyle, X. Meng and N. Tenenbaum (2014). "Efficacy and safety of fingolimod in Hispanic patients with multiple sclerosis: pooled clinical trial analyses." Advances in Therapy 31(10): 1072-1081.	Irrelevant comparator/ intervention
Clerico, M., G. Contessa and L. Durelli (2007). "Interferon-beta1a for the treatment of multiple sclerosis." Expert Opinion on Biological Therapy 7(4): 535-542.	Irrelevant study type
Clerico, M., I. Schiavetti, S. F. Mercanti, F. Piazza, D. Gned, V. B. Morra, R. Lanzillo, A. Ghezzi, A. Bianchi, G. Salemi, S. Realmuto, P. Sola, F. Vitetta, P. Cavalla, D. Paolicelli, M. Trojano, M. P. Sormani and L. Durelli (2014) "Treatment of relapsing-remitting multiple sclerosis after 24 doses of natalizumab: Evidence from an italian spontaneous, prospective, and observational study (the TY-STOP study)." JAMA Neurology 71, 954-960 DOI: 10.1001/jamaneurol.2014.1200.	Irrelevant study type
Cohen, J. A., A. J. Coles, D. L. Arnold, C. Confavreux, E. J. Fox, H. P. Hartung, E. Havrdova, K. W. Selmaj, H. L. Weiner, E. Fisher, V. V. Brinar, G. Giovannoni, M. Stojanovic, B. I. Ertik, S. L. Lake, D. H. Margolin, M. A. Panzara, D. A. Compston and CARE-MS I investigators (2012). "Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial." Lancet 380(9856): 1819-1828.	Irrelevant comparator/ intervention
Cohen, J. A., Barkhof, F., Comi, G., Hartung, H. P., Khatri, B. O., Montalban, X., . . . Kappos, L. (2010). Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med, 362(5), 402-415. doi: 10.1056/NEJMoa0907839	Irrelevant comparator/ intervention
Cohen, J. A., Coles, A. J., Arnold, D. L., Confavreux, C., Fox, E. J., Hartung, H. P., . . . investigators, C.-M. I. (2012). Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet, 380(9856), 1819-1828. doi: http://dx.doi.org/10.1016/S0140-6736(12)61769-3	Irrelevant comparator/ intervention
Cohen, J. A., F. Barkhof, G. Comi, G. Izquierdo, B. Khatri, X. Montalban, J. Pelletier, B.	Irrelevant

Eckert, D. A. Haring and G. Francis (2013). "Fingolimod versus intramuscular interferon in patient subgroups from TRANSFORMS." Journal of Neurology 260(8): 2023-2032.	comparator/ intervention
Cohen, J. A., G. R. Cutter, J. S. Fischer, A. D. Goodman, F. R. Heidenreich, M. F. Kooijmans, A. W. Sandrock, R. A. Rudick, J. H. Simon, N. A. Simonian, E. C. Tsao and J. N. Whitaker (2002) "Benefit of interferon beta-1a on MSFC progression in secondary progressive MS." Neurology 59, 679-687.	DMT used with a non-recommended dose regimen
Cohen, J. A., G. R. Cutter, J. S. Fischer, A. D. Goodman, F. R. Heidenreich, M. F. Kooijmans, A. W. Sandrock, R. A. Rudick, J. H. Simon, N. A. Simonian, E. C. Tsao and J. N. Whitaker (2002) "Benefit of interferon beta-1a on MSFC progression in secondary progressive MS." Neurology 59, 679-687.	DMT used with a non-recommended dose regimen
Cohen, J. A., M. Rovaris, A. D. Goodman, D. Ladkani, D. Wynn and M. Filippi (2007) "Randomized, double-blind, dose-comparison study of glatiramer acetate in relapsing-remitting MS." Neurology 68, 939-944 DOI: 10.1212/01.wnl.0000257109.61671.06.	Irrelevant comparator/ intervention/ population
Coles, A. J., C. L. Twyman, D. L. Arnold, J. A. Cohen, C. Confavreux, E. J. Fox, H. P. Hartung, E. Havrdova, K. W. Selmaj, H. L. Weiner, T. Miller, E. Fisher, R. Sandbrink, S. L. Lake, D. H. Margolin, P. Oyuela, M. A. Panzara, D. A. Compston and CARE-MS II investigators (2012). "Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial." Lancet 380(9856): 1829-1839.	Irrelevant comparator/ intervention
Coles, A. J., Compston, D. A., Selmaj, K. W., Lake, S. L., Moran, S., Margolin, D. H., . . . Tandon, P. K. (2008). Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med, 359(17), 1786-1801. doi: 10.1056/NEJMoa0802670	Irrelevant comparator/ intervention
Coles, A. J., D. A. Compston, K. W. Selmaj, S. L. Lake, S. Moran, D. H. Margolin, K. Norris and P. K. Tandon (2008) "Alemtuzumab vs. interferon beta-1a in early multiple sclerosis." The New England journal of medicine 359, 1786-1801 DOI: 10.1056/NEJMoa0802670.	Irrelevant comparator/ intervention
Coles, A. J., E. Fox, A. Vladic, S. K. Gazda, V. Brinar, K. W. Selmaj, A. D. Bass, D. R. Wynn, D. H. Margolin, S. L. Lake, S. Moran, J. Palmer, M. S. Smith and D. A. Compston (2011) "Alemtuzumab versus interferon ?-1a in early relapsing-remitting multiple sclerosis: post-hoc and subset analyses of clinical efficacy outcomes." The Lancet. Neurology 10, 338-348 DOI: 10.1016/S1474-4422(11)70020-5.	Irrelevant comparator/ population
Coles, A. J., E. Fox, A. Vladic, S. K. Gazda, V. Brinar, K. W. Selmaj, A. Skoromets, I. Stolyarov, A. Bass, H. Sullivan, D. H. Margolin, S. L. Lake, S. Moran, J. Palmer, M. S. Smith and D. A. Compston (2012). "Alemtuzumab more effective than interferon beta-1a at 5-year follow-up of CAMMS223 clinical trial." Neurology 78(14): 1069-1078.	Irrelevant comparator/ intervention
Coles, A. J., Twyman, C. L., Arnold, D. L., Cohen, J. A., Confavreux, C., Fox, E. J., . . . investigators, C.-M. I. (2012). Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet, 380(9856), 1829-1839. doi: http://dx.doi.org/10.1016/S0140-6736(12)61768-1	Irrelevant comparator/ intervention
Comi, G., F. Barkhof, L. Durelli, G. Edan, O. Fernandez, M. Filippi, H. P. Hartung, O. R. Hommes, P. Seeldrayers and P. Soelberg-Sorensen (1995). "Early treatment of multiple sclerosis with Rebif (recombinant human interferon beta): design of the study." Multiple Sclerosis 1 Suppl 1: S24-27.	Protocol only with no results
Comi, G., Filippi, M., Barkhof, F., Durelli, L., Edan, G., Fernandez, O., . . . Hommes, O. R. (2001). Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. Lancet, 357(9268), 1576-1582.	DMT used with a non-recommended dose regimen

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Comi, G., P. O'Connor, X. Montalban, J. Antel, E. W. Radue, G. Karlsson, H. Pohlmann, S. Aradhye and L. Kappos (2010) "Phase II study of oral fingolimod (FTY720) in multiple sclerosis: 3-year results." Multiple sclerosis (Houndmills, Basingstoke, England) 16, 197-207 DOI: 10.1177/1352458509357065.	Irrelevant comparator/ intervention
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Cooper, K., J. Bryant, P. Harris, E. Loveman, J. Jones and K. Welch. (2013). "Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis: A Single Technology Appraisal. SHTAC report." from http://www.nets.nihr.ac.uk/projects/hta/128301.	Irrelevant comparator/ intervention
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De Stefano, N., G. Comi, L. Kappos, M. S. Freedman, C. H. Polman, B. M. Uitdehaag, B. Hennessy, F. Casset-Semanaz, L. Lehr, B. Stubinski, D. L. Jack and F. Barkhof (2014). "Efficacy of subcutaneous interferon beta-1a on MRI outcomes in a randomised controlled trial of patients with clinically isolated syndromes." Journal of Neurology, Neurosurgery & Psychiatry 85(6): 647-653.	Irrelevant outcome
De Stefano N, Curtin F, Stubinski B, Blevins G, Drulovic J, Issard D, Shotekov P, Gasperini C; IMPROVE Study Investigators. Rapid benefits of a new formulation of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis. Mult Scler. 2010 Jul;16(7):888-92.	Irrelevant outcome
Deisenhammer, F. and H. Hegen (2012). "Alemtuzumab more effective than interferon beta-1a at 5-year follow-up of CAMMS223 clinical trial." Neurology 79(10): 1071-1072.	Irrelevant study type
Del Santo, F., D. Maratea, V. Fadda, S. Trippoli and A. Messori (2012). "Treatments for relapsing-remitting multiple sclerosis: summarising current information by network meta-analysis." European Journal of Clinical Pharmacology 68(4): 441-448.	SRs that didn't enable to locate further primary studies
Edan, G., L. Kappos, X. Montalban, C. H. Polman, M. S. Freedman, H. P. Hartung, D. Miller, F. Barkhof, J. Herrmann, V. Lanius, B. Stemper, C. Pohl, R. Sandbrink, D. Pleimes and B. S. Group (2014). "Long-term impact of interferon beta-1b in patients with CIS: 8-year follow-up of BENEFIT." Journal of Neurology, Neurosurgery & Psychiatry 85(11): 1183-1189.	Irrelevant comparator/ population/ study type
Etemadifar, M., Janghorbani, M., & Shaygannejad, V. (2007). Comparison of interferon beta products and azathioprine in the treatment of relapsing-remitting multiple sclerosis. J Neurol, 254(12), 1723-1728. doi: 10.1007/s00415-007-0637-1	Irrelevant comparator/ intervention
Etemadifar, M., M. Janghorbani and V. Shaygannejad (2007) "Comparison of interferon beta	Irrelevant

products and azathioprine in the treatment of relapsing-remitting multiple sclerosis." Journal of neurology 254, 1723-1728 DOI: 10.1007/s00415-007-0637-1.	comparator/ population
Evidence of interferon beta-1a dose response in relapsing-remitting MS: the OWIMS Study. The Once Weekly Interferon for MS Study Group. (1999). Neurology, 53(4), 679-686.	DMT used with a non-recommended dose regimen
Filippi, M., M. Rovaris, M. Inglese, F. Barkhof, N. Stefano, S. Smith and G. Comi (2004) "Interferon beta-1a for brain tissue loss in patients at presentation with syndromes suggestive of multiple sclerosis: a randomised, double-blind, placebo-controlled trial." Lancet (London, England) 364, 1489-1496 DOI: 10.1016/S0140-6736(04)17271-1.	DMT used with a non-recommended dose regimen
Fox, E., D. Arnold, V. Brinar, J. Cohen, A. Coles and C. Confavreux (2012) "Relapse outcomes with alemtuzumab vs. Rebif(registered trademark) in treatment-naive relapsing-remitting multiple sclerosis (CARE-MS I): Secondary and tertiary endpoints." Neurology 78.	Irrelevant comparator/ intervention
Fox, E., K. Edwards, G. Burch, D. R. Wynn, C. LaGanke, H. Crayton, S. F. Hunter, C. Huffman, E. Kim, L. Pestreich, K. McCague, L. Barbato and E. s. investigators (2014). "Outcomes of switching directly to oral fingolimod from injectable therapies: Results of the randomized, open-label, multicenter, Evaluate Patient OutComes (EPOC) study in relapsing multiple sclerosis." Multiple Sclerosis and Related Disorders 3(5): 607-619.	Irrelevant comparator/ intervention
Fox, R. J., B. A. Cree, J. De Seze, R. Gold, H. P. Hartung, D. Jeffery, L. Kappos, M. Kaufman, X. Montalban, B. Weinstock-Guttman, B. Anderson, A. Natarajan, B. Ticho, P. Duda and Restore (2014). "MS disease activity in RESTORE: a randomized 24-week natalizumab treatment interruption study.[Erratum appears in Neurology. 2015 Feb 24;84(8):862 Note: multiple investigator names added]." Neurology 82(17): 1491-1498.	Irrelevant comparator/ intervention
Fox, R. J., B. A. Cree, J. Sèze, R. Gold, H. P. Hartung, D. Jeffery, L. Kappos, M. Kaufman, X. Montalbán, B. Weinstock-Guttman, B. Anderson, A. Natarajan, B. Ticho, P. Duda and Restore (2014) "MS disease activity in RESTORE: a randomized 24-week natalizumab treatment interruption study." Neurology 82, 1491-1498 DOI: 10.1212/WNL.0000000000000355.	Irrelevant population
Freedman, M. S. (2014). "Evidence for the efficacy of interferon beta-1b in delaying the onset of clinically definite multiple sclerosis in individuals with clinically isolated syndrome." Therapeutic Advances in Neurological Disorders 7(6): 279-288.	Irrelevant intervention/ population
Freedman, M. S., J. S. Wolinsky, B. Wamil, C. Confavreux, G. Comi, L. Kappos, T. P. Olsson, A. Miller, H. Benzerdjeb, H. Li, C. Simonson, P. W. O'Connor, G. Teriflunomide Multiple Sclerosis Trial and M. R. I. A. C. the (2012). "Teriflunomide added to interferon-beta in relapsing multiple sclerosis: a randomized phase II trial." Neurology 78(23): 1877-1885.	Irrelevant intervention
Freedman, M. S., P. Truffinet, G. Comi, L. Kappos, A. E. Miller, T. P. Olsson, M. Benamor, S. Chambers and P. W. O'Connor (2015). "A randomized trial of teriflunomide added to glatiramer acetate in relapsing multiple sclerosis." Multiple Sclerosis Journal - Experimental, Translational and Clinical 1: 1-10.	Irrelevant intervention
Freedman, M. S., Wolinsky, J. S., Wamil, B., Confavreux, C., Comi, G., Kappos, L., . . . the, M. R. I. A. C. (2012). Teriflunomide added to interferon-beta in relapsing multiple sclerosis: a randomized phase II trial. Neurology, 78(23), 1877-1885. doi: http://dx.doi.org/10.1212/WNL.0b013e318258f7d4	Irrelevant comparator/ intervention
Frohman, E. M., E. Havrdova, F. Lublin, F. Barkhof, A. Achiron, M. K. Sharief, O. Stuve, M. K. Racke, L. Steinman, H. Weiner, M. Olek, R. Zivadinov, J. Corboy, C. Raine, G. Cutter, J. Richert and M. Filippi (2006). "Most patients with multiple sclerosis or a clinically isolated	Irrelevant study type

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Giovannoni, G., E. Southam and E. Waubant (2012). "Systematic review of disease-modifying therapies to assess unmet needs in multiple sclerosis: tolerability and adherence." Multiple Sclerosis 18(7): 932-946.	SRs that didn't enable to locate further primary studies
Giovannoni, G., G. Comi, S. Cook, K. Rammohan, P. Rieckmann and P. Soelberg-Sorensen (2013) "Safety and efficacy of oral cladribine in patients with relapsing-remitting multiple sclerosis: Results from the 96 week phase IIIB extension trial to the clarity study." Neurology 80.	Irrelevant intervention
Gobbi, C., D. S. Meier, F. Cotton, M. Sintzel, D. Leppert, C. R. Guttmann and C. Zecca (2013). "Interferon beta 1b following natalizumab discontinuation: one year, randomized, prospective, pilot trial." BMC Neurology 13: 101.	Irrelevant comparator/ intervention/ study type
Goodin, D. S., A. T. Reder, G. C. Ebers, G. Cutter, M. Kremenchutzky, J. Oger, D. Langdon, M. Rametta, K. Beckmann, T. M. DeSimone and V. Knappertz (2012). "Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFNbeta-1b trial." Neurology 78(17): 1315-1322.	Irrelevant comparator/ intervention/ study type
Goodin, D. S., G. C. Ebers, G. Cutter, S. D. Cook, T. O'Donnell, A. T. Reder, M. Kremenchutzky, J. Oger, M. Rametta, K. Beckmann and V. Knappertz (2012). "Cause of death in MS: long-term follow-up of a randomised cohort, 21 years after the start of the pivotal IFNbeta-1b study." BMJ Open 2(6).	Irrelevant intervention/ study type
Gotkine, M. (2008) "Neuromyelitis optica and the Optic Neuritis Treatment Trial." Archives of neurology 65, 1545-1546.	Irrelevant study type
Govindappa, K., J. Sathish, K. Park, J. Kirkham and M. Pirmohamed (2015). "Development of interferon beta-neutralising antibodies in multiple sclerosis--a systematic review and meta-analysis." European Journal of Clinical Pharmacology 71(11): 1287-1298.	Irrelevant outcome/ study type
Hadden, R. D., B. Sharrack, S. Bensa, S. E. Soudain and R. A. Hughes (1999). "Randomized trial of interferon beta-1a in chronic inflammatory demyelinating polyradiculoneuropathy." Neurology 53(1): 57-61.	Irrelevant population
Hadjigeorgiou, G. M., C. Doxani, M. Miligkos, P. Ziakas, G. Bakalos, D. Papadimitriou, T. Mprotsis, N. Grigoriadis and E. Zintzaras (2013). "A network meta-analysis of randomized controlled trials for comparing the effectiveness and safety profile of treatments with marketing authorization for relapsing multiple sclerosis." Journal of Clinical Pharmacy & Therapeutics 38(6): 433-439.	SRs that didn't enable to locate further primary studies
Hartung, H. P., M. S. Freedman, C. H. Polman, G. Edan, L. Kappos, D. H. Miller, X. Montalban, F. Barkhof, J. Petkau, R. White, V. Sahajpal, V. Knappertz, K. Beckmann, V. Lanius, R. Sandbrink, C. Pohl and B. S. Group (2011). "Interferon beta-1b-neutralizing antibodies 5 years after clinically isolated syndrome.[Erratum appears in Neurology. 2011 Sep 27;77(13):1317]." Neurology 77(9): 835-843.	Irrelevant study type
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Havrdova, E., G. Giovannoni, D. Stefoski, K. Umans, S. Greenberg and L. Mehta (2013) "Proportion of disease-activity free patients with relapsing-remitting multiple sclerosis following 1 year of treatment with daclizumab high-yield process in the select study." Neurology 80.	Conference abstract

Havrdova, E., Zivadinov, R., Krasensky, J., Dwyer, M. G., Novakova, I., Dolezal, O., . . . Horakova, D. (2009). Randomized study of interferon beta-1a, low-dose azathioprine, and low-dose corticosteroids in multiple sclerosis. Mult Scler, 15(8), 965-976. doi: 10.1177/1352458509105229	Irrelevant comparator/ intervention
Hersh, C. M. and J. A. Cohen (2014). "Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis." Immunotherapy 6(3): 249-259.	Irrelevant study type
Hutchinson, M., R. J. Fox, D. H. Miller, J. T. Phillips, M. Kita, E. Havrdova, J. O'Gorman, R. Zhang, M. Novas, V. Viglietta and K. T. Dawson (2013). "Clinical efficacy of BG-12 (dimethyl fumarate) in patients with relapsing-remitting multiple sclerosis: subgroup analyses of the CONFIRM study." Journal of Neurology 260(9): 2286-2296.	SRs that didn't enable to locate further primary studies
Hutchinson, M., R. J. Fox, E. Havrdova, N. C. Kurukulasuriya, S. P. Sarda, S. Agarwal, M. K. Siddiqui, A. Taneja and B. Deniz (2014). "Efficacy and safety of BG-12 (dimethyl fumarate) and other disease-modifying therapies for the treatment of relapsing-remitting multiple sclerosis: a systematic review and mixed treatment comparison." Current Medical Research & Opinion 30(4): 613-627.	SRs that didn't enable to locate further primary studies
Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, Fischer JS, Goodkin DE, Granger CV, Simon JH, et al. A phase III trial of intramuscular recombinant interferon beta as treatment for exacerbating-remitting multiple sclerosis: design and conduct of study and baseline characteristics of patients. Multiple Sclerosis Collaborative Research Group (MSCRG). Mult Scler. 1995 Jun;1(2):118-35. PubMed PMID: 9345462.	Protocol only with no results
Jacobs, L. D., R. W. Beck and J. H. Simon (2001). "Interferon beta-1a prevented the development of clinically definite multiple sclerosis after a first demyelinating event." Evidence-Based Medicine 6(3): 78.	Irrelevant study type
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Johnson, K. P., B. R. Brooks, C. C. Ford, A. D. Goodman, R. P. Lisak, L. W. Myers, A. A. Pruitt, M. A. Rizzo, J. W. Rose, L. P. Weiner and J. S. Wolinsky (2003) "Glatiramer acetate (Copaxone): comparison of continuous versus delayed therapy in a six-year organized multiple sclerosis trial." Multiple sclerosis (Houndmills, Basingstoke, England) 9, 585-591.	Irrelevant population
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Kamm, C. P., M. El-Koussy, S. Humpert, O. Findling, F. von Bredow, Y. Burren, G. Schwegler, D. Schott, F. Donati, M. Muller, N. Goebels, F. Muller, J. Slotboom, B. Tettenborn, L. Kappos, Y. Naegelin and H. P. Mattle (2012). "Atorvastatin added to interferon beta for relapsing multiple sclerosis: a randomized controlled trial." Journal of Neurology 259(11): 2401-2413.	Irrelevant comparator/ intervention
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Kappos, L., A. Traboulsee, C. Constantinescu, J. P. Erälinna, F. Forrestal, P. Jongen, J. Pollard, M. Sandberg-Wollheim, C. Sindic, B. Stubinski, B. Uitdehaag and D. Li (2006) "Long-term subcutaneous interferon beta-1a therapy in patients with relapsing-remitting MS."	Irrelevant population/ study type

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Kappos, L., Antel, J., Comi, G., Montalban, X., O'Connor, P., Polman, C. H., . . . Radue, E. W. (2006). Oral fingolimod (FTY720) for relapsing multiple sclerosis. N Engl J Med, 355(11), 1124-1140. doi: 10.1056/NEJMoa052643	Irrelevant comparator/ intervention
Kappos, L., G. Edan, M. Freedman, X. Montalban, D. Miller and C. Polman (2013) "Benefit 11: Long-term follow-up study of patients with clinically isolated syndrome treated with interferon beta-1b." 333.	Conference abstract
Kappos, L., Gold, R., Miller, D. H., Macmanus, D. G., Havrdova, E., Limmroth, V., . . . O'Neill, G. N. (2008). Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. Lancet, 372(9648), 1463-1472. doi: 10.1016/s0140-6736(08)61619-0	Irrelevant comparator/ intervention
Kappos, L., H. Wiendl, K. Selmaj, D. L. Arnold, E. Havrdova, A. Boyko, M. Kaufman, J. Rose, S. Greenberg, M. Sweetser, K. Riester, G. O'Neill and J. Elkins (2015). "Daclizumab HYP versus Interferon Beta-1a in Relapsing Multiple Sclerosis." New England Journal of Medicine 373(15): 1418-1428.	Irrelevant comparator/ intervention
Kappos, L., M. S. Freedman, C. H. Polman, G. Edan, H. P. Hartung, D. H. Miller, X. Montalban, F. Barkhof, E. W. Radu, C. Metzig, L. Bauer, V. Lanius, R. Sandbrink, C. Pohl and B. S. Group (2009). "Long-term effect of early treatment with interferon beta-1b after a first clinical event suggestive of multiple sclerosis: 5-year active treatment extension of the phase 3 BENEFIT trial." Lancet Neurology 8(11): 987-997.	Irrelevant intervention/ study type
Kappos, L., M. S. Freedman, C. H. Polman, G. Edan, H. P. Hartung, D. H. Miller, X. Montalbán, F. Barkhof, E. W. Radü, L. Bauer, S. Dahms, V. Lanius, C. Pohl and R. Sandbrink (2007) "Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study." Lancet (London, England) 370, 389-397 DOI: 10.1016/S0140-6736(07)61194-5.	Irrelevant intervention/ study type
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La Mantia, L., C. Di Pietrantonj, M. Rovaris, G. Rigon, S. Frau, F. Berardo, A. Gandini, A. Longobardi, B. Weinstock-Guttman and A. Vaona (2015). "Comparative efficacy of interferon beta versus glatiramer acetate for relapsing-remitting multiple sclerosis." Journal of Neurology, Neurosurgery & Psychiatry 86(9): 1016-1020.	SRs that didn't enable to locate further primary studies
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Clinical Symptom of Multiple Sclerosis." ClinicalTrials Gov, National Institutes of Health [http://www clinicaltrials gov].	with no results
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Perry, M., S. Swain, S. Kemmis-Betty, P. Cooper, H. Guideline Development Group of the National Institute for and E. Care (2014). "Multiple sclerosis: summary of NICE guidance." BMJ 349: g5701.	Irrelevant study type
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Roskell, N. S., E. A. Zimovetz, C. E. Rycroft, B. J. Eckert and D. A. Tyas (2012). "Annualized relapse rate of first-line treatments for multiple sclerosis: a meta-analysis, including indirect comparisons versus fingolimod." Current Medical Research & Opinion 28(5): 767-780.	SRs that didn't enable to locate further primary studies
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acetate: a multicentre, multinational extension of the European/Canadian double-blind, placebo-controlled, MRI-monitored trial." Multiple sclerosis (Houndmills, Basingstoke, England) 13, 502-508 DOI: 10.1177/1352458506070704.	study type
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Saida, T., K. Tashiro, Y. Itoyama, T. Sato, Y. Ohashi, Z. Zhao and S. Interferon Beat-1b Multiple (2005). "Interferon beta-1b is effective in Japanese RRMS patients - A randomized, multicenter study." Neurology 64(4): 621-630.	DMT used with a non-recommended dose regimen
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Sellner, J., M. Boggild, M. Clanet, R. Q. Hintzen, Z. Illes, X. Montalban, R. A. Du Pasquier, C. H. Polman, P. S. Sorensen and B. Hemmer (2010). "EFNS guidelines on diagnosis and management of neuromyelitis optica." European Journal of Neurology 17(8): 1019-1032.	Irrelevant intervention/ study type
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Simon, J. H., L. D. Jacobs, M. Campion, K. Wende, N. Simonian, D. L. Cookfair, R. A. Rudick, R. M. Herndon, J. R. Richert, A. M. Salazar, J. J. Alam, J. S. Fischer, D. E. Goodkin, C. V. Granger, M. Lajaunie, A. L. Martens-Davidson, M. Meyer, J. Sheeder, K. Choi, A. L. Scherzinger, D. M. Bartoszak, D. N. Bourdette, J. Braiman, C. M. Brownscheidle and R. H. Whitham (1998) "Magnetic resonance studies of intramuscular interferon beta-1a for relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group." Annals of neurology 43, 79-87 DOI: 10.1002/ana.410430114.	Irrelevant outcome
Soilu-Hanninen, M., J. Aivo, B. M. Lindstrom, I. Elovaara, M. L. Sumelahti, M. Farkkila, P. Tienari, S. Atula, T. Sarasoja, L. Herrala, I. Keskinarkaus, J. Kruger, T. Kallio, M. A. Rocca and M. Filippi (2012). "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 & Psychiatry 83(5): 565-571.	Irrelevant comparator/ intervention
Sorensen, P. S., Lisby, S., Grove, R., Derosier, F., Shackelford, S., Havrdova, E., . . . Filippi, M. (2014). Safety and efficacy of ofatumumab in relapsing-remitting multiple sclerosis: a phase 2 study. Neurology, 82(7), 573-581. doi: 10.1212/wnl.0000000000000125	Irrelevant comparator/ intervention
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Tolley, K., M. Hutchinson, X. You, P. Wang, B. Sperling, A. Taneja, M. K. Siddiqui and E. Kinter (2015). "A Network Meta-Analysis of Efficacy and Evaluation of Safety of Subcutaneous Pegylated Interferon Beta-1a versus Other Injectable Therapies for the Treatment of Relapsing-Remitting Multiple Sclerosis." PLoS ONE [Electronic Resource] 10(6): e0127960.	SRs that didn't enable to locate further primary studies
Tsivgoulis, G., A. H. Katsanos, N. Grigoriadis, G. M. Hadjigeorgiou, I. Heliopoulos, C. Kilidireas and K. Voumvourakis (2015). "The effect of disease modifying therapies on brain atrophy in patients with relapsing-remitting multiple sclerosis: a systematic review and meta-analysis." PLoS ONE [Electronic Resource] 10(3): e0116511.	Irrelevant outcome/ study type
Tsivgoulis, G., A. H. Katsanos, N. Grigoriadis, G. M. Hadjigeorgiou, I. Heliopoulos, P. Papathanasopoulos, C. Kilidireas, K. Voumvourakis, E. Dardiotis and Helani (2015). "The Effect of Disease Modifying Therapies on Disease Progression in Patients with Relapsing-Remitting Multiple Sclerosis: A Systematic Review and Meta-Analysis." PLoS ONE [Electronic Resource] 10(12): e0144538.	SRs that didn't enable to locate further primary studies
Tsivgoulis, G., A. H. Katsanos, N. Grigoriadis, G. M. Hadjigeorgiou, I. Heliopoulos, P. Papathanasopoulos, E. Dardiotis, C. Kilidireas, K. Voumvourakis and Helani (2015). "The effect of disease-modifying therapies on brain atrophy in patients with clinically isolated syndrome: a systematic review and meta-analysis." Therapeutic Advances in Neurological Disorders 8(5): 193-202.	Irrelevant outcome/ study type/ population
Vermersch, P., A. Czlonkowska, L. M. Grimaldi, C. Confavreux, G. Comi, L. Kappos, T. P. Olsson, M. Benamor, D. Bauer, P. Truffinet, M. Church, A. E. Miller, J. S. Wolinsky, M. S. Freedman, P. O'Connor and T. T. Group (2014). "Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial." Multiple Sclerosis 20(6): 705-716.	Irrelevant comparator/ intervention
Vermersch, P., Czlonkowska, A., Grimaldi, L. M., Confavreux, C., Comi, G., Kappos, L., . . . Group, T. T. (2014). Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. Mult Scler, 20(6), 705-716. doi: http://dx.doi.org/10.1177/1352458513507821	Irrelevant intervention
Vollmer, T. L., P. S. Sorensen, K. Selmaj, F. Zipp, E. Havrdova, J. A. Cohen, N. Sasson, Y. Gilgun-Sherki, D. L. Arnold and B. S. Group (2014). "A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis." Journal of Neurology 261(4): 773-783.	Conference abstract
Vollmer, T., D. Jeffery, D. Goodin, L. Kappos, F. Lublin and E. W. Radue (2013) "Long-term safety of fingolimod in patients with relapsing-remitting multiple sclerosis: Results from phase 3 freedoms II extension study." Neurology 80.	Irrelevant comparator/ intervention
Vollmer, T., H. Panitch, A. Bar-Or, J. Dunn, M. S. Freedman, S. K. Gazda, D. Campagnolo, F. Deutsch and D. L. Arnold (2008) "Glatiramer acetate after induction therapy with mitoxantrone in relapsing multiple sclerosis." Multiple sclerosis (Houndmills, Basingstoke, England) 14, 663-670 DOI: 10.1177/1352458507085759.	Irrelevant comparator/ population
Voskuhl, R. R., H. Wang, T. C. Wu, N. L. Sicotte, K. Nakamura, F. Kurth, N. Itoh, J. Bardens, J. T. Bernard, J. R. Corboy, A. H. Cross, S. Dhib-Jalbut, C. C. Ford, E. M. Frohman,	Irrelevant comparator/ intervention

B. Giesser, D. Jacobs, L. H. Kasper, S. Lynch, G. Parry, M. K. Racke, A. T. Reder, J. Rose, D. M. Wingerchuk, A. J. MacKenzie-Graham, D. L. Arnold, C. H. Tseng and R. Elashoff (2016). "Estriol combined with glatiramer acetate for women with relapsing-remitting multiple sclerosis: a randomised, placebo-controlled, phase 2 trial." Lancet Neurology 15(1): 35-46.	
Waubant, E., A. H. Maghzi, N. Revirajan, R. Spain, L. Julian, E. M. Mowry, J. Marcus, S. Liu, C. Jin, A. Green, C. E. McCulloch and D. Pelletier (2014). "A randomized controlled phase II trial of riluzole in early multiple sclerosis." Annals of Clinical & Translational Neurology 1(5): 340-347.	Irrelevant comparator/ intervention
Waubant, E., D. Pelletier, M. Mass, J. A. Cohen, M. Kita, A. Cross, A. Bar-Or, T. Vollmer, M. Racke, O. Stuve, S. Schwid, A. Goodman, N. Kachuck, J. Preiningerova, B. Weinstock-Guttman, P. A. Calabresi, A. Miller, M. Mokhtarani, D. Ikle, S. Murphy, H. Kopetskie, L. Ding, E. Rosenberg, C. Spencer, S. S. Zamvil and I. T. N. S. S. Grp (2012). "Randomized controlled trial of atorvastatin in clinically isolated syndrome The STAyCIS study." Neurology 78(15): 1171-1178.	Irrelevant comparator/ intervention
Weinshenker, B. G. (2014). "Review: In relapsing-remitting multiple sclerosis, disease-modifying agents reduce annual relapse rates." Annals of Internal Medicine 160(6): JC5.	Conference abstract
Weinstock-Guttman, B., S. L. Galetta, G. Giovannoni, E. Havrdova, M. Hutchinson, L. Kappos, P. W. O'Connor, J. T. Phillips, C. Polman, W. H. Stuart, F. Lynn and C. Hotermans (2012). "Additional efficacy endpoints from pivotal natalizumab trials in relapsing-remitting MS." Journal of Neurology 259(5): 898-905.	Irrelevant comparator/ intervention
Wolinsky, J. S., Narayana, P. A., O'Connor, P., Coyle, P. K., Ford, C., Johnson, K., . . . Ladkani, D. (2007). Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. Ann Neurol, 61(1), 14-24. doi: 10.1002/ana.21079	Irrelevant population
Wolinsky, J. S., P. A. Narayana, P. O'Connor, P. K. Coyle, C. Ford, K. Johnson, A. Miller, L. Pardo, S. Kadosh and D. Ladkani (2007) "Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial." Annals of neurology 61, 14-24 DOI: 10.1002/ana.21079.	Irrelevant population
Wolinsky, J. S., T. E. Borresen, D. W. Dietrich, D. Wynn, Y. Sidi, J. R. Steinerman, V. Knappertz, S. Kolodny and G. S. Group (2015). "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 4(4): 370-376.	Irrelevant study type
Wynn, D., Kaufman, M., Montalban, X., Vollmer, T., Simon, J., Elkins, J., . . . Rose, J. W. (2010). Daclizumab in active relapsing multiple sclerosis (CHOICE study): a phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta. Lancet Neurol, 9(4), 381-390. doi: 10.1016/s1474-4422(10)70033-8	Irrelevant intervention
Zagmutt, F. J. and C. A. Carroll (2015). "Meta-analysis of adverse events in recent randomized clinical trials for dimethyl fumarate, glatiramer acetate and teriflunomide for the treatment of relapsing forms of multiple sclerosis." International Journal of Neuroscience 125(11): 798-807.	SRs that didn't enable to locate further primary studies
Ziemssen, T., J. Hoffman, R. Apfel and S. Kern (2008) "Effects of glatiramer acetate on fatigue and days of absence from work in first-time treated relapsing-remitting multiple sclerosis." Health and quality of life outcomes 6.	Irrelevant population/ study type
Zintzaras, E., C. Doxani, T. Mprotsis, C. H. Schmid and G. M. Hadjigeorgiou (2012).	SRs that didn't enable to locate

"Network analysis of randomized controlled trials in multiple sclerosis." Clinical Therapeutics 34(4): 857-869.e859.	further primary studies
Zivadinov, R., M. G. Dwyer, D. P. Ramasamy, M. D. Davis, J. R. Steinerman and O. Khan (2015). "The Effect of Three Times a Week Glatiramer Acetate on Cerebral T1 Hypointense Lesions in Relapsing-Remitting Multiple Sclerosis." Journal of Neuroimaging 25(6): 989-995.	Irrelevant outcome

22 **Appendix 4: Studies included in the clinical effectiveness review with relevant publications**

Study ID	Title	Full article(s) – main	Full article(s) - other
ADVANCE 2014	A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of PEGylated Interferon Beta-1a (BIIB017) in Subjects With Relapsing Multiple Sclerosis	Calabresi 2014[211]	Arnold 2014[212] (MRI), Newsome 2015[213] (HRQoL)
AVANTAGE 2014	Safety Study in Relapsing-remitting Multiple Sclerosis (RRMS) Patients Receiving Betaferon or Rebif	No formal publication, results on company website[180] and ClinicalTrials.gov	
BECOME 2009	Phase IV, Rater-blinded, Randomized Study, Comparing 250 mg of Betaseron With 20 mg of Copaxone in Patients With the Relapsing-remitting(RR) or CIS Forms of ms Using 3 Tesla(3T) Magnetic Resonance Imaging (MRI) With Triple-dose Gadolinium	Cadavid 2009[182]	Cadavid 2011[210]
BENEFIT 2006	The BEtaferon in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) trial	Kappos 2006[169]	Polman 2008[177] (Subgroup analysis), Penner 2012[178] (cognitive performance in CIS)
BEYOND 2009	International, Randomized, Multicenter, Phase IIIb Study in Patients With Relapsing-Remitting Multiple Sclerosis Comparing Over a Treatment Period of at Least 104 Weeks: 1. Double-Blinded Safety, Tolerability, and Efficacy of Betaseron/ Betaferon 250 µg (8 MIU) and Betaseron/-Betaferon 500 µg (16 MIU), Both Given Subcutaneously Every Other Day, and 2. Rater-Blinded Safety, Tolerability, and Efficacy of Betaseron/-Betaferon s.c. Every Other Day With Copaxone 20 mg s.c. Once Daily.	O'Connor 2009[188]	Filippi 2011[276] (Post hoc analysis of MRI scans)
Bornstein 1987	A pilot trial of Cop 1 in exacerbating-remitting multiple sclerosis	Bornstein 1987[168]	
BRAVO 2014	A Multinational, Multicenter, Randomized, Parallel-group Study Performed in Subjects With RRMS to Assess the Efficacy, Safety and Tolerability of Laquinimod Over Placebo in a Double-blind Design and a Reference Arm of Interferon β-1a (Avonex®) in a Rater-blinded Design.	Vollmer 2014[196]	
Calabrese 2012	Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing–remitting multiple sclerosis	Calabrese 2012[186]	

CHAMPS 2000	Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis	Jacobs 2000[170]	Beck 2002[174] (Subgroup analysis, CHAMPS 2001[277] (Subgroup of acute optic neuritis), O'Connor 2003[278] (Subgroup analysis), O'Connor 2009[175] (Subgroup analysis)
CombiRx 2013	A Multi-Center, Double-Blind, Randomized Study Comparing the Combined Use of Interferon Beta-1a and Glatiramer Acetate to Either Agent Alone in Patients With Relapsing-Remitting Multiple Sclerosis (CombiRx)	Lublin 2013[189]	Lindsey 2012[279] (protocol)
CONFIRM 2012	A Randomized, Multicenter, Placebo-Controlled and Active Reference (Glatiramer Acetate) Comparison Study to Evaluate the Efficacy and Safety of BG00012 in Subjects With Relapsing-Remitting Multiple Sclerosis	Fox 2012[214]	Kita 2014[280] (HRQoL)
Cop1 MSSG 1995		Johnson 1995[215] (initial findings)	Johnson 1998[216] (final results)
ECGASG 2001	European/Canadian Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of the Effects of Glatiramer Acetate on Magnetic Resonance Imaging–Measured Disease Activity and Burden in Patients with Relapsing Multiple Sclerosis	Comi 2001[217]	
ESG 1998	Placebo-controlled multicentre randomised trial of interferon-1b in treatment of secondary progressive multiple sclerosis	European Study Group on Interferon Beta-1b in secondary progressive MS 1998[220]	Kappos 2001[223] (Final results)
Etemadifar 2006	Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing–remitting multiple sclerosis	Etemadifar 2006[183]	
EVIDENCE 2007	Full Results of the Evidence of Interferon Dose-Response-European North American Comparative Efficacy (EVIDENCE) Study: A Muhicenter, Randomized, Assessor-Blinded Comparison of Low-Dose Weekly Versus High-Dose, High-Frequency Interferon 13-1a for Relapsing Multiple Sclerosis	Schwid 2007[193]	Panitch 2002[191] (comparative results), Panitch 2005[192] (final comparative results), Sandberg-Wollheim 2005[204] (AEs)
GALA 2013	Three Times Weekly Glatiramer Acetate in Relapsing–Remitting Multiple Sclerosis	Khan 2013[219]	
GATE 2015	Multi-centre, Randomized, Double-blind, Placebo-controlled, Parallel-group, 9 Month, Equivalence Trial Comparing the Efficacy and Safety and Tolerability of GTR (Synthon BV) to Copaxone® (Teva) in Subjects With Relapsing Remitting	Cohen 2015[218]	

	Multiple Sclerosis Followed by an Open-label 15 Month GTR Treatment Part Evaluating the Long-term GTR Treatment Effects		
IFNB MSSG 1995	Interferon beta-lb is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial	IFNB Multiple Sclerosis Study Group 1993[207]	IFNB Multiple Sclerosis Study Group 1995[208] (additional data and further details)
IMPROVE 2012	A Two-arm, Randomized, Double-blind, Control Group-compared, Multicenter, Phase IIIb Study With Monthly MRI and Biomarker Assessments to Evaluate the Efficacy, Safety, and Tolerability of Rebif® New Formulation (IFN Beta-1a) in Subjects With Relapsing Remitting Multiple Sclerosis	De Stefano 2012[205]	
INCOMIN 2001	Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN)	Durelli 2002[194]	
Kappos 2011	Phase II, Multicenter, Randomized, Parallel-Group, Partially Blinded, Placebo and Avonex Controlled Dose Finding Study to Evaluate the Efficacy As Measured by Brain MRI Lesions, and Safety of 2 Dose Regimens of Ocrelizumab in Patients With RRMS	Kappos 2011[197]	
Knobler 1993	Systemic Recombinant Human Interferon-ß Treatment of Relapsing-Remitting Multiple Sclerosis: Pilot Study Analysis and Six-Year Follow-Up	Knobler 1993[209]	
Mokhber 2014	Cognitive dysfunction in patients with multiple sclerosis treated with different types of interferon beta: A randomized clinical trial	Mokhber 2014[184]	Mokhber 2015[185] (HRQoL)
MSCRG 1996	Intramuscular Interferon Beta-la for Disease Progression in Relapsing Multiple Sclerosis	Jacobs 1996[198]	Fischer 2000,[201] Goodkin 1998,[200] Granger 2003,[202] Miller 2011,[203] Rudick 1997[199]
NASG 2004	Interferon beta-1b in secondary progressive MS	Panitch 2004[221]	
Pakdaman 2007	Effect of early interferon beta-1a therapy on conversion to multiple sclerosis in Iranian patients with a first demyelinating event	Pakdaman 2007[171]	
PreCISe 2009	A Multinational, Multicenter, Randomized, Double-Blind, Placebo Controlled, Parallel Group Study to Evaluate the Effect of Early Glatiramer Acetate Treatment in Delaying the Conversion to Clinically Definite Multiple Sclerosis (CDMS) of Subjects Presenting With Clinically Isolated Syndrome (CIS)	Comi 2009[172]	

PRISMS 1998	Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis	PRISMS Study Group 1998[187]	Patten 2001[206] (depression), Gold 2005[281] (4 year safety and tolerability)
REFLEX 2012	A Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter Clinical Trial of Rebif New Formulation (44 Microgram [Mcg] Three Times Weekly [Tiw] and 44 Mcg Once Weekly [ow]) in Subjects at High Risk of Converting to Multiple Sclerosis (REFLEX)	Comi 2012[173]	Freedman 2014[176] (Subgroup analysis), CADTH 2013[282]
REFORMS 2012	A Randomized, Multicenter, Two Arm, Open Label, Twelve Week Phase IIIb Study to Evaluate the Tolerability of Rebif (New Formulation) (IFN Beta-1a) and Betaseron (IFN Beta-1b) in IFN-naive Subjects With Relapsing Remitting Multiple Sclerosis (RRMS) Followed by a Single Arm, Eighty-two Week Minimum, Rebif (New Formulation) Only Safety Extension	Singer 2012[195]	
REGARD 2008	Phase IV, Multicenter, Open Label, Randomized Study of Rebif® 44 mcg Administered Three Times Per Week by Subcutaneous Injection Compared With Copaxone® 20 mg Administered Daily by Subcutaneous Injection in the Treatment of Relapsing Remitting Multiple Sclerosis	Mikol 2008[190]	
REMAIN 2012	Phase IV, Multicenter, Open Label, Randomized 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	Rieckmann 2012[181]	
Schwartz 1997	The Quality-of-Life Effects of Interferon Beta-1b in Multiple Sclerosis	Schwartz 1997[179]	
SPECTRIMS 2001	Randomized controlled trial of interferon beta-1a in secondary progressive MS	SPECTRIMS Study Group 2001[222]	

23 Appendix 5: Overview of systematic reviews in RRMS, SPMS and CIS: methods and results

23.1 *Objective*

To provide an overview of systematic reviews, published in the last five years, of studies that assessed the cost-effectiveness of treating relapsing remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS) and/or clinically isolated syndrome (CIS).

Search strategy. The following electronic databases were searched from January 2011 to January 2016: MEDLINE (Ovid); MEDLINE In-Process Citations and Daily Update (Ovid); Embase (Ovid); Cochrane Library (Wiley), including NHS EED, and HTA databases; Science Citation Index (Web of Knowledge), Research Papers in Economics (RePEC) and the Cost-effectiveness Analysis (CEA) Registry. The database searches were kept broad, with search terms for MS and CIS combined with economic / HRQoL terms and systematic reviews terms (based on recognised search filters [224-227] where appropriate. Searches for MS and CIS were performed separately, but results were deduplicated and then combined for assessment. A full record of searches is provided at the end of this appendix. The searches were limited to reviews published in or after 2011. All bibliographic records identified through the electronic searches were collected in a managed reference database. The reference lists of included studies were also checked. Grey literature searches was undertaken using the online resources of various regulatory bodies, health service research agencies, professional societies and patient organisations.

Based on the quality assessment of these reviews, we considered six studies[230, 232-236] to be methodological robust and likely to capture economic analyses pre 2012. Hence, we have undertaken a search of primary studies (relapsisng remitting multiple sclerosis) with a search limited to 2012 and later.

Study selection. Selection of studies was undertaken by PA and checked by HM using the following defined criteria.

Inclusion criteria. Systematic reviews of economic evaluations that involve the use of economic models in RRMS/SPMS/CIS were included. Systematic reviews of health-related quality of life (HRQoL) studies in RRMS/SPMS/CIS were also be selected at this stage for later review.

Quality appraisal. The studies were appraised against A Measurement Tool to Assess Systematic Reviews (AMSTAR) framework for best practice in undertaking systematic reviews. AMSTAR assessment tool consists of series of criteria/questions (e.g. a priori design, study selection and data extraction, comprehensive literature search or methods used to combine the findings) to check whether these have been satisfactorily reported. Appraisal of the methodological quality of these studies was undertaken by two reviewers (HM and PA). Studies quality assessed by one reviewer was cross-checked by the other. Any disagreements were resolved by discussion or by recourse to a third-party reviewer (JM).

Results. The electronic database searches identified 1566 records (Figure 36). After removing duplicates, 1023 records were screened for inclusion. On the basis of title and abstract, 966 records were excluded and the remaining 57 records were included for full-text screening. A further 48 articles were excluded at the full-text

stage, leaving nine systematic reviews[230-238]. Nine systematic reviews included eight economic evaluation studies[230-237] and one systematic review[238] on studies that used a generic tool to measure HRQoL for people with multiple sclerosis.

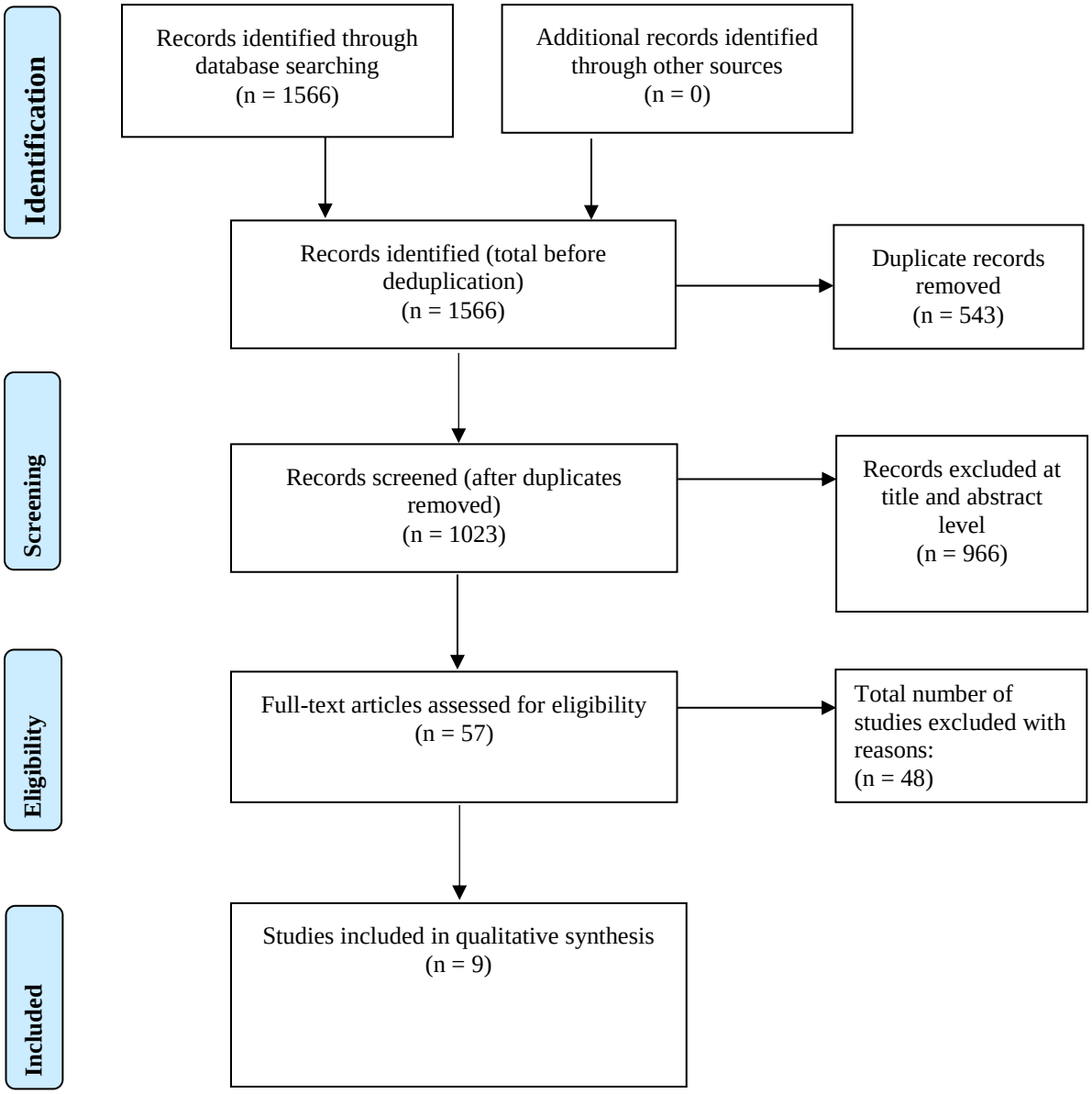

Figure 36: PRISMA flowchart, review of systematic reviews of economic evaluations

23.2 *Summary*

We have identified nine[230-238] systematic reviews published since January 2011, which included eight[230-237] reviews on economic evaluation studies and one[238] review which looked at generic tools used to measure health-related quality of life in people with multiple sclerosis.

We appraised these studies against the AMSTAR methodological assessment tool. Details on how each review performed can be found in Table 90. Based on our appraisal, systematic reviews generally performed satisfactorily in terms of stating an 'a prori' design of the review, stating the characteristics of all included studies, and stating the status of the publication. Though helpful, these reviews were subjected to some limitations. First, it was unclear in most studies if authors undertook study selection and data extraction in duplicate. Second, while some studies[230, 232, 236] provided a list of included studies, some authors[231, 233-235, 237, 238] have not provided a list of excluded studies. Third, it as unclear or not stated if authors assessed and/or documented the scientific quality of the included studies.

23.3 *Full record of searches*

23.3.1 MS searches

Medline (Ovid), searched 26/01/2016

Exact database: Ovid MEDLINE(R) 1946 to January Week 2 2016

1	exp Multiple Sclerosis/	46764
2	multiple sclerosis.tw.	49799
3	1 or 2	57188
4	exp Economics/	517314
5	exp "Costs and Cost Analysis"/	193082
6	Health Status/	63909
7	exp "Quality of Life"/	131614
8	exp Quality-Adjusted Life Years/	7896
9	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.	475628
10	(health state* or health status).tw.	41055
11	(qaly* or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or HUI).tw.	140813
12	(markov or time trade off or TTO or standard gamble or hrql or hrqol or disabilit* or disutilit*).tw.	133533
13	(quality adj2 life).tw.	154937
14	(decision adj2 model).tw.	4073
15	(visual analog* scale* or discrete choice experiment* or health* year* equivalen* or (willing* adj2 pay)).tw.	33173
16	("resource use" or resource utili?ation).tw.	9570
17	(well-being or wellbeing).tw.	46483

18	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	1328233
19	3 and 18	9165
20	(metaanalys* or meta analys* or meta-analys*).tw.	69140
21	(systematic* and review*).mp.	94951
22	meta analysis.pt.	60117
23	(literature and review*).mp.	315101
24	(review* adj10 (model* or cost* or economic* or "quality of life" or HRQoL or HRQL or utilit*)).tw.	37856
25	20 or 21 or 22 or 23 or 24	452492
26	19 and 25	551
27	limit 19 to systematic reviews	409
28	26 or 27	698
29	limit 28 to yr="2011 -Current"	305

Medline In-Process & Other Non-Indexed Citations (Ovid), searched 26/01/2016

Exact database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 25, 2016

1	multiple sclerosis.tw.	4878
2	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.	69030
3	(health state* or health status).tw.	4219
4	(qaly* or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or HUI).tw.	19706
5	(markov or time trade off or TTO or standard gamble or hrql or hrqol or disabilit* or disutilit*).tw.	16928
6	(quality adj2 life).tw.	22185
7	(decision adj2 model).tw.	500
8	(visual analog* scale* or discrete choice experiment* or health* year* equivalen* or (willing* adj2 pay)).tw.	5276
9	("resource use" or resource utili?ation).tw.	1372
10	(well-being or wellbeing).tw.	6440
11	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	126738
12	1 and 11	1295
13	(metaanalys* or meta analys* or meta-analys*).tw.	14035
14	(systematic* and review*).tw.	18717
15	(literature and review*).tw.	40052
16	(review* adj10 (model* or cost* or economic* or "quality of life" or HRQoL or HRQL or utilit*)).tw.	6244
17	13 or 14 or 15 or 16	62995
18	12 and 17	93
19	limit 12 to systematic reviews	63
20	18 or 19	105

21	limit 20 to yr="2011 -Current"	91

Embase (Ovid), searched 26/01/2016

Exact database: Embase 1974 to 2016 Week 04

1	multiple sclerosis/	93609
2	multiple sclerosis.tw.	80240
3	1 or 2	101212
4	exp health economics/	677659
5	exp health status/	164988
6	exp "quality of life"/	325811
7	exp quality adjusted life year/	15391
8	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.	713057
9	(health state* or health status).tw.	57400
10	(qaly* or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF6D or SF-6D or HUI).tw.	223035
11	(markov or time trade off or TTO or standard gamble or hrql or hrqol or disabilit* or disutilit*).tw.	208655
12	(quality adj2 life).tw.	270996
13	(decision adj2 model).tw.	6739
14	(visual analog* scale* or discrete choice experiment* or health* year* equivalen*).tw.	49099
15	("resource use" or resource utili?ation).tw.	17555
16	(well-being or wellbeing or (willing* adj2 pay)).tw.	74545
17	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	1972705
18	3 and 17	20936
19	meta analysis/	103317
20	(metaanalys* or meta analys* or meta-analys*).tw.	110582
21	"systematic review"/	100520
22	(systematic* adj3 review*).tw.	103537
23	(literature adj3 review*).tw.	245646
24	(review* adj10 (model* or cost* or economic* or "quality of life" or HRQoL or HRQL or utilit*)).tw.	56320
25	19 or 20 or 21 or 22 or 23 or 24	486435
26	18 and 25	994
27	limit 18 to "systematic review"	312
28	26 or 27	994
29	limit 28 to yr="2011 -Current"	566

DARE (Cochrane Library), searched 13/01/2016

ID	Search	Hits

#1	MeSH descriptor: [Multiple Sclerosis] explode all trees	1916
#2	multiple sclerosis:ti,ab,kw	4938
#3	#1 or #2	4942
#4	MeSH descriptor: [Economics] explode all trees	25789
#5	MeSH descriptor: [Costs and Cost Analysis] explode all trees	23940
#6	MeSH descriptor: [Health Status] explode all trees	5540
#7	MeSH descriptor: [Quality of Life] explode all trees	15431
#8	MeSH descriptor: [Quality-Adjusted Life Years] explode all trees	3942
#9	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*):ti,ab,kw	51646
#10	(health next (state* or status)):ti,ab,kw	7475
#11	(qaly* or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or HUI):ti,ab,kw	12645
#12	(markov or "time trade off" or TTO or "standard gamble" or hrql or hrqol or disabilit* or disutilit*):ti,ab,kw	18569
#13	(quality near/2 life):ti,ab,kw	42732
#14	(decision near/2 model):ti,ab,kw	393
#15	((visual next analog* next scale*) or ("discrete choice" next experiment*) or (health* next year* next equivalen*) or (willing* near/2 pay)):ti,ab,kw	19706
#16	("resource use" or resource next utili?ation):ti,ab,kw	1571
#17	(well-being or wellbeing):ti,ab,kw	5981
#18	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17	125705
#19	#3 and #18 Publication Year from 2011 to 2016	1048

Total all databases: 1048

Other Reviews (DARE): 11

HTA (CRD), searched 13/01/2016

Any field: multiple sclerosis
AND
Publication year 2011 to 2016
AND
HTA selected

Total: 38

NHS EED (Cochrane Library), searched 13/01/2016

n.b. Since March 2015, NHS EED is no longer updated

ID	Search	Hits
#1	MeSH descriptor: [Multiple Sclerosis] explode all trees	1916
#2	multiple sclerosis:ti,ab,kw	4938
#3	#1 or #2	4942
#4	(metaanalys* or (meta next analys*) or meta-analys*):ti,ab,kw	26655
#5	review* or literature or systematic*:ti,ab,kw	112066
#6	#4 or #5	114328
#7	#3 and #6 Publication Year from 2011 to 2016	282

All databases: 282

Economic Evaluations (NHS EED): 31

Science Citation Index (Web of Knowledge), searched 26/01/2016

# 8	394	#7 AND #2 AND #1 *Indexes=SCI-EXPANDED Timespan=2011-2016*
# 7	232,254	#6 OR #5 OR #4 OR #3 *Indexes=SCI-EXPANDED Timespan=2011-2016*
# 6	24,398	TS=(review* NEAR/10 (model* or cost* or economic* or "quality of life" or HRQoL or HRQL or utilit*)) *Indexes=SCI-EXPANDED Timespan=2011-2016*
# 5	99,993	TS=(literature AND review*) *Indexes=SCI-EXPANDED Timespan=2011-2016*
# 4	60,945	TS=(systematic* AND review*) *Indexes=SCI-EXPANDED Timespan=2011-2016*
# 3	102,963	TS=(metaanalys* or (meta NEAR/1 analys*)) *Indexes=SCI-EXPANDED Timespan=2011-2016*
# 2	573,437	TS=("quality of life" or QoL or hrql or hrqol or ("quality adjusted life" NEAR/1 year*) or QALY* or cost* or economic* or pharmacoeconomic* or pharmaco-economic* or euro-qol or utilit* or disutilit* or euroqol or "euro qol" or EQ5D or EQ-5D or SF-36 or SF36 or SF-6D or SF6D or HUI or (time NEAR/1 trade*) or TTO or "standard gamble" or markov or (decision NEAR/2 model*) or (visual NEAR/1 analog*) or "discrete choice" or ((health* NEAR/1 year*) NEAR/1 equivalen*) or (health NEAR/1 stat*) or "willingness to pay" or "resource use" or (resource NEAR/1 utili?ation) or wellbeing or well-being) *Indexes=SCI-EXPANDED Timespan=2011-2016*
# 1	29,661	TS="multiple sclerosis" *Indexes=SCI-EXPANDED Timespan=2011-2016*

RePEc, searched 13/01/2016

EconPapers

Free text: "multiple sclerosis"

125

Sorted by item date

Total number published from 2011 to 2016: 36

CEA Registry, searched 13/01/2016

Contained details of articles up to 2013 at time of search

Basic Search

Articles

Full Search Contents: multiple sclerosis

Total number published from 2011 to 2016: 14

ScHARR HUD, searched 13/01/2016

multiple sclerosis in any field

AND

2011 to 2016 in Year Published

Total: 9

23.3.2 CIS searches

Medline (Ovid), searched 10/02/2016

Exact database: Ovid MEDLINE(R) 1946 to January Week 4 2016

1	Demyelinating Diseases/	10446
2	Myelitis, Transverse/	1153
3	exp Optic Neuritis/	6737
4	Encephalomyelitis, Acute Disseminated/	1689
5	Demyelinating Autoimmune Diseases, CNS/	316
6	demyelinating disease*.tw.	4725
7	transverse myelitis.tw.	1356
8	neuromyelitis optica.tw.	1735
9	optic neuritis.tw.	3792
10	acute disseminated encephalomyelitis.tw.	1098
11	devic.tw.	107
12	ADEM.tw.	574
13	demyelinating disorder.tw.	335
14	clinically isolated syndrome.tw.	644
15	first demyelinating event.tw.	68
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	24564
17	exp Economics/	517857
18	exp "Costs and Cost Analysis"/	193384
19	Health Status/	64061
20	exp "Quality of Life"/	131967
21	exp Quality-Adjusted Life Years/	7948
22	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.	476878
23	(health state* or health status).tw.	41167
24	(qaly* or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or HUI).tw.	141292
25	(markov or time trade off or TTO or standard gamble or hrql or hrqol or disabilit* or disutilit*).tw.	133897
26	(quality adj2 life).tw.	155431
27	(decision adj2 model).tw.	4092
28	(visual analog* scale* or discrete choice experiment* or health* year* equivalen* or (willing* adj2 pay)).tw.	33282
29	("resource use" or resource utili?ation).tw.	9601
30	(well-being or wellbeing).tw.	46641
31	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	1331084
32	(metaanalys* or meta analys* or meta-analys*).tw.	69583
33	(systematic* and review*).mp.	95472
34	meta analysis.pt.	60490

35	(literature and review*).mp.	315829
36	(review* adj10 (model* or cost* or economic* or "quality of life" or HRQoL or HRQL or utilit*)).tw.	37973
37	32 or 33 or 34 or 35 or 36	453843
38	16 and 31	1437
39	37 and 38	82
40	limit 38 to systematic reviews	51
41	39 or 40	107
42	limit 41 to yr="2011 -Current"	51

Total minus duplicates with MS cost SRs search: 11

Medline In-process, searched 11/02/2016

Exact database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations February 10, 2016

1	demyelinating disease*.tw.	406
2	transverse myelitis.tw.	148
3	neuromyelitis optica.tw.	322
4	optic neuritis.tw.	360
5	acute disseminated encephalomyelitis.tw.	128
6	devic.tw.	6
7	ADEM.tw.	84
8	demyelinating disorder.tw.	56
9	clinically isolated syndrome.tw.	118
10	first demyelinating event.tw.	6
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	1259
12	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.	69098
13	(health state* or health status).tw.	4217
14	(qaly* or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or HUI).tw.	19723
15	(markov or time trade off or TTO or standard gamble or hrql or hrqol or disabilit* or disutilit*).tw.	16916
16	(quality adj2 life).tw.	22287
17	(decision adj2 model).tw.	492
18	(visual analog* scale* or discrete choice experiment* or health* year* equivalen* or (willing* adj2 pay)).tw.	5321
19	("resource use" or resource utili?ation).tw.	1372
20	(well-being or wellbeing).tw.	6423
21	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	126925
22	(metaanalys* or meta analys* or meta-analys*).tw.	13978
23	(systematic* and review*).tw.	18746
24	(literature and review*).tw.	40310

25	(review* adj10 (model* or cost* or economic* or "quality of life" or HRQoL or HRQL or utilit*)).tw.	6282
26	22 or 23 or 24 or 25	63191
27	11 and 21	186
28	limit 27 to systematic reviews	7
29	26 and 27	12
30	28 or 29	14
31	limit 30 to yr="2011 -Current"	11

Total minus duplicates with MS cost SRs search: 5

Embase (Ovid), searched 11/02/2016

Exact database: Embase 1974 to 2016 Week 06

1	demyelinating disease/	12216
2	myelitis/	6771
3	optic neuritis/	6979
4	acute disseminated encephalomyelitis/	1378
5	myelooptic neuropathy/	4897
6	demyelinating disease*.tw.	7443
7	transverse myelitis.tw.	2462
8	neuromyelitis optica.tw.	4162
9	optic neuritis.tw.	6551
10	acute disseminated encephalomyelitis.tw.	1762
11	devic.tw.	229
12	ADEM.tw.	1211
13	demyelinating disorder.tw.	624
14	clinically isolated syndrome.tw.	1758
15	first demyelinating event.tw.	159
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	34739
17	exp health economics/	679154
18	exp health status/	165534
19	exp "quality of life"/	327227
20	exp quality adjusted life year/	15498
21	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.	715448
22	(health state* or health status).tw.	57542
23	(qaly* or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF6D or SF-6D or HUI).tw.	223904
24	(markov or time trade off or TTO or standard gamble or hrql or hrqol or disabilit* or disutilit*).tw.	209301
25	(quality adj2 life).tw.	272302

26	(decision adj2 model).tw.	6788
27	(visual analog* scale* or discrete choice experiment* or health* year* equivalen*).tw.	49341
28	("resource use" or resource utili?ation).tw.	17623
29	(well-being or wellbeing or (willing* adj2 pay)).tw.	74888
30	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29	1979047
31	meta analysis/	103826
32	(metaanalys* or meta analys* or meta-analys*).tw.	111288
33	"systematic review"/	101172
34	(systematic* adj3 review*).tw.	104294
35	(literature adj3 review*).tw.	246476
36	(review* adj10 (model* or cost* or economic* or "quality of life" or HRQoL or HRQL or utilit*)).tw.	56523
37	31 or 32 or 33 or 34 or 35 or 36	488476
38	16 and 30	3989
39	37 and 38	212
40	limit 38 to "systematic review"	64
41	39 or 40	212
42	limit 41 to yr="2011 -Current"	113

Total minus duplicates with MS cost SRs search: 47

DARE (Cochrane Library), searched 13/01/2016

#1	MeSH descriptor: [Demyelinating Diseases] this term only	71
#2	MeSH descriptor: [Myelitis, Transverse] this term only	6
#3	MeSH descriptor: [Optic Neuritis] explode all trees	95
#4	MeSH descriptor: [Encephalomyelitis, Acute Disseminated] this term only	3
#5	MeSH descriptor: [Demyelinating Autoimmune Diseases, CNS] this term only	2
#6	demyelinating next disease*:ti,ab,kw (Word variations have been searched)	186
#7	transverse myelitis:ti,ab,kw (Word variations have been searched)	14
#8	neuromyelitis optica:ti,ab,kw (Word variations have been searched)	20
#9	optic neuritis:ti,ab,kw (Word variations have been searched)	220
#10	acute disseminated encephalomyelitis:ti,ab,kw (Word variations have been searched)	13
#11	devic:ti,ab,kw (Word variations have been searched)	2
#12	ADEM:ti,ab,kw (Word variations have been searched)	4
#13	demyelinating disorder:ti,ab,kw (Word variations have been searched)	49
#14	clinically isolated syndrome:ti,ab,kw (Word variations have been searched)	114
#15	first demyelinating event:ti,ab,kw (Word variations have been searched)	72
#16	single demyelinating event:ti,ab,kw (Word variations have been searched)	9
#17	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16	561
#18	MeSH descriptor: [Economics] explode all trees	26697
#19	MeSH descriptor: [Costs and Cost Analysis] explode all trees	24728
#20	MeSH descriptor: [Health Status] explode all trees	6149
#21	MeSH descriptor: [Quality of Life] explode all trees	17692
#22	MeSH descriptor: [Quality-Adjusted Life Years] explode all trees	4063
#23	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*):ti,ab,kw	53199
#24	(health next (state* or status)):ti,ab,kw	7906

#25	(qaly* or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or HUI):ti,ab,kw	13317
#26	(markov or "time trade off" or TTO or "standard gamble" or hrql or hrqol or disabilit* or disutilit*):ti,ab,kw	19514
#27	(quality near/2 life):ti,ab,kw	44945
#28	(decision near/2 model):ti,ab,kw	418
#29	((visual next analog* next scale*) or ("discrete choice" next experiment*) or (health* next year* next equivalen*) or (willing* near/2 pay)):ti,ab,kw	20672
#30	("resource use" or resource next utili?ation):ti,ab,kw	1657
#31	(well-being or wellbeing):ti,ab,kw	6305
#32	#18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31	130941
#33	#17 and #32 Publication Year from 2011 to 2016	97

Total all databases: 97

Other Reviews (DARE): 0

NHS EED and HTA database (Cochrane Library), searched 11/02/2016

#1	MeSH descriptor: [Demyelinating Diseases] this term only	71
#2	MeSH descriptor: [Myelitis, Transverse] this term only	6
#3	MeSH descriptor: [Optic Neuritis] explode all trees	95
#4	MeSH descriptor: [Encephalomyelitis, Acute Disseminated] this term only	3
#5	MeSH descriptor: [Demyelinating Autoimmune Diseases, CNS] this term only	2
#6	demyelinating next disease*:ti,ab,kw (Word variations have been searched)	186
#7	transverse myelitis:ti,ab,kw (Word variations have been searched)	14
#8	neuromyelitis optica:ti,ab,kw (Word variations have been searched)	20
#9	optic neuritis:ti,ab,kw (Word variations have been searched)	220
#10	acute disseminated encephalomyelitis:ti,ab,kw (Word variations have been searched)	13
#11	devic:ti,ab,kw (Word variations have been searched)	2
#12	ADEM:ti,ab,kw (Word variations have been searched)	4
#13	demyelinating disorder:ti,ab,kw (Word variations have been searched)	49
#14	clinically isolated syndrome:ti,ab,kw (Word variations have been searched)	114
#15	first demyelinating event:ti,ab,kw (Word variations have been searched)	72
#16	single demyelinating event:ti,ab,kw (Word variations have been searched)	9
#17	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 Publication Year from 2011 to 2016	241

Total all databases: 241

Technology Assessments (HTA database): 1

Economic Evaluations (NHS EED): 2

Science Citation Index (Web of Knowledge), searched 24/02/2016

# 18	41	#17 *Indexes=SCI-EXPANDED Timespan=2011-2016*
# 17	59	#16 AND #11 AND #10 *Indexes=SCI-EXPANDED Timespan=All years*
# 16	497,345	#15 OR #14 OR #13 OR #12 *Indexes=SCI-EXPANDED Timespan=All years*

# 15	62,256	TS=(review* NEAR/10 (model* or cost* or economic* or "quality of life" or HRQoL or HRQL or utilit*)) *Indexes=SCI-EXPANDED Timespan=All years*
# 14	253,207	TS=(literature AND review*) *Indexes=SCI-EXPANDED Timespan=All years*
# 13	104,464	TS=(systematic* AND review*) *Indexes=SCI-EXPANDED Timespan=All years*
# 12	168,986	TS=(metaanalys* or (meta NEAR/1 analys*)) *Indexes=SCI-EXPANDED Timespan=All years*
# 11	1,495,884	TS=("quality of life" or QoL or hrql or hrqol or ("quality adjusted life" NEAR/1 year*) or QALY* or cost* or economic* or pharmacoeconomic* or pharmaco-economic* or euro-qol or utilit* or disutilit* or euroqol or "euro qol" or EQ5D or EQ-5D or SF-36 or SF36 or SF-6D or SF6D or HUI or (time NEAR/1 trade*) or TTO or "standard gamble" or markov or (decision NEAR/2 model*) or (visual NEAR/1 analog*) or "discrete choice" or ((health* NEAR/1 year*) NEAR/1 equivalen*) or (health NEAR/1 stat*) or "willingness to pay" or "resource use" or (resource NEAR/1 utili?ation) or wellbeing or well-being) *Indexes=SCI-EXPANDED Timespan=All years*
# 10	16,921	#9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 9	96	TS="first demyelinating event" *Indexes=SCI-EXPANDED Timespan=All years*
# 8	1,202	TS="clinically isolated syndrome" *Indexes=SCI-EXPANDED Timespan=All years*
# 7	690	TS="ADEM" *Indexes=SCI-EXPANDED Timespan=All years*
# 6	464	TS="devic" *Indexes=SCI-EXPANDED Timespan=All years*
# 5	1,605	TS=("acute disseminated" NEAR/1 encephalomyelitis) *Indexes=SCI-EXPANDED Timespan=All years*
# 4	3,547	TS="neuromyelitis optica" *Indexes=SCI-EXPANDED Timespan=All years*
# 3	4,593	TS="optic neuritis" *Indexes=SCI-EXPANDED Timespan=All years*
# 2	1,703	TS=(transverse NEAR/1 myelitis) *Indexes=SCI-EXPANDED Timespan=All years*
# 1	6,814	TS=(demyelinating NEAR/2 (disease* OR disorder*)) *Indexes=SCI-EXPANDED Timespan=All years*

Total minus duplicates with MS cost SRs search: 4

RePEc, searched 24/02/2016

EconPapers first search

Free text: demyelinating OR myelitis OR "neuromyelitis optica" OR "optic neuritis" OR "acute disseminated encephalomyelitis" OR "clinically isolated syndrome"

2

Sorted by item date

Total number published from 2011 to 2016: 1

EconPapers second search

Keywords and Title: devic OR ADEM

0

Total: 1

Total minus duplicates with MS cost SRs search: 1

CEA Registry, searched 24/02/2016

Contains details of articles up to 2013

Basic Search

Articles

Full Search Contents: demyelinating: 3

Full Search Contents: myelitis: 1

Full Search Contents: neuromyelitis optica: 0

Full Search Contents: optic neuritis: 0

Full Search Contents: encephalomyelitis: 0

Full Search Contents: clinically isolated syndrome: 2

Total: 6

Total number published from 2011 to 2016: 1

Total minus duplicates with MS cost SRs search: 0

ScHARR HUD, searched 24/02/2016

demyelinating in any field: 0

myelitis in any field: 0

neuromyelitis optica in any field: 0

optic neuritis in any field: 0

acute disseminated encephalomyelitis in any field: 0

clinically isolated syndrome in any field: 0

Total: 0

23.3.3 Grey literature

Searches of websites were undertaken concurrently for both clinical effectiveness and cost-effectiveness. For a record of these searches, see Appendix 1.

Table 90: Quality assessment of systematic reviews of economic evaluations

Criteria	Study								
	Allen et al., 2015[230]	Castrop et al., 2013[231]	Guo et al., 2014[232]	Hawton et al., 2013[233]	Owens et al., 2013[234]	Thompson et al., 2013[235]	Yamamoto and Campbell 2012[236]	Zalesak et al., 2014[237]	Kuspinar et al., 2014[238]
Was an 'a priori' design provided?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was there duplicate study selection and data extraction?	N	U	Y	U	N	N	U	U	N
Was a comprehensive literature search performed?	Y Sensitive subject search used in multiple sources including NICE website, but UK terms added to database searches using .mp., which may be a concern because it reduced numbers considerably	N Just MEDLINE (PubMed) using just 2 broad MeSH terms – one for MS and one for 'costs and cost analysis' (assume exploded?). No free text or other searching. No specific terms for CIS	Y MEDLINE (PubMed) using just specific 'cost-benefit analysis' MeSH term with MS in all fields and generic and brand names for DMTs. References of included after Title/Abstract sift checked	Y Multiple sources searched. References of retrieved studies and existing review articles checked and citation searches undertaken	N Non-systematic search Just MEDLINE (PubMed) Unclear if MeSH heading Health Care Economics and Organizations was exploded, but some free text terms used. No other searching for results section undertaken	Y? MEDLINE (Ovid and PubMed) using just 2 exploded broad MeSH terms – one for MS and one for 'costs and cost analysis'. References of published (included?) studies checked	Y? MEDLINE (PubMed) using just specific 'cost-benefit analysis' with 'the general search term' MS (assume free text and MeSH?). Generic and brand names for DMTs incorporated - unclear how, but numbers in flowshart imply combined with AND.	U	Y Multiple databases searched using search strategy appropriate to the specific measures of interest, but no general HQoL terms used.

Criteria	Study								
	Allen et al., 2015[230]	Castrop et al., 2013[231]	Guo et al., 2014[232]	Hawton et al., 2013[233]	Owens et al., 2013[234]	Thompson et al., 2013[235]	Yamamoto and Campbell 2012[236]	Zalesak et al., 2014[237]	Kuspinar et al., 2014[238]
							CEA Registry and NHS EED also searched		
Was the status of publication (i.e. grey literature) used as an inclusion criterion?	N	N	Y	Y	Y	Y	Y	Y	Y
Was a list of studies (included and excluded) provided?	Included – Y (18, relating to 12 models) Excluded – Y (8)	Included – Y (4) Excluded – N	Included – Y (12) Excluded – Y (13)	Included – Y (38) Excluded – N (20)	Included – Y (53 on cost, cost-effectiveness, productivity decline, or abstenteeism)	Included – Y (35) Excluded – N	Included – Y (22) Excluded – Y (28)	N	Included – Y (15) Excluded – N
Were the characteristics of the included studies provided?	Y	Y	Y	Y	Y	Y	Y	N	Y
Was the scientific quality of the included studies assessed and documented?	Y	Y	U	N	N	N	Y	N	Y
Was the scientific quality of the	Y	Y	U	NA	NA	NA	Y	NA	Y

Criteria	Study								
	Allen et al., 2015[230]	Castrop et al., 2013[231]	Guo et al., 2014[232]	Hawton et al., 2013[233]	Owens et al., 2013[234]	Thompson et al., 2013[235]	Yamamoto and Campbell 2012[236]	Zalesak et al., 2014[237]	Kuspinar et al., 2014[238]
included studies used appropriately in formulating conclusions?									
Were the methods used to combine the findings of studies appropriate?	NA	NA	NA	NA	NA	NA	NA	NA	Y
Was the likelihood of publication bias assessed?	NA	NA	NA	NA	NA	NA	NA	NA	Y
Was the conflict of interest stated?	Y	Y	Y	N	Y	Y	Y	Y	Y
Additional criteria used by the assessment group									
Search date	03/03/2014	14/12/2012	01/04/2013	12/2011	15/09/2011	26/04/2012	09/2012	Unclear	08/10/2013
Scope	RRMS, DMTs, UK, cost-effectiveness models	CIS, Interferon beta, comparative, cost and cost-effectiveness	MS, DMTs, cost-effectiveness models	MS, cost-effectiveness	MS, DMTs, cost and cost-effectiveness	MS, DMTs, cost-effectiveness models	MS, DMTs, cost-effectiveness	MS, Breast Cancer and Rheumatoid Arthritis, specialty medicines, market research and cost-effectiveness	MS, Specific generic utility measures (HUI, EQ-5D, SF-6D, Quality of Well-Being)

CIS, clinically isolated syndrome; DMT, disease modifying treatment; EQ-5D, eurqol five dimensions; HUI, health utility index; MS, multiple sclerosis; N-no; NA-not applicable; SF-6D, short form six dimensions; U-unclear; Y-yes;

24 Appendix 6: Cost-effectiveness review of clinically isolated syndrome studies

24.1 *Full record of searches*

24.1.1 Main search

Medline (Ovid), searched 06/04/2016

Exact database: Ovid MEDLINE(R) 1946 to March Week 4 2016

1	Demyelinating Diseases/	10532
2	Myelitis, Transverse/	1165
3	exp Optic Neuritis/	6821
4	Encephalomyelitis, Acute Disseminated/	1696
5	Demyelinating Autoimmune Diseases, CNS/	323
6	demyelinating disease*.tw.	4779
7	transverse myelitis.tw.	1371
8	neuromyelitis optica.tw.	1786
9	optic neuritis.tw.	3828
10	acute disseminated encephalomyelitis.tw.	1109
11	devic.tw.	107
12	ADEM.tw.	583
13	demyelinating disorder.tw.	339
14	clinically isolated syndrome.tw.	660
15	first demyelinating event.tw.	69
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	24812
17	exp Economics/	522024
18	exp "Costs and Cost Analysis"/	195358
19	exp Quality-Adjusted Life Years/	8146
20	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.	484557
21	(decision adj2 model).tw.	4186
22	("resource use" or resource utili?ation).tw.	9821
23	(qaly* or (generic adj2 (instrument* or measure*)) or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or Health Utilities Index or HUI or 15D or Assessment of Quality of Life or AQOL or Quality of Well-Being or QWB).tw.	27152
24	17 or 18 or 19 or 20 or 21 or 22 or 23	885600
25	16 and 24	195

Medline In-Process & Other Non-Indexed Citations (Ovid), searched 06/04/2016

Exact database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations April 05, 2016

1	demyelinating disease*.tw.	415
2	transverse myelitis.tw.	150
3	neuromyelitis optica.tw.	329
4	optic neuritis.tw.	380
5	acute disseminated encephalomyelitis.tw.	136
6	devic.tw.	6
7	ADEM.tw.	85
8	demyelinating disorder.tw.	58
9	clinically isolated syndrome.tw.	122
10	first demyelinating event.tw.	6
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	1298
12	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.	71278
13	(decision adj2 model).tw.	511
14	("resource use" or resource utili?ation).tw.	1444
15	(qaly* or (generic adj2 (instrument* or measure*)) or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or Health Utilities Index or HUI or 15D or Assessment of Quality of Life or AQOL or Quality of Well-Being or QWB).tw.	3504
16	quality-adjusted life year*.tw.	949
17	12 or 13 or 14 or 15 or 16	74654
18	11 and 17	23

Embase (Ovid), searched 06/04/2016

Exact database: Embase 1974 to 2016 Week 14

1	demyelinating disease/	12351
2	myelitis/	6889
3	optic neuritis/	7109
4	acute disseminated encephalomyelitis/	1437
5	myelooptic neuropathy/	4987
6	demyelinating disease*.tw.	7511
7	transverse myelitis.tw.	2498
8	neuromyelitis optica.tw.	4242
9	optic neuritis.tw.	6631
10	acute disseminated encephalomyelitis.tw.	1792
11	devic.tw.	231
12	ADEM.tw.	1224
13	demyelinating disorder.tw.	633
14	clinically isolated syndrome.tw.	1789
15	first demyelinating event.tw.	159
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	35248

17	multiple sclerosis/	94999
18	multiple sclerosis.tw.	81514
19	17 or 18	102763
20	exp *health economics/	212668
21	exp quality adjusted life year/	15786
22	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).ti.	164671
23	(decision adj2 model).tw.	6901
24	("resource use" or resource utili?ation).tw.	17938
25	(qaly* or (generic adj2 (instrument* or measure*)) or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or Health Utilities Index or HUI or 15D or Assessment of Quality of Life or AQOL or Quality of Well-Being or QWB).tw.	50631
26	20 or 21 or 22 or 23 or 24 or 25	371080
27	16 and 26	173

NHS EED and HTA database (Cochrane Library), searched 06/04/2016

ID	Search	Hits
#1	MeSH descriptor: [Demyelinating Diseases] this term only	71
#2	MeSH descriptor: [Myelitis, Transverse] this term only	6
#3	MeSH descriptor: [Optic Neuritis] explode all trees	95
#4	MeSH descriptor: [Encephalomyelitis, Acute Disseminated] this term only	3
#5	MeSH descriptor: [Demyelinating Autoimmune Diseases, CNS] this term only	2
#6	demyelinating next disease*:ti,ab,kw (Word variations have been searched)	187
#7	transverse myelitis:ti,ab,kw (Word variations have been searched)	14
#8	neuromyelitis optica:ti,ab,kw (Word variations have been searched)	20
#9	optic neuritis:ti,ab,kw (Word variations have been searched)	222
#10	acute disseminated encephalomyelitis:ti,ab,kw (Word variations have been searched)	13
#11	devic:ti,ab,kw (Word variations have been searched)	3
#12	ADEM:ti,ab,kw (Word variations have been searched)	4
#13	demyelinating disorder:ti,ab,kw (Word variations have been searched)	49
#14	clinically isolated syndrome:ti,ab,kw (Word variations have been searched)	116
#15	first demyelinating event:ti,ab,kw (Word variations have been searched)	72
#16	single demyelinating event:ti,ab,kw (Word variations have been searched)	9
#17	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16	566

Total all databases: 566

Technology Assessments: 2

Economic Evaluations: 3

Science Citation Index and Conference Proceedings – Science (Web of Knowledge), searched 06/04/2016

# 14	210	#13 AND #10 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 13	1,335,874	#11 or #12 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*

# 12	80,174	TS=((“quality adjusted life” NEAR/1 year*) or QALY* or (generic NEAR/2 (instrument* or measure*)) or euro-qol or euroqol or “euro qol” or EQ5D or EQ-5D or SF-36 or SF36 or SF-6D or SF6D or "health utilities index" or HUI or 15D or "assessment of quality of life" or AQOL or "Quality of Well-Being" or QWB or (decision NEAR/2 model*) or “resource use” or (resource NEAR/1 utili?ation)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 11	1,280,769	TS=(cost* or economic* or pharmacoeconomic* or pharmaco-economic*) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 10	17,216	#9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 9	96	TS="first demyelinating event" *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 8	1,225	TS="clinically isolated syndrome" *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 7	711	TS="ADEM" *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 6	474	TS="devic" *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 5	1,620	TS=("acute disseminated" NEAR/1 encephalomyelitis) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 4	3,616	TS="neuromyelitis optica" *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 3	4,703	TS="optic neuritis" *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 2	1,732	TS=(transverse NEAR/1 myelitis) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 1	6,912	TS=(demyelinating NEAR/2 (disease* OR disorder*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*

RePEc, searched 06/04/2016

EconPapers first search

Free text: demyelinating OR myelitis OR "neuromyelitis optica" OR "optic neuritis" OR "acute disseminated encephalomyelitis" OR "clinically isolated syndrome"

2

EconPapers second search

Keywords and Title: devic OR ADEM

0

Total: 2

CEA Registry, searched 06/04/2016

Contains details of articles up to 2014 at time of search

Basic Search

Articles

Full Search Contents: demyelinating: 3

Full Search Contents: myelitis: 1

Full Search Contents: neuromyelitis optica: 0

Full Search Contents: optic neuritis: 0

Full Search Contents: encephalomyelitis: 0

Full Search Contents: clinically isolated syndrome: 2

Total: 6

ScHARR HUD, searched 06/04/2016

demyelinating in any field: 0

myelitis in any field: 0

neuromyelitis optica in any field: 0

optic neuritis in any field: 0

acute disseminated encephalomyelitis in any field: 0

clinically isolated syndrome in any field: 0

Total: 0

24.1.2 Additional search

CIS (or RRMS post 2011) registers or cohort natural history

Medline (Ovid), searched 16/06/2016

1	Demyelinating Diseases/
2	Myelitis, Transverse/
3	exp Optic Neuritis/
4	Encephalomyelitis, Acute Disseminated/
5	Demyelinating Autoimmune Diseases, CNS/
6	demyelinating disease*.tw.
7	transverse myelitis.tw.
8	neuromyelitis optica.tw.
9	optic neuritis.tw.

10	acute disseminated encephalomyelitis.tw.
11	devic.tw.
12	ADEM.tw.
13	demyelinating disorder.tw.
14	clinically isolated syndrome.tw.
15	first demyelinating event.tw.
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17	exp Registries/
18	(registry or registries).tw.
19	(register or registers).tw.
20	17 or 18 or 19
21	exp Cohort Studies/
22	(cohort adj (study or studies)).tw.
23	cohort analy$.tw.
24	(follow up adj (study or studies)).tw.
25	21 or 22 or 23 or 24
26	natural history.tw.
27	natural course.tw.
28	untreated.tw.
29	(("no" or "not") adj2 (treat* or therap*)).tw.
30	(natural adj2 (progression or development)).tw.
31	26 or 27 or 28 or 29 or 30
32	16 and 20
33	16 and 25 and 31
34	32 or 33
35	Multiple Sclerosis, Relapsing-Remitting/
36	relapsing remitting multiple sclerosis.tw.
37	35 or 36
38	limit 37 to yr="2011 -Current"
39	20 and 38
40	25 and 31 and 38
41	39 or 40
42	34 or 41

Table 91: Studies excluded from the cost-effectiveness review of CIS

	Reference	Reason for exclusion
1.	Casado V, Gubieras L, Romero-Pinel L, Matas E, Bau L, Lopez M, *et al.* Cost of the diagnosis of multiple sclerosis. *J Neurol*. 2009;256:S126.	Not full economic evaluation
2.	Fredrikson S, Prayoonwiwat N, Wicklein EM, Scherer P, Langdon D. Psychosocial aspects of clinically isolated syndrome (CIS) in Asia: Baseline data from the CogniCIS study Asian cohort. *J Neurol Sci*. 2009;285:S95.	Not an economic analysis
3.	Fredrikson S, Wicklein EM, Prayoonwiwat N, Beckmann K, Scherer P, Langdon D. Cognitive performance and health-related quality of life in clinically isolated syndrome (CIS) suggestive of multiple sclerosis: 2-year data from CogniCIS, a multinational, longitudinal study. *Eur J Neurol*. 2010;17:57.	Not an economic analysis
4.	Prayoonwiwat N, Nidhinandana S, Chankrachang S, Asawavichienjinda T, Tantirittisak T, Fredrikson S, *et al.* Psychosocial aspects of clinically isolated syndrome (CIS) in Asia: Baseline data from the cognicis study asian cohort. *Mult Scler*. 2010;16 (2):266-7.	Not an economic analysis
5.	Sanchez-Solino O, Grau C, Parra JC, Arroyo E. Quality of life in patients with high-risk clinically isolated syndrome treated with Avonex: Interim results of the AREMIN study. *J Neurol*. 2010;257:S190.	Not an economic analysis
6.	Stourac P, Horakova D, Tyblova M, Klimova E, Szilasiova J, Fenclova I, *et al.* Interim analysis of AMETYST: A phase 4 observational study of the impact of intramuscular interferon b-1a on quality of life, disability, and cognition in patients with clinically isolated syndrome/clinically definite multiple sclerosis. *Mult Scler*. 2012;1):486.	No model included
7.	Vermersch P, de Seze J, Delisse B, Lamaire S, Stojkovic T. Quality of life in multiple sclerosis: influence of interferon-beta 1a (Avonex (R)) treatment. *Mult Scler*. 2002;8(5):377-81.	Not an economic analysis

24.2 ***Blank data extraction form for cost-effectiveness studies (clinically isolated syndrome)***

Date:
Study ID:
Name of first reviewer:
Name of second reviewer:

Study details	
Study title	
First author	
Co-authors	
Source of publication Journal yy;vol(issue):pp	
Language	
Publication type	
Inclusion criteria/study eligibility/PICOS	
Population	
Intervention(s)	
Comparator(s)	
Outcome(s)	
Study design	
Methods	
Setting and location	
Study perspective	
Comparators	
Time horizon	
Discount rate	
Outcomes	
Measurement of effectiveness	
Measurement and valuation of preference based outcomes	
Resource use and costs	
Currency, price date and conversion	
Model type	
Assumptions	
Analytical methods	
Results	
Study parameters	
Incremental costs and outcomes	
Characterising uncertainty	
Study findings	
Limitations	
Generalisability	
Source of funding	
Conflicts of interest	
Comments	
Authors conclusion	
Reviewer's conclusion	

24.3 ***Quality assessment of economic evaluations in clinically isolated syndrome***

Table 92: CHEERS quality assessment for economic evaluations in CIS

Assessment	**Studies**								
	Fredrikson et al., 2013[239]	Iskedjian et al., 2005[242]	Lazzaro et al., 2009[241]	Kobelt et al., 2007[240]	Arbizu et al, 2009[243]	Caloyeras et al., 2009[245]	Caloyeras et al., 2008[244]	Caloyeras et al., 2012[246]	Zarco et al., 2014[247]
Title	Y	Y	Y	Y	Y	Y	Y	Y	Y
Abstract	Y	Y	Y	Y	Y	Y	Y	N	Y
Introduction									
Background and objectives	Y	Y	Y	N	Y	Y	Y	Y	Y
Methods									
Target population and subgroups	Y	Y	Y	Y	Y	Y	Y	Y	Y
Setting and location	N	N	N	N	Y	Y	Y	Y	Y
Study perspective	Y	Y	Y	Y	Y	Y	Y	Y	Y
Comparators	Y	Y	Y	Y	Y	Y	Y	Y	Y
Time horizon	Y	Y	Y	Y	Y	Y	Y	Y	Y
Discount rate	Y	Y	Y	Y	Y	Y	Y	Y	Y
Choice of health outcomes	Y	Y	Y	Y	Y	Y	Y	Y	Y
Measurement of effectiveness	Y	Y	Y	Y	UNC	UNC	Y	Y	Y
Measurement and valuation of preference-based outcomes	N	N	N	N	UNC	UNC	Y	Y	N/A
Estimating resources and costs	Y	Y	Y	N	Y	Y	Y	Y	Y
Currency, price date, and conversion	Y	Y	Y	Y	Y	Y	Y	Y	Y
Choice of model	Y	Y	Y	Y	UNC	UNC	UNC	Y	Y
Assumptions	Y	Y	Y	N	UNC	UNC	Y	Y	UNC
Analytical methods	Y	Y	Y	Y	Y	Y	Y	N	Y
Study parameters (results)	Y	Y	Y	Y	UNC	UNC	Y	N	Y
Incremental costs and outcomes	Y	Y	Y	Y	UNC	UNC	Y	Y	Y
Characterising uncertainty	Y	Y	Y	Y	UNC	UNC	UNC	N	Y
Study findings (discussion)	Y	Y	Y	Y	Y	Y	Y	Y	Y
Limitations	Y	Y	Y	N	UNC	UNC	UNC	Y	Y

Assessment	Studies								
	Fredrikson et al., 2013[239]	Iskedjian et al., 2005[242]	Lazzaro et al., 2009[241]	Kobelt et al., 2007[240]	Arbizu et al, 2009[243]	Caloyeras et al., 2009[245]	Caloyeras et al., 2008[244]	Caloyeras et al., 2012[246]	Zarco et al., 2014[247]
Generalizability	Y	Y	Y	UNC	UNC	UNC	UNC	Y	Y
Other									
Source of funding (other)	Y	Y	Y	N	UNC	UNC	UNC	Y	N
Conflicts of interest	Y	Y	Y	N	UNC	UNC	UNC	Y	N
N, no; N/A, not applicable; Y, yes; UNC-unclear									

Table 93: Philips' quality assessment for studies including an economic model in CIS

Philips' criteria		Studies								
		Fredrikson et al., 2013[239]	Iskedjian et al., 2005[242]	Lazzaro et al., 2009[241]	Kobelt et al., 2007[240]	Arbizu et al., 2009[243]	Caloyeras et al., 2008[244]	Caloyeras et al., 2009[245]	Caloyeras et al., 2012[246]	Zarco et al., 2014[247]
Structure										
1.	Is there a clear statement of the decision problem?	Y	Y	Y	Y	Y	Y	Y	Y	Y
2.	Is the objective of the model specified and consistent with the stated decision problem?	Y	Y	Y	Y	Y	Y	Y	Y	Y
3.	Is the primary decision maker specified?	Y	Y	Y	Y	Y	Y	Y	Y	Y
4.	Is the perspective of the model stated clearly?	Y	Y	Y	Y	Y	Y	Y	Y	Y
5.	Are the model inputs consistent with the stated perspective?	Y	Y	Y	UNC	UNC	Y	Y	Y	Y
6.	Has the scope of the model been stated and justified?	Y	Y	Y	UNC	UNC	Y	UNC	Y	Y
7.	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Y	Y	Y	Y	UNC	UNC	UNC	Y	Y

Philips' criteria		Studies								
		Fredrikson et al., 2013[239]	Iskedjian et al., 2005[242]	Lazzaro et al., 2009[241]	Kobelt et al., 2007[240]	Arbizu et al., 2009[243]	Caloyeras et al., 2008[244]	Caloyeras et al., 2009[245]	Caloyeras et al., 2012[246]	Zarco et al., 2014[247]
8.	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Y	Y	Y	UNC	UNC	UNC	UNC	Y	N
9.	Are the sources of the data used to develop the structure of the model specified?	Y	Y	Y	UNC	UNC	Y	UNC	Y	Y
10.	Are the causal relationships described by the model structure justified appropriately?	Y	Y	Y	UNC	UNC	UNC	UNC	Y	UNC
11.	Are the structural assumptions transparent and justified?	Y	Y	Y	UNC	UNC	UNC	UNC	Y	UNC
12.	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Y	Y	Y	UNC	UNC	UNC	UNC	Y	UNC
13.	Is there a clear definition of the options under evaluation?	Y	Y	Y	Y	Y	Y	Y	Y	Y
14.	Have all feasible and practical options been evaluated?	N	N	N	N	Y	Y	Y	N	N
15.	Is there justification for the exclusion of feasible options?	N	N	N	N	UNC	N/A	UNC	N	N
16.	Is the chosen model type appropriate given the decision problem and specified casual relationships within the model?	Y	Y	Y	Y	Y	Y	Y	Y	N
17.	Is the time horizon of the model sufficient to reflect all important differences between the options?	Y	N	Y	Y	Y	Y	Y	Y	N
18.	Are the time horizon of the model, the duration of treatment	Y	Y	Y	UNC	Y	Y	Y	Y	Y

Philips' criteria		Studies								
		Fredrikson et al., 2013[239]	Iskedjian et al., 2005[242]	Lazzaro et al., 2009[241]	Kobelt et al., 2007[240]	Arbizu et al., 2009[243]	Caloyeras et al., 2008[244]	Caloyeras et al., 2009[245]	Caloyeras et al., 2012[246]	Zarco et al., 2014[247]
	and the duration of treatment described and justified?									
19.	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Y	Y	Y	UNC	Y	Y	Y	Y	N
20.	Is the cycle length defined and justified in terms of the natural history of disease?	Y	Y	Y	N	Y	Y	Y	Y	N/A
Data										
21.	Are the data identification methods transparent and appropriate given the objectives of the model?	Y	Y	Y	UNC	UNC	UNC	UNC	Y	UNC
22.	Where choices have been made between data sources are these justified appropriately?	N	N	N	UNC	UNC	UNC	UNC	Y	UNC
23.	Has particular attention been paid to identifying data for the important parameters of the model?	UNC	Y	Y	UNC	UNC	UNC	UNC	UNC	UNC
24.	Has the quality of the data been assessed appropriately?	UNC	N	N	UNC	UNC	UNC	UNC	UNC	UNC
25.	Where expert opinion has been used are the methods described and justified?	Y	Y	Y	UNC	UNC	UNC	UNC	N	UNC
26.	Is the data modelling methodology based on justifiable statistical and epidemiological	Y	Y	Y	UNC	UNC	UNC	UNC	Y	UNC

Philips' criteria		Studies								
		Fredrikson et al., 2013[239]	Iskedjian et al., 2005[242]	Lazzaro et al., 2009[241]	Kobelt et al., 2007[240]	Arbizu et al., 2009[243]	Caloyeras et al., 2008[244]	Caloyeras et al., 2009[245]	Caloyeras et al., 2012[246]	Zarco et al., 2014[247]
	techniques?									
27.	Is the choice of baseline data described and justified?	Y	Y	Y	UNC	UNC	UNC	UNC	Y	Y
28.	Are transition probabilities calculated appropriately?	Y	Y	Y	UNC	UNC	UNC	UNC	Y	UNC
29.	Has a half-cycle correction been applied to both costs and outcomes?	N	N	N	UNC	UNC	UNC	UNC	N	N/A
30.	If not, has the omission been justified?	N	N	N	UNC	UNC	UNC	UNC	N	N/A
31.	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	N	N	N	UNC	UNC	UNC	UNC	Y	UNC
32.	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	Y	Y	Y	UNC	Y	Y	UNC	Y	N/A
33.	Have alternative extrapolation assumptions been explored through sensitivity analysis?	N	N	N	UNC	UNC	UNC	UNC	Y	N/A
34.	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	Y	Y	Y	UNC	UNC	UNC	UNC	Y	N/A
35.	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis	Y	N	N	UNC	UNC	UNC	UNC	UNC	Y
36.	Are the costs incorporated into	Y	Y	Y	Y	Y	Y	Y	Y	Y

Philips' criteria		Studies								
		Fredrikson et al., 2013[239]	Iskedjian et al., 2005[242]	Lazzaro et al., 2009[241]	Kobelt et al., 2007[240]	Arbizu et al., 2009[243]	Caloyeras et al., 2008[244]	Caloyeras et al., 2009[245]	Caloyeras et al., 2012[246]	Zarco et al., 2014[247]
	the model justified?									
37.	Has the source for all costs been described?	Y	Y	Y	N	UNC	UNC	UNC	Y	Y
38.	Have discount rates been described and justified given the target decision maker?	Y	Y	Y	Y	Y	Y	Y	Y	Y
39.	Are the utilities incorporated into the model appropriate?	UNC	Y	Y	Y	Y	Y	Y	Y	Y
40.	Is the source of utility weights referenced?	Y	Y	Y	N	UNC	Y	UNC	Y	Y
41.	Are the methods of derivation for the utility weights justified?	Y	Y	N	N	UNC	UNC	UNC	Y	UNC
42.	Have all data incorporated into the model been described and referenced in sufficient detail?	Y	Y	N	N	UNC	UNC	UNC	Y	N
43.	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate?)	Y	Y	Y	N	UNC	UNC	UNC	Y	UNC
44.	Is the process of data incorporation transparent?	UNC	UNC	Y	N	UNC	UNC	UNC	UNC	N
45.	If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?	N	N	N	N	UNC	UNC	UNC	N	Y
46.	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	N	N	N	N	UNC	UNC	UNC	N	UNC
47.	Have the four principal types of uncertainty been addressed?	N	N	N	N	UNC	UNC	UNC	N	N

Philips' criteria		Studies								
		Fredrikson et al., 2013[239]	Iskedjian et al., 2005[242]	Lazzaro et al., 2009[241]	Kobelt et al., 2007[240]	Arbizu et al., 2009[243]	Caloyeras et al., 2008[244]	Caloyeras et al., 2009[245]	Caloyeras et al., 2012[246]	Zarco et al., 2014[247]
48.	If not, has the omission of particular forms of uncertainty been justified?	N	N	N	N	UNC	UNC	UNC	UNC	N
49.	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	Y	Y	Y	UNC	UNC	UNC	UNC	N	N
50.	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	N	N	N	N	UNC	UNC	UNC	N	N
51.	Has heterogeneity been dealt with by running the model separately for different sub-groups?	N/A	N/A	N/A	UNC	UNC	UNC	UNC	N	N
52.	Are the methods of assessment of parameter uncertainty appropriate?	Y	Y	Y	Y	UNC	UNC	UNC	Y	Y
53.	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Y	Y	Y	UNC	UNC	UNC	UNC	N/A	Y
54.	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	UNC	UNC	UNC	UNC	UNC	UNC	UNC	UNC	N
55.	Are any counterintuitive results from the model explained and justified?	N/A	Y	N/A	UNC	UNC	UNC	UNC	UNC	N/A
56.	If the model has been calibrated against independent data, have any differences been explained and justified?	N/A	N/A	N/A	UNC	UNC	UNC	UNC	N/A	UNC

Philips' criteria		Studies								
		Fredrikson et al., 2013[239]	Iskedjian et al., 2005[242]	Lazzaro et al., 2009[241]	Kobelt et al., 2007[240]	Arbizu et al., 2009[243]	Caloyeras et al., 2008[244]	Caloyeras et al., 2009[245]	Caloyeras et al., 2012[246]	Zarco et al., 2014[247]
57.	Have the results been compared with those of previous models and any differences in results explained?	Y	Y	Y	UNC	UNC	UNC	UNC	N	Y

N- No; N/A- Not Applicable; Y- Yes; UNC-Unclear

25 Appendix 7: Cost-effectiveness review of relapsing remitting multiple sclerosis studies

25.1 *Full record of searches*

25.1.1 Main searches: 2012 to 2016 searches

Medline (Ovid), searched 05/04/2016

Exact database: Ovid MEDLINE(R) 1946 to March Week 4 2016

1	exp Multiple Sclerosis/	47422
2	multiple sclerosis.tw.	50604
3	1 or 2	58051
4	exp Economics/	522024
5	exp "Costs and Cost Analysis"/	195358
6	exp Quality-Adjusted Life Years/	8146
7	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.	484557
8	(decision adj2 model).tw.	4186
9	("resource use" or resource utili?ation).tw.	9821
10	(qaly* or (generic adj2 (instrument* or measure*)) or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or Health Utilities Index or HUI or 15D or Assessment of Quality of Life or AQOL or Quality of Well-Being or QWB).tw.	27152
11	4 or 5 or 6 or 7 or 8 or 9 or 10	885600
12	3 and 11	1860
13	limit 12 to yr="2012 -Current"	507

Medline In-Process & Other Non-Indexed Citations (Ovid), searched 05/04/2016

Exact database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations April 04, 2016

1	multiple sclerosis.tw.	4995
2	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.	71051
3	(decision adj2 model).tw.	511
4	("resource use" or resource utili?ation).tw.	1438
5	(qaly* or (generic adj2 (instrument* or measure*)) or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or Health Utilities Index or HUI or 15D or Assessment of Quality of Life or AQOL or Quality of Well-Being or QWB).tw.	3483
6	quality-adjusted life year*.tw.	945
7	2 or 3 or 4 or 5 or 6	74406
8	1 and 7	239
9	limit 8 to yr="2012 -Current"	198

Embase (Ovid), searched 05/04/2016

Exact database: Embase 1974 to 2016 Week 14

1	multiple sclerosis/	94999
2	multiple sclerosis.tw.	81514
3	1 or 2	102763
4	exp *health economics/	212668
5	exp quality adjusted life year/	15786
6	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).ti.	164671
7	(decision adj2 model).tw.	6901
8	("resource use" or resource utili?ation).tw.	17938
9	(qaly* or (generic adj2 (instrument* or measure*)) or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or Health Utilities Index or HUI or 15D or Assessment of Quality of Life or AQOL or Quality of Well-Being or QWB).tw.	50631
10	4 or 5 or 6 or 7 or 8 or 9	371080
11	3 and 10	2024
12	limit 11 to yr="2012 -Current"	988
13	limit 12 to (conference abstract or conference paper or conference proceeding or "conference review")	550
14	12 not 13	438

NHS EED and HTA database (Cochrane Library), searched 05/04/2016

ID	Search	Hits
#1	MeSH descriptor: [Multiple Sclerosis] explode all trees	2127
#2	multiple sclerosis:ti,ab,kw	5131
#3	#1 or #2 Publication Year from 2012 to 2016	2064

Total all databases: 2064

Technology Assessments: 30

Economic Evaluations: 27

Science Citation Index (Web of Knowledge), searched 05/04/2016

# 7	315	#5 not #6 *Indexes=SCI-EXPANDED Timespan=2012-2016*
# 6	157	(#5) *AND* DOCUMENT TYPES: (Meeting Abstract OR Meeting Summary OR Proceedings Paper) *Indexes=SCI-EXPANDED Timespan=2012-2016*
# 5	472	#4 AND #1 *Indexes=SCI-EXPANDED Timespan=2012-2016*
# 4	73,283	#3 OR #2 *Indexes=SCI-EXPANDED Timespan=2012-2016*
# 3	24,433	TS=((“quality adjusted life” NEAR/1 year*) or QALY* or (generic NEAR/2 (instrument* or measure*)) or euro-qol or euroqol or “euro qol” or EQ5D or EQ-5D or SF-36 or SF36 or SF-6D or SF6D or "health utilities index" or HUI or 15D or

		"assessment of quality of life" or AQOL or "Quality of Well-Being" or QWB or (decision NEAR/2 model*) or “resource use” or (resource NEAR/1 utili?ation)) *Indexes=SCI-EXPANDED Timespan=2012-2016*
# 2	53,184	TI=(cost* or economic* or pharmacoeconomic* or pharmaco-economic*) *Indexes=SCI-EXPANDED Timespan=2012-2016*
# 1	87,043	TS="multiple sclerosis" *Indexes=SCI-EXPANDED Timespan=All years*

RePEc, searched 05/04/2016

EconPapers

Free text: "multiple sclerosis"

128

Sorted by item date

Total number published from 2012 to 2016: 32

CEA Registry, searched 05/04/2016

Contained details of articles up to 2014 at time of search

Basic Search

Articles

Full Search Contents: multiple sclerosis

Total number published from 2012 to 2016: 17

ScHARR HUD, searched 05/04/2016

multiple sclerosis in any field

AND

2012 to 2016 in Year Published

Total: 7

25.1.2 Main searches: HRQoL studies with generic measures up to 2011

Medline (Ovid), searched 06/04/2016

Exact database: Ovid MEDLINE(R) 1946 to March Week 4 2016

1	exp Multiple Sclerosis/	47422
2	multiple sclerosis.tw.	50604
3	1 or 2	58051
4	(qaly* or (generic adj2 (instrument* or measure*)) or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or Health Utilities Index or HUI or 15D or Assessment of Quality of Life or AQOL or Quality of Well-Being or QWB).tw.	27152

5	3 and 4	355
6	limit 5 to yr="1902 - 2011"	248

Medline In-Process & Other Non-Indexed Citations (Ovid), searched 06/04/2016

Exact database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations April 05, 2016

1	multiple sclerosis.tw.	5010
2	(qaly* or (generic adj2 (instrument* or measure*)) or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or Health Utilities Index or HUI or 15D or Assessment of Quality of Life or AQOL or Quality of Well-Being or QWB).tw.	3504
3	1 and 2	46
4	limit 3 to yr="1860 - 2011"	7

Embase (Ovid), searched 06/04/2016

Exact database: Embase 1974 to 2016 Week 14

1	multiple sclerosis/	94999
2	multiple sclerosis.tw.	81514
3	1 or 2	102763
4	(qaly* or (generic adj2 (instrument* or measure*)) or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or Health Utilities Index or HUI or 15D or Assessment of Quality of Life or AQOL or Quality of Well-Being or QWB).tw.	50631
5	3 and 4	885
6	limit 5 to yr="1902 - 2011"	427
7	limit 6 to (conference abstract or conference paper or conference proceeding or "conference review")	158
8	6 not 7	269

Science Citation Index (Web of Knowledge), searched 06/04/2016

# 5	332	#3 not #4 *Indexes=SCI-EXPANDED Timespan=1900-2011*
# 4	19	(#3) *AND* DOCUMENT TYPES: (Meeting Abstract OR Meeting Summary OR Proceedings Paper) *Indexes=SCI-EXPANDED Timespan=1900-2011*
# 3	351	#2 AND #1 *Indexes=SCI-EXPANDED Timespan=1900-2011*
# 2	20,713	TS=(QALY* or (generic NEAR/2 (instrument* or measure*)) or euro-qol or euroqol or “euro qol” or EQ5D or EQ-5D or SF-36 or SF36 or SF-6D or SF6D or "health utilities index" or HUI or 15D or "assessment of quality of life" or AQOL or "Quality of Well-Being" or QWB) *Indexes=SCI-EXPANDED Timespan=1900-2011*
# 1	61,623	TS="multiple sclerosis" *Indexes=SCI-EXPANDED Timespan=1900-2011*

CEA Registry, searched 06/04/2016

Contains details of articles up to 2014 at time of search

Basic Search

Articles

Full Search Contents: multiple sclerosis

Total number published from 1997 to 2011: 22

ScHARR HUD, searched 06/04/2016

multiple sclerosis in any field

AND

2000 to 2011 in Year Published

Total: 2

25.1.3 Additional searches

Targeted database search to identify any additional multiple sclerosis patient registries that include data from before 1995

Medline (Ovid), searched 31/05/2016

1	exp Multiple Sclerosis/	48148
2	multiple sclerosis.tw.	51476
3	1 or 2	58975
4	exp Registries/	67800
5	(registry or registries).tw.	70207
6	(register or registers).tw.	45934
7	4 or 5 or 6	140237
8	3 and 7	755
9	limit 8 to yr="1902 - 2005"	178

25.2 *Excluded studies (cost-effectiveness studies and health related quality of life studies)*

Table 94: Studies excluded from systematic review of cost-effectiveness in RRMS

	Reference	**Reason for exclusion**
1.	Guia de practica clinica sobre la atencion a las personas con esclerosis multiple. [Clinical practice guideline of care for people with multiple sclerosis]	Non-English language

	Barcelona: Catalan Agency for Health Information, Assessment and Quality (CAHIAQ -formerly CAHTA). 2012.	
2.	Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis. Health Technology Assessment, 2013 ERG report: Cooper, K, Bryant J, Harris P, Loveman E, Jones J, Welch K. Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis: A Single Technology Appraisal. SHTAC, 2013.	Intervention not of interest
3.	Teriflunomide for the treatment of relapsing forms of multiple sclerosis (Project record). 2013 [cited; Available from: http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32013000872/frame.html.	Intervention not of interest
4.	Dimethyl fumarate for the treatment of relapsing remitting multiple sclerosis (Project record). 2013 [cited; Available from: http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32013000873/frame.html.	Intervention not of interest
5.	Abolfazli R, Hosseini A, Gholami K, Javadi MR, Torkamandi H, Emami S. Quality of Life Assessment in Patients with Multiple Sclerosis Receiving Interferon Beta-1a: A Comparative Longitudinal Study of Avonex and Its Biosimilar CinnoVex. *ISRN Neurology*. 2012;2012:786526.	Intervention not of interest
6.	Acaster S, Perard R, Chauhan D, Lloyd AJ. A forgotten aspect of the NICE reference case: an observational study of the health related quality of life impact on caregivers of people with multiple sclerosis. *BMC Health Serv Res*. 2013;13:346.	Not relevant
7.	Ayuso GI. [Multiple sclerosis: socioeconomic effects and impact on quality of life]. *Med Clin (Barc)*. 2014;143 Suppl 3:7-12. Esclerosis multiple: impacto socioeconomico y en la calidad de vida de los pacientes.	Not relevant
8.	Baumstarck K, Butzkueven H, Fernandez O, Flachenecker P, Stecchi S, Idiman E, *et al.* Responsiveness of the Multiple Sclerosis International Quality of Life questionnaire to disability change: a longitudinal study. *Health & Quality of Life Outcomes*. 2013;11:127.	Generic preference-based measure not used
9.	Baumstarck K, Pelletier J, Aghababian V, Reuter F, Klemina I, Berbis J, *et al.* Is the concept of quality of life relevant for multiple sclerosis patients with cognitive impairment? Preliminary results of a cross-sectional study. *PLoS ONE [Electronic Resource]*. 2012;7(1):e30627.	Generic preference-based measure not used
10.	Baumstarck K, Pelletier J, Boucekine M, Auquier P, MusiQo Lsg. Predictors of quality of life in patients with relapsing-remitting multiple sclerosis: a 2-year longitudinal study. *Rev Neurol (Paris)*. 2015;171(2):173-80.	Generic preference-based measure not used
11.	Baumstarck K, Pelletier J, Butzkueven H, Fernandez O, Flachenecker P, Idiman E, *et al.* Health-related quality of life as an independent predictor of long-term disability for patients with relapsing-remitting multiple sclerosis. *Eur J Neurol*. 2013;20(6):907-14, e78-9.	Generic preference-based measure not used
12.	Beckerman H, Kempen JC, Knol DL, Polman CH, Lankhorst GJ, de Groot V. The first 10 years with multiple sclerosis: the longitudinal course of daily functioning. *J Rehabil Med*. 2013;45(1):68-75.	Generic preference-based measure not used
13.	Bergvall N, Tambour M, Henriksson F, Fredrikson S. Cost-minimization analysis of fingolimod compared with natalizumab for the treatment of relapsing-remitting multiple sclerosis in Sweden. *J Med Econ*. 2013;16(3):349-57.	Intervention not of interest
14.	Boeru G, Milanov I, De Robertis F, Kozubski W, Lang M, Rojas-Farreras S, *et al.* ExtaviJect 30G device for subcutaneous self-injection of interferon beta-1b for multiple sclerosis: a prospective European study. *Medical Devices Evidence and Research*. 2013;6:175-84.	Not relevant
15.	Boucekine M, Loundou A, Baumstarck K, Minaya-Flores P, Pelletier J, Ghattas B, *et al.* Using the random forest method to detect a response shift in the quality of life of multiple sclerosis patients: a cohort study. *BMC Med Res*	Generic preference-based measure not used

	Methodol. 2013;13:20.	
16.	Brandes DW, Raimundo K, Agashivala N, Kim E. Implications of real-world adherence on cost-effectiveness analysis in multiple sclerosis. *J Med Econ*. 2013;16(4):547-51.	Not relevant
17.	Brown MG. Cost of disease-modifying therapies for multiple sclerosis. *Neurology*. 2015;84(21):e181-5.	Not a full economic analysis
18.	Buchanan RJ, Johnson O, Zuniga MA, Carrillo-Zuniga G, Chakravorty BJ. Health-related quality of life among Latinos with multiple sclerosis. *Journal of Social Work in Disability & Rehabilitation*. 2012;11(4):240-57.	Generic preference-based measure not used
19.	Buhse M, Della Ratta C, Galiczewski J, Eckardt P. Caregivers of older persons with multiple sclerosis: determinants of health-related quality of life. *J Neurosci Nurs*. 2015;47(2):E2-E12.	Not relevant
20.	Calkwood J, Cree B, Crayton H, Kantor D, Steingo B, Barbato L, *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: Analyses of the EPOC trial. *BMC Neurol*. 2014;14 (1) (no pagination)(220).	Intervention not of interest
21.	Caloyeras JP, Zhang B, Wang C, Eriksson M, Fredrikson S, Beckmann K, et al. Cost-effectiveness analysis of interferon beta-1b for the treatment of patients with a first clinical event suggestive of multiple sclerosis. Clin Ther. 2012;34(5):1132-44	Not relevant for RRMS review
22.	Campbell JD, Ghushchyan V, Brett McQueen R, Cahoon-Metzger S, Livingston T, Vollmer T, *et al.* Burden of multiple sclerosis on direct, indirect costs and quality of life: National US estimates. *Multiple Sclerosis and Related Disorders*. 2014;3(2):227-36.	Results not reported by EDSS level
23.	Campbell JD, McQueen RB, Miravalle A, Corboy JR, Vollmer TL, Nair K. Comparative effectiveness of early natalizumab treatment in JC virus-negative relapsing-remitting multiple sclerosis. *Am J Manag Care*. 2013;19(4):278-85.	Intervention not of interest
24.	Carlson JJ, Hansen RN, Dmochowski RR, Globe DR, Colayco DC, Sullivan SD. Estimating the cost-effectiveness of onabotulinumtoxinA for neurogenic detrusor overactivity in the United States. *Clin Ther*. 2013;35(4):414-24.	Intervention not of interest
25.	Chruzander C, Ytterberg C, Gottberg K, Einarsson U, Widen Holmqvist L, Johansson S. A 10-year follow-up of a population-based study of people with multiple sclerosis in Stockholm, Sweden: changes in health-related quality of life and the value of different factors in predicting health-related quality of life. *J Neurol Sci*. 2014;339(1-2):57-63.	Results not reported by EDSS level
26.	Cioncoloni D, Innocenti I, Bartalini S, Santarnecchi E, Rossi S, Rossi A, *et al.* Individual factors enhance poor health-related quality of life outcome in multiple sclerosis patients. Significance of predictive determinants. *J Neurol Sci*. 2014;345(1-2):213-9.	Generic preference-based measure not used
27.	Coleman CI, Sidovar MF, Roberts MS, Kohn C. Impact of mobility impairment on indirect costs and health-related quality of life in multiple sclerosis. *PLoS ONE [Electronic Resource]*. 2013;8(1):e54756.	Generic measure not used; indirect costs estimated
28.	Crespo C, Izquierdo G, Garcia-Ruiz A, Granell M, Brosa M. Cost minimisation analysis of fingolimod vs natalizumab as a second line of treatment for relapsing-remitting multiple sclerosis. *Neurologia*. 2014;29(4):210-7.	Interventions not of interest
29.	de la Rosa RS, García-Bujalance L, Meca-Lallana J. Cost analysis of glatiramer acetate versus interferon-ß for relapsing-remitting multiple sclerosis in patients with spasticity: the Escala study. *Health Economics Review*. 2015;5(1):1-9.	No decision analytical model
30.	Devy R, Lehert P, Varlan E, Genty M, Edan G. A short and validated multiple sclerosis-specific health-related quality of life measurement for routine medical practice. *Eur J Neurol*. 2013;20(6):935-41.	Generic preference-based measure not used
31.	Di Filippo M, Proietti S, Gaetani L, Gubbiotti M, Di Gregorio M, Eusebi P, *et al.* Lower urinary tract symptoms and urodynamic dysfunction in clinically isolated syndromes suggestive of multiple sclerosis. *Eur J Neurol*. 2014;21(4):648-53.	Generic preference-based measure not used

32.	Ertekin O, Ozakbas S, Idiman E. Caregiver burden, quality of life and walking ability in different disability levels of multiple sclerosis. *NeuroRehabilitation*. 2014;34(2):313-21.	Generic preference-based measure not used
33.	Fernandez-Munoz JJ, Moron-Verdasco A, Cigaran-Mendez M, Munoz-Hellin E, Perez-de-Heredia-Torres M, Fernandez-de-las-Penas C. Disability, quality of life, personality, cognitive and psychological variables associated with fatigue in patients with multiple sclerosis. *Acta Neurol Scand*. 2015;132(2):118-24.	Generic preference-based measure not used
34.	Fiest KM, Fisk JD, Patten SB, Tremlett H, Wolfson C, Warren S, *et al.* Comorbidity is associated with pain-related activity limitations in multiple sclerosis. *Multiple Sclerosis and Related Disorders*. 2015;4(5):470-6.	Not relevant
35.	Fines P, Garner R, Bancej C, Bernier J, Manuel DG. Development and implementation of microsimulation models of neurological conditions. *Health Rep*. 2016;27(3):3-9.	Not relevant
36.	Flensner G, Landtblom AM, Soderhamn O, Ek AC. Work capacity and health-related quality of life among individuals with multiple sclerosis reduced by fatigue: a cross-sectional study. *BMC Public Health*. 2013;13:224.	Generic preference-based measure not used
37.	Fogarty E, Walsh C, Adams R, McGuigan C, Barry M, Tubridy N. Relating health-related Quality of Life to disability progression in multiple sclerosis, using the 5-level EQ-5D. *Mult Scler*. 2013;19(9):1190-6.	No decision analytical model
38.	Fredrikson S, McLeod E, Henry N, Pitcher A, Lowin J, Cuche M, et al. A cost-effectiveness analysis of subcutaneous interferon beta-1a 44mcg 3-times a week vs no treatment for patients with clinically isolated syndrome in Sweden. J Med Econ. 2013;16(6):756-62.	Not relevant for RRMS review
39.	Garattini L, Ghislandi F, Da Costa MR. Cost-Effectiveness Modeling in Multiple Sclerosis: Playing Around with Non-Healthcare Costs? *Pharmacoeconomics*. 2015;33(12):1241-4.	Not relevant
40.	Gavelova M, Nagyova I, Rosenberger J, Krokavcova M, Gdovinova Z, Groothoff JW, *et al.* Importance of an individual's evaluation of functional status for health-related quality of life in patients with multiple sclerosis. *Disability & Health Journal*. 2015;8(3):372-9.	Generic preference-based measure not used
41.	Ghajarzadeh M, Azizi S, Moghadasi AN, Sahraian MA, Azimi A, Mohammadifar M, *et al.* Validity and Reliability of the Persian Version of the PERception de la Scle'rose En Plaques et de ses Pousse'es Questionnaire Evaluating Multiple Sclerosis-related Quality of Life. *Int J Prev Med*. 2016;7:25.	Generic preference-based measure not used
42.	Giordano A, Ferrari G, Radice D, Randi G, Bisanti L, Solari A, *et al.* Health-related quality of life and depressive symptoms in significant others of people with multiple sclerosis: a community study. *Eur J Neurol*. 2012;19(6):847-54.	Not relevant
43.	Goodwin E, Green C. A Quality-Adjusted Life-Year Measure for Multiple Sclerosis: Developing a Patient-Reported Health State Classification System for a Multiple Sclerosis-Specific Preference-Based Measure. *Value Health*. 2015;18(8):1016-24.	Generic preference-based measure not used
44.	Goodwin E, Green C, Spencer A. Estimating a Preference-Based Index for an Eight-Dimensional Health State Classification System for Multiple Sclerosis. *Value Health*. 2015;18(8):1025-36.	Generic preference-based measure not used
45.	Grytten N, Aarseth JH, Espeset K, Berg Johnsen G, Wehus R, Lund C, *et al.* Health-related quality of life and disease-modifying treatment behaviour in relapsing-remitting multiple sclerosis--a multicentre cohort study. *Acta Neurol Scand*. 2012;Supplementum.(195):51-7.	Generic preference-based measure not used
46.	Hadianfard H, Ashjazadeh N, Feridoni S, Farjam E. The role of psychological resilience, severity of disease and treatment adherence in the prediction of health-related quality of life in patients with multiple sclerosis. *Neurology Asia*. 2015;20(3):263-8.	Generic preference-based measure not used
47.	Hawton A, Green C, Telford C, Zajicek J, Wright D. Using the Multiple Sclerosis Impact Scale to estimate health state utility values: mapping from the MSIS-29, version 2, to the EQ-5D and the SF-6D. *Value Health*.	Excluded from systematic review, but retained for

	2012;15(8):1084-91.	information on inputs
48.	Hawton A, Green C, Telford CJ, Wright DE, Zajicek JP. The use of multiple sclerosis condition-specific measures to inform health policy decision-making: mapping from the MSWS-12 to the EQ-5D. *Mult Scler*. 2012;18(6):853-61.	Excluded from systematic review, but retained for information on inputs
49.	Heisen M, Treur MJ, van der Hel WS, Frequin ST, Groot MT, Verheggen BG. Fingolimod reduces direct medical costs compared to natalizumab in patients with relapsing-remitting multiple sclerosis in The Netherlands. *J Med Econ*. 2012;15(6):1149-58.	Interventions not of interest; not full economic analysis
50.	Jones KH, Ford DV, Jones PA, John A, Middleton RM, Lockhart-Jones H, *et al.* How people with multiple sclerosis rate their quality of life: an EQ-5D survey via the UK MS register. *PLoS ONE [Electronic Resource]*. 2013;8(6):e65640.	Excluded from systematic review, but retained for information on inputs
51.	Kappos L, Gold R, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, *et al.* Quality of life outcomes with BG-12 (dimethyl fumarate) in patients with relapsing-remitting multiple sclerosis: the DEFINE study. *Mult Scler*. 2014;20(2):243-52.	Not relevant
52.	Karampampa K, Gustavsson A, Miltenburger C, Eckert B. Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from five European countries. *Mult Scler*. 2012;18(2 Suppl):7-15.	Excluded from systematic review, but retained for information on inputs
53.	Karampampa K, Gustavsson A, Miltenburger C, Kindundu CM, Selchen DH. Treatment experience, burden, and unmet needs (TRIBUNE) in multiple sclerosis: the costs and utilities of MS patients in Canada. *J Popul Ther Clin Pharmacol*. 2012;19(1):e11-25.	Excluded from systematic review, but retained for information on inputs
54.	Karampampa K, Gustavsson A, Miltenburger C, Kindundu CM, Selchen DH. Treatment experience, burden, and unmet needs (Tribune) in multiple sclerosis study: The costs and utilities of MS patients in Canada. *J Popul Ther Clin Pharmacol*. 2012;19(1):11-25.	Excluded from systematic review, but retained for information on inputs
55.	Karampampa K, Gustavsson A, Miltenburger C, Mora S, Arbizu T. Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from Spain. *Mult Scler*. 2012;18(2 Suppl):35-9.	Excluded from systematic review, but retained for information on inputs
56.	Karampampa K, Gustavsson A, Miltenburger C, Neidhardt K, Lang M. Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from Germany. *Mult Scler*. 2012;18(2 Suppl):23-7.	Excluded from systematic review, but retained for information on inputs
57.	Karampampa K, Gustavsson A, Miltenburger C, Teruzzi C, Fattore G. Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from Italy. *Mult Scler*. 2012;18(2 Suppl):29-34.	Excluded from systematic review, but retained for information on inputs
58.	Karampampa K, Gustavsson A, Miltenburger C, Tyas D. Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from the United Kingdom. *Mult Scler*. 2012;18(2 Suppl):41-5.	Excluded from systematic review, but retained for information on inputs
59.	Karampampa K, Gustavsson A, van Munster ET, Hupperts RM, Sanders EA, Mostert J, *et al.* Treatment experience, burden, and unmet needs (TRIBUNE) in Multiple Sclerosis study: the costs and utilities of MS patients in The	Excluded from systematic review, but retained for

	Netherlands. *J Med Econ*. 2013;16(7):939-50.	information on inputs
60.	Kerling A, Keweloh K, Tegtbur U, Kuck M, Grams L, Horstmann H, *et al.* Physical capacity and quality of life in patients with multiple sclerosis. *NeuroRehabilitation*. 2014;35(1):97-104.	Generic preference based measure not used
61.	Khan F, Amatya B, Kesselring J. Longitudinal 7-year follow-up of chronic pain in persons with multiple sclerosis in the community. *J Neurol*. 2013;260(8):2005-15.	Generic preference based measure not used
62.	Kinkel RP, Laforet G, You X. Disease-related determinants of quality of life 10 years after clinically isolated syndrome. *International Journal of Ms Care*. 2015;17(1):26-34.	Generic preference based measure not used
63.	Kita M, Fox RJ, Gold R, Giovannoni G, Phillips JT, Sarda SP, *et al.* Effects of delayed-release dimethyl fumarate (DMF) on health-related quality of life in patients with relapsing-remitting multiple sclerosis: an integrated analysis of the phase 3 DEFINE and CONFIRM studies. *Clin Ther*. 2014;36(12):1958-71.	Intervention not of interest
64.	Klevan G, Jacobsen CO, Aarseth JH, Myhr KM, Nyland H, Glad S, *et al.* Health related quality of life in patients recently diagnosed with multiple sclerosis. *Acta Neurol Scand*. 2014;129(1):21-6.	Generic preference based measure not used
65.	Kohlmann T, Wang C, Lipinski J, Hadker N, Caffrey E, Epstein M, *et al.* The impact of a patient support program for multiple sclerosis on patient satisfaction and subjective health status. *J Neurosci Nurs*. 2013;45(3):E3-14.	Not relevant
66.	Kohn CG, Sidovar MF, Kaur K, Zhu Y, Coleman CI. Estimating a minimal clinically important difference for the EuroQol 5-Dimension health status index in persons with multiple sclerosis. *Health & Quality of Life Outcomes*. 2014;12:66.	Not relevant
67.	Kuspinar A, Mayo NE. Do generic utility measures capture what is important to the quality of life of people with multiple sclerosis? *Health & Quality of Life Outcomes*. 2013;11:71.	Excluded from systematic review, but retained for information on inputs
68.	Labuz-Roszak B, Kubicka-Baczyk K, Pierzchala K, Horyniecki M, Machowska-Majchrzak A, Augustynska-Mutryn D, *et al.* [Quality of life in multiple sclerosis--association with clinical features, fatigue and depressive syndrome]. *Psychiatr Pol*. 2013;47(3):433-42. Jakosc zycia chorych na stwardnienie rozsiane--zwiazek z cechami klinicznymi choroby, zespolem zmeczenia i objawami depresyjnymi.	Excluded from systematic review, but retained for information on inputs
69.	Learmonth YC, Hubbard EA, McAuley E, Motl RW. Psychometric properties of quality of life and health-related quality of life assessments in people with multiple sclerosis. *Qual Life Res*. 2014;23(7):2015-23.	Generic preference based measure not used
70.	Limone BL, Sidovar MF, Coleman CI. Estimation of the effect of dalfampridine-ER on health utility by mapping the MSWS-12 to the EQ-5D in multiple sclerosis patients. *Health & Quality of Life Outcomes*. 2013;11:105.	Intervention not of interest
71.	Lukoschek C, Sterr A, Claros-Salinas D, Gutler R, Dettmers C. Fatigue in Multiple Sclerosis Compared to Stroke. *Frontiers in neurology [electronic resource]*. 2015;6:116.	Not relevant
72.	Magistrale G, Pisani V, Argento O, Incerti CC, Bozzali M, Cadavid D, *et al.* Validation of the World Health Organization Disability Assessment Schedule II (WHODAS-II) in patients with multiple sclerosis. *Mult Scler*. 2015;21(4):448-56.	Not relevant
73.	Marrie RA, Horwitz R, Cutter G, Tyry T. Cumulative impact of comorbidity on quality of life in MS. *Acta Neurol Scand*. 2012;125(3):180-6.	Generic measure not used
74.	Maruszczak MJ, Montgomery SM, Griffiths MJ, Bergvall N, Adlard N. Cost-utility of fingolimod compared with dimethyl fumarate in highly active relapsing-remitting multiple sclerosis (RRMS) in England. *J Med Econ*. 2015;18(11):874-85.	Interventions not in scope
75.	Maurer M, Comi G, Freedman MS, Kappos L, Olsson TP, Wolinsky JS, *et al.* Multiple sclerosis relapses are associated with increased fatigue and reduced	Interventions not in scope

	health-related quality of life - A post hoc analysis of the TEMSO and TOWER studies. *Multiple Sclerosis and Related Disorders*. 2016;7:33-40.	
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MS HRQoL generic measures up to 2011 1 or 1,3 or unsure for full text screen

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78.	Parkin D, McNamee P, Jacoby A, Miller P, Thomas S, Bates D. A cost-utility analysis of interferon beta for multiple sclerosis. *Health Technol Assess*. 1998;2(4):1-45.	Economic analysis pre-2012
79.	Parkin D, Rice N, Jacoby A, Doughty J. Use of a visual analogue scale in a daily patient diary: modelling cross-sectional time-series data on health-related quality of life. *Soc Sci Med*. 2004;59(2):351-60.	Not relevant
80.	Patti F, Amato MP, Battaglia MA, Pitaro M, Russo P, Solaro C, *et al.* Caregiver quality of life in multiple sclerosis: a multicentre Italian study. *Mult Scler*. 2007;13(3):412-9.	Not relevant
81.	Patti F, Cacopardo M, Palermo F, Ciancio MR, Lopes R, Restivo D, *et al.* Health-related quality of life and depression in an Italian sample of multiple sclerosis patients. *J Neurol Sci*. 2003;211(1-2):55-62.	Cargiver quality of life
82.	Patti F, Russo P, Pappalardo A, Macchia F, Civalleri L, Paolillo A, *et al.* Predictors of quality of life among patients with multiple sclerosis: An Italian cross-sectional study. *J Neurol Sci*. 2007;252(2):121-9.	Not relevant
83.	Pfennings L, Cohen L, Ader H, Polman C, Lankhorst G, Smits R, *et al.* Exploring differences between subgroups of multiple sclerosis patients in health-related quality of life. *J Neurol*. 1999;246(7):587-91.	Not relevant
84.	Pfennings LE, Van der Ploeg HM, Cohen L, Bramsen I, Polman CH, Lankhorst GJ, *et al.* A health-related quality of life questionnaire for multiple sclerosis patients. *Acta Neurol Scand*. 1999;100(3):148-55.	No generic preference-based measure used
85.	Phillips CJ. The cost of multiple sclerosis and the cost effectiveness of disease-modifying agents in its treatment. *CNS Drugs*. 2004;18(9):561-74.	Economic analysis pre-2012
86.	Phillips CJ, Gilmour L, Gale R, Palmer M. A cost utility model of interferon beta-1b in the treatment of relapsing-remitting multiple sclerosis. *J Med Econ*. 2001;4(35-50):35-50.	Economic analysis pre-2012
87.	Phillips JT, Giovannoni G, Lublin FD, O'Connor PW, Polman CH, Willoughby E, *et al.* Sustained improvement in Expanded Disability Status Scale as a new efficacy measure of neurological change in multiple sclerosis: treatment effects with natalizumab in patients with relapsing multiple sclerosis. *Mult Scler*. 2011;17(8):970-9.	Not relevant
88.	Pittock SJ, Mayr WT, McClelland RL, Jorgensen NW, Weigand SD,	No relevant

	Noseworthy JH, *et al.* Quality of life is favorable for most patients with multiple sclerosis: a population-based cohort study. *Arch Neurol*. 2004;61(5):679-86.	information
89.	Popova EV, Riabukhina OV, Vorob'eva OV, Malkova NA, Boiko AN. Changes in quality of life in patients with remitted multiple sclerosis during the specific treatment with disease-modifying drugs: a comparative study of populations of Moscow and Novosibirsk. *Zhurnal Nevrologii I Psikhiatrii Imeni S S Korsakova*. 2010;110(5):67-70.	No relevant information
90.	Pozzilli C, Palmisano L, Mainero C, Tomassini V, Marinelli F, Ristori G, *et al.* Relationship between emotional distress in caregivers and health status in persons with multiple sclerosis. *Mult Scler*. 2004;10(4):442-6.	Carers' disutilities
91.	Prosser LA, Kuntz KM, Bar-Or A, Weinstein MC. Patient and community preferences for treatments and health states in multiple sclerosis. *Mult Scler*. 2003;9(3):311-9.	Results not reported for all EDSS levels
92.	Prosser LA, Kuntz KM, Bar-Or A, Weinstein MC. Cost-effectiveness of interferon beta-1a, interferon beta-1b, and glatiramer acetate in newly diagnosed non-primary progressive multiple sclerosis. *Value Health*. 2004;7(5):554-68.	Economic analysis pre-2012
93.	Putzki N, Fischer J, Gottwald K, Reifschneider G, Ries S, Siever A, *et al.* Quality of life in 1000 patients with early relapsing-remitting multiple sclerosis. *Eur J Neurol*. 2009;16(6):713-20.	Excluded from systematic review, but retained for information on inputs
94.	Riazi A, Hobart JC, Lamping DL, Fitzpatrick R, Freeman JA, Jenkinson C, *et al.* Using the SF-36 measure to compare the health impact of multiple sclerosis and Parkinson's disease with normal population health profiles. *J Neurol Neurosurg Psychiatry*. 2003;74(6):710-4.	No generic preference-based measure used
95.	Rivera-Navarro J, Benito-Leon J, Oreja-Guevara C, Pardo J, Dib WB, Orts E, *et al.* Burden and health-related quality of life of Spanish caregivers of persons with multiple sclerosis. *Mult Scler*. 2009;15(11):1347-55.	Carers' disutilities
96.	Robinson D, Jr., Zhao N, Gathany T, Kim LL, Cella D, Revicki D. Health perceptions and clinical characteristics of relapsing-remitting multiple sclerosis patients: baseline data from an international clinical trial. *Curr Med Res Opin*. 2009;25(5):1121-30.	No generic preference-based measure used
97.	Rothwell PM, McDowell Z, Wong CK, Dorman PJ. Doctors and patients don't agree: cross sectional study of patients' and doctors' perceptions and assessments of disability in multiple sclerosis. *BMJ*. 1997;314(7094):1580-3.	Not relevant
98.	Rubio-Terres C, Aristegui Ruiz I, Medina Redondo F, Izquierdo Ayuso G. [Cost-utility analisys of multiple sclerosis treatment with glatiramer acetate or interferon beta in Spain]. *Farmacia Hospitalaria*. 2003;27(3):159-65. Analisis coste utilidad del tratamiento de la esclerosis multiple remitente-recidivante con acetato de glatiramero o interferon beta en Espana.	Economic analysis pre-2012
99.	Rubio-Terres C, Dominguez-Gil Hurle A. [Cost-utility analysis of relapsing-remitting multiple sclerosis treatment with azathioprine or interferon beta in Spain]. *Rev Neurol*. 2005;40(12):705-10. Analisis coste-utilidad del tratamiento de la esclerosis multiple remitente-recidivante con azatioprina o interferon beta en Espana.	Economic analysis pre-2012
100.	Rudick RA, Miller D, Hass S, Hutchinson M, Calabresi PA, Confavreux C, *et al.* Health-related quality of life in multiple sclerosis: effects of natalizumab. *Ann Neurol*. 2007;62(4):335-46.	Intervention is not of interest
101.	Rudick RA, Miller DM. Health-related quality of life in multiple sclerosis - Current evidence, measurement and effects of disease severity and treatment.	No generic preference-based

	Cns Drugs. 2008;22(10):827-39.	measure used
102.	Sehanovic A, Dostovic Z, Smajlovic D, Avdibegovic E. Quality of life in patients suffering from Parkinson's disease and multiple sclerosis. *Med Arh*. 2011;65(5):291-4.	No generic preference-based measure used
103.	Senol V, Sipahioglu MH, Ozturk A, Argun M, Utas C. Important determinants of quality of life in a peritoneal dialysis population in Turkey. *Ren Fail*. 2010;32(10):1196-201.	Not relevant
104.	Shawaryn MA, Schiaffino KM, LaRocca NG, Johnston MV. Determinants of health-related quality of life in multiple sderosis: the role of illness intrusiveness. *Mult Scler*. 2002;8(4):310-8.	Utility values not reported
105.	Solari A, Radice D. Health status of people with multiple sclerosis: a community mail survey. *Neurol Sci*. 2001;22(4):307-15.	No generic preference-based measure used
106.	Szilasiova J, Krokavcova M, Gdovinova Z, Rosenberger J, Van Dijk JP. Quality of life in patients with multiple sclerosis in Eastern Slovakia. *Disabil Rehabil*. 2011;33(17-18):1587-93.	No generic preference-based measure used
107.	Tatarinova M, Fokin IV, Boiko AN. [Quality of life in multiple sclerosis and pharmaco-economic studies]. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2002;Suppl:76-80. Kachestvo zhizni bol'nykh rasseiannym sklerozom i nekotorye podkhody k farmakoekonomicheskim issledovaniiam.	Full-text not available in English Language
108.	Thompson JP, Noyes K, Dorsey ER, Schwid SR, Holloway RG. Quantitative risk-benefit analysis of natalizumab. *Neurology*. 2008;71(5):357-64.	Economic analysis pre-2012, but provides useful information on utility values by EDSS
109.	Turpin KV, Carroll LJ, Cassidy JD, Hader WJ. Deterioration in the health-related quality of life of persons with multiple sclerosis: the possible warning signs. *Mult Scler*. 2007;13(8):1038-45.	Not relevant
110.	Vermersch P, de Seze J, Delisse B, Lemaire S, Stojkovic T. Quality of life in multiple sclerosis: influence of interferon-beta1 a (Avonex) treatment. *Mult Scler*. 2002;8(5):377-81.	No generic preference-based measure used
111.	Vickrey BG, Hays RD, Genovese BJ, Myers LW, Ellison GW. Comparison of a generic to disease-targeted health-related quality-of-life measures for multiple sclerosis. *J Clin Epidemiol*. 1997;50(5):557-69.	No generic preference-based measure used
112.	Vickrey BG, Hays RD, Harooni R, Myers LW, Ellison GW. A health-related quality of life measure for multiple sclerosis. *Qual Life Res*. 1995;4(3):187-206.	No generic preference-based measure used

25.3 ***Blank data extraction form for cost-effectiveness studies(relapsing remitting multiple sclerosis)***

Date:
Study ID:
Name of first reviewer:
Name of second reviewer:

Study details	
Study title	
First author	
Co-authors	
Source of publication Journal yy;vol(issue):pp	
Language	
Publication type	
Inclusion criteria/study eligibility/PICOS	
Population	
Intervention(s)	
Comparator(s)	
Outcome(s)	
Study design	
Methods	
Setting and location	
Study perspective	
Comparators	
Time horizon	
Discount rate	
Outcomes	
Measurement of effectiveness	
Measurement and valuation of preference based outcomes	
Resource use and costs	
Currency, price date and conversion	
Model type	
Assumptions	
Analytical methods	
Results	
Study parameters	
Incremental costs and outcomes	
Characterising uncertainty	
Discussion	
Study findings	
Limitations	
Generalisability	
Other	
Source of funding	
Conflicts of interest	
Comments	
Authors conclusion	
Reviewer's conclusion	

25.4 ***Quality assessment of model-based cost-effectiveness studies (relapsing remitting multiple sclerosis)***

Table 95: CHEERS quality assessment checklist for economic evaluations in RRMS

Assessment	Studies									
	Sanchez-de la Rosa et al., 2012[248]	Nikfar et al., 2013[249]	Agashivala & Kim, 2012[250]	Palace et al., 2015[149]	Pan et al., 2012[251]	Darbà et al, 2014[252]	Imani et al, 2012[253]	Dembek et al, 2014[254]	Chevalier et al, 2016[255]	Lee et al., 2012[256]
Title	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Abstract	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Introduction										
Background and objectives	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Methods										
Target population and subgroups	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Setting and location	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Study perspective	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Comparators	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Time horizon	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Discount rate	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Choice of health outcomes	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Measurement of effectiveness	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Measurement and valuation of preference-based outcomes	Y	Y	N/A	Y	Y	N/A	N	Y	Y	Y
Estimating resources and costs	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Currency, price date, and conversion	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Choice of model	Y	Y	N	Y	Y	Y	N	Y	Y	Y

Assessment	Studies									
	Sanchez-de la Rosa et al., 2012[248]	Nikfar et al., 2013[249]	Agashivala & Kim, 2012[250]	Palace et al., 2015[149]	Pan et al., 2012[251]	Darbà et al, 2014[252]	Imani et al, 2012[253]	Dembek et al, 2014[254]	Chevalier et al, 2016[255]	Lee et al., 2012[256]
Assumptions	Y	Y	Y	Y	Y	N	N	Y	Y	Y
Analytical methods	Y	Y	N	Y	Y	UNC	N	Y	Y	Y
Results										
Study parameters	Y	Y	N	Y	Y	N	Y	N	N	Y
Incremental costs and outcomes	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Characterising uncertainty	Y	Y	N	Y	Y	N	N	N	Y	N
Discussion										
Study findings	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Limitations	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Generalizability	Y	Y	N	Y	Y	N	Y	Y	N	Y
Other										
Source of funding	Y	Y	Y	Y	Y	Y	UNC	Y	Y	Y
Conflicts of interest	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
N- No; N/A- Not Applicable; Y- Yes; UNC-Unclear										

Table 96: Philips' quality assessment checklist for economic evaluations in RRMS

Philips' criteria		Studies									
		Sanchez-de la Rosa et al., 2012[248]	Nikfar et al., 2013[249]	Agashivala & Kim, 2012[250]	Palace et al., 2015[149]	Pan et al., 2012[251]	Darbà et al, 2014[252]	Imani et al, 2012[253]	Dembek et al, 2014[254]	Chevalier et al, 2016[255]	Lee et al., 2012[256]
STRUCTURE											
1.	Is there a clear statement of the decision problem?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2.	Is the objective of the model specified and consistent with the stated decision problem?	Y	Y	UNC	Y	Y	Y	Y	Y	Y	Y
3.	Is the primary decision maker specified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4.	Is the perspective of the model stated clearly?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
5.	Are the model inputs consistent with the stated perspective?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
6.	Has the scope of the model been stated and justified?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
7.	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
8.	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Y	Y	UNC	Y	Y	UNC	Y	Y	Y	Y
9.	Are the sources of the data used to develop the structure of the model specified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
10.	Are the causal relationships described by the model structure	Y	Y	UNC	Y	Y	Y	Y	Y	Y	Y

Philips' criteria		Studies									
		Sanchez-de la Rosa et al., 2012[248]	Nikfar et al., 2013[249]	Agashivala & Kim, 2012[250]	Palace et al., 2015[149]	Pan et al., 2012[251]	Darbà et al, 2014[252]	Imani et al, 2012[253]	Dembek et al, 2014[254]	Chevalier et al, 2016[255]	Lee et al., 2012[256]
	justified appropriately?										
11.	Are the structural assumptions transparent and justified?	Y	Y	UNC	Y	Y	N	Y	Y	Y	Y
12.	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Y	Y	UNC	Y	Y	UNC	Y	Y	Y	Y
13.	Is there a clear definition of the options under evaluation?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
14.	Have all feasible and practical options been evaluated?	Y	N	N	N	N	N	Y	Y	Y	N
15.	Is there justification for the exclusion of feasible options?	N/A	N	UNC	N	N	N	N/A	N/A	N/A	N
16.	Is the chosen model type appropriate given the decision problem and specified casual relationships within the model?	Y	Y	UNC	Y	Y	N	Y	Y	Y	Y
17.	Is the time horizon of the model sufficient to reflect all important differences between the options?	N	Y	N	N	Y	Y	Y	Y	Y	N
18.	Are the time horizon of the model, the duration of treatment and the duration of treatment described and justified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
19.	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the	Y	Y	UNC	Y	Y	N	Y	Y	Y	Y

Philips' criteria		Studies									
		Sanchez-de la Rosa et al., 2012[248]	Nikfar et al., 2013[249]	Agashivala & Kim, 2012[250]	Palace et al., 2015[149]	Pan et al., 2012[251]	Darbà et al, 2014[252]	Imani et al, 2012[253]	Dembek et al, 2014[254]	Chevalier et al, 2016[255]	Lee et al., 2012[256]
	impact of interventions?										
20.	Is the cycle length defined and justified in terms of the natural history of disease?	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
DATA											
21.	Are the data identification methods transparent and appropriate given the objectives of the model?	Y	Y	Y	Y	N	Y	N	Y	Y	Y
22.	Where choices have been made between data sources are these justified appropriately?	UNC	N	UNC	N	N	Y	N	Y	Y	Y
23.	Has particular attention been paid to identifying data for the important parameters of the model?	UNC	UNC	UNC	UNC	N	N	N	UNC	Y	UNC
24.	Has the quality of the data been assessed appropriately?	N	N	N	N	N	N	N	N	N	N
25.	Where expert opinion has been used are the methods described and justified?	N/A	N/A	N	N/A	N/A	N/A	N/A	N/A	Y	N
26.	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	Y	Y	UNC	Y	N	Y	UNC	N	Y	Y
27.	Is the choice of baseline data described and justified?	Y	Y	Y	Y	Y	Y	UNC	Y	Y	Y

Philips' criteria		Studies									
		Sanchez-de la Rosa et al., 2012[248]	Nikfar et al., 2013[249]	Agashivala & Kim, 2012[250]	Palace et al., 2015[149]	Pan et al., 2012[251]	Darbà et al, 2014[252]	Imani et al, 2012[253]	Dembek et al, 2014[254]	Chevalier et al, 2016[255]	Lee et al., 2012[256]
28.	Are transition probabilities calculated appropriately?	UNC	UNC	UNC	UNC	UNC	UNC	UNC	UNC	UNC	UNC
29.	Has a half-cycle correction been applied to both costs and outcomes?	N/A	N	N	N	N	N	N	N	N	N
30.	If not, has the omission been justified?	N/A	N	N	N	N	N	N	N	N	N
31.	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	UNC	UNC	Y	Y	UNC	Y	UNC	Y	Y	Y
32.	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	N/A	UNC	N/A	N	N	UNC	N	Y	UNC	N
33.	Have alternative extrapolation assumptions been explored through sensitivity analysis?	N/A	N	Y	N/A	N	N	UNC	N	UNC	N
34.	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	N/A	N	N/A	UNC	UNC	UNC	UNC	Y	Y	UNC
35.	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis	N/A	N	N/A	N	N	N	UNC	N	Y	UNC
36.	Are the costs incorporated into the model justified?	Y	Y	Y	Y	Y	N	Y	Y	Y	Y

Philips' criteria		Studies									
		Sanchez-de la Rosa et al., 2012[248]	Nikfar et al., 2013[249]	Agashivala & Kim, 2012[250]	Palace et al., 2015[149]	Pan et al., 2012[251]	Darbà et al, 2014[252]	Imani et al, 2012[253]	Dembek et al, 2014[254]	Chevalier et al, 2016[255]	Lee et al., 2012[256]
37.	Has the source for all costs been described?	Y	Y	Y	Y	Y	Y	UNC	Y	Y	Y
38.	Have discount rates been described and justified given the target decision maker?	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
39.	Are the utilities incorporated into the model appropriate?	Y	Y	N/A	Y	Y	N/A	N	Y	Y	Y
40.	Is the source of utility weights referenced?	Y	Y	N/A	Y	Y	N/A	Y	Y	Y	Y
41.	Are the methods of derivation for the utility weights justified?	Y	Y	N/A	Y	Y	N/A	N	Y	Y	Y
42.	Have all data incorporated into the model been described and referenced in sufficient detail?	N	N	Y	N	N	Y	N	N	Y	Y
43.	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate?)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
44.	Is the process of data incorporation transparent?	N	N	Y	N	N	N	N	N	N	Y
45.	If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?	N	N/A	N/A	N	N	N	UNC	N	N	N
46.	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	N/A	N/A	N/A	N/A	N/A	UNC	UNC	UNC	Y	N
47.	Have the four principal types of	N	N	N	N	N	N	UNC	Y	Y	N

Philips' criteria		Studies									
		Sanchez-de la Rosa et al., 2012[248]	Nikfar et al., 2013[249]	Agashivala & Kim, 2012[250]	Palace et al., 2015[149]	Pan et al., 2012[251]	Darbà et al, 2014[252]	Imani et al, 2012[253]	Dembek et al, 2014[254]	Chevalier et al, 2016[255]	Lee et al., 2012[256]
	uncertainty been addressed?										
48.	If not, has the omission of particular forms of uncertainty been justified?	N	N	N	N	N	N	UNC	N	N/A	N
49.	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	N	N	N	N	N	N	N	N	N	N
50.	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	N	N	N	N	N	N	N	N	N	N
51.	Has heterogeneity been dealt with by running the model separately for different sub-groups?	N	N	N	N	N	N	N	Y	N	N
52.	Are the methods of assessment of parameter uncertainty appropriate?	Y	Y	UNC	Y	Y	UNC	N	UNC	Y	Y
53.	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Y	Y	UNC	Y	Y	N	N	N	N/A	N
54.	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	N	N	N	N	N	N	N	N	N	N
55.	Are any counterintuitive results from the model explained and justified?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Y	N/A	Y

Philips' criteria		Studies									
		Sanchez-de la Rosa et al., 2012[248]	Nikfar et al., 2013[249]	Agashivala & Kim, 2012[250]	Palace et al., 2015[149]	Pan et al., 2012[251]	Darbà et al, 2014[252]	Imani et al, 2012[253]	Dembek et al, 2014[254]	Chevalier et al, 2016[255]	Lee et al., 2012[256]
56.	If the model has been calibrated against independent data, have any differences been explained and justified?	N	N	N/A	N/A	N/A	N	N	N	N/A	N
57.	Have the results been compared with those of previous models and any differences in results explained?	Y	Y	N	Y	Y	N	Y	Y	N	Y
N- No; N/A- Not Applicable; Y- Yes; UNC-Unclear											

25.5 ***Results of additional searches***

Multiple sclerosis registries

Potentially relevant studies
Bronnum-Hansen, H., et al. (1994). "Survival of patients with multiple sclerosis in Denmark: a nationwide, long-term epidemiologic survey." Neurology 44(10): 1901-1907
Bronnum-Hansen, H., et al. (1995). "[Survival in disseminated sclerosis in Denmark. A nation-wide study of the period 1948-1986]." Ugeskrift for Laeger 157(51): 7131-7135.
Confavreux, C. (1994). "Establishment and use of multiple sclerosis registers--EDMUS." Annals of Neurology 36 Suppl: S136-139.
Flachenecker, P., et al. (2005). "[MS registry in Germany--design and first results of the pilot phase]." Nervenarzt 76(8): 967-975.
A prospective study of the incidence, prevalence and mortality of multiple sclerosis in Leeds." Journal of Neurology 249(3): 260-265.
Koch-Henriksen, N. (1999). "The Danish Multiple Sclerosis Registry: a 50-year follow-up." Multiple Sclerosis 5(4): 293-296.
Trojano, M. (2004). "Can databasing optimise patient care?" Journal of Neurology 251 Suppl 5: v79-v82

Natural history cohorts: we have undertaken this search in order to identify any natural history cohorts on people who have been diagnosed with clinically isolated syndrome.

Search strategy

Medline (Ovid), searched 15/06/2016

Ovid MEDLINE(R) 1946 to June Week 1 2016

1.	Demyelinating Diseases/	10651
2.	Myelitis, Transverse/	1188
3.	exp Optic Neuritis/	6937
4.	Encephalomyelitis, Acute Disseminated/	1743
5.	Demyelinating Autoimmune Diseases, CNS/	334
6.	demyelinating disease*.tw.	4890
7.	transverse myelitis.tw.	1406
8.	neuromyelitis optica.tw.	1863
9.	optic neuritis.tw.	3891
10.	acute disseminated encephalomyelitis.tw.	1149
11.	devic.tw.	108
12.	ADEM.tw.	610
13.	demyelinating disorder.tw.	352
14.	clinically isolated syndrome.tw.	684
15.	first demyelinating event.tw.	71
16.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	25242
17.	exp Registries/	68513
18.	(registry or registries).tw.	70985
19.	(register or registers).tw.	46371
20.	17 or 18 or 19	141663

21.	exp Cohort Studies/	1554538
22.	(cohort adj (study or studies)).tw.	102915
23.	cohort analy$.tw.	4303
24.	(follow up adj (study or studies)).tw.	39204
25.	21 or 22 or 23 or 24	1585425
26.	16 and 20	85
27.	16 and 25	2328
28.	natural history.tw.	36960
29.	natural course.tw.	6144
30.	untreated.tw.	135224
31.	(("no" or "not") adj2 (treat* or therap*)).tw.	163332
32.	(natural adj2 (progression or development)).tw.	2055
33.	28 or 29 or 30 or 31 or 32	332054
34.	16 and 25 and 33	99
35.	exp Multiple Sclerosis/	48381
36.	multiple sclerosis.tw.	51775
37.	35 or 36	59297
38.	25 and 33 and 37	414
39.	Multiple Sclerosis, Relapsing-Remitting/	4313
40.	relapsing remitting multiple sclerosis.tw.	2275
41.	39 or 40	5120
42.	25 and 33 and 41	133
43.	26 or 34 or 42	302

26 Appendix 8: Details of resource use to derive costs inputs

We document here our calculations for resources used to derive annual unit costs for use in our CIS model.

Table 97: Cost for monitoring people with CIS receiving best supportive care

Resource use	Quantity	Description	Unit costs (£,2015)	Source
MRI	1	RD01A	137.23	NHS reference costs 2014/15[275]
Neurologist visit	1	Outpatient attendance, Neurology 400	175.76	Assumption and consultation with clinical expert (Prof. Olga Ciccarelli, University College London, 2016, personal communication) NHS reference costs 2014/15[275]
MS nurse visit	2	15 minutes	18.75	Assumption and consultation with clinical expert (Prof. Olga Ciccarelli, University College London, 2016, personal communication); Curtis and Burns 2015[260]
Estimated cost for monitoring people with CIS receiving best supportive care				**£350.49**

[1]We assumed a nurse specialist (community) employed on the NHS scale agenda for change Band 6 would require 15 minutes of contact time with a patient receiving disease modifying treatment. £75 per hour of patient-related work (see Table 10.4, p172 in Curtis and Burns 2015[260])

Table 98: Initial cost for monitoring in the first year of commencing DMTs

Resource use	Quantity	Description	Unit costs (£,2015)	Source
Investigations				
Full blood counts	5	DAPS05- haematology	3.01	Assumptions and consultation with clinical expert on the number of FBC, LFTs and renal function tests NHS reference costs 2014/15[275]
Liver function tests	5	DAPS04- clinical biochemistry	1.19	
Thyroid function test	1	DAPS09- Other	7.13	
Renal function tests	5	DAPS04- clinical biochemistry	1.19	
MRI	1	RD01A	137.23	NHS reference costs 2014/15[275]
Neurologist visit	2	Outpatient attendance, Neurology 400	175.76	Assumption and consultation with clinical expert (Prof. Olga Ciccarelli, University College London, 2016, personal communication) NHS reference costs 2014/15[275]
MS nurse visit	2	15 minutes	18.75	Assumption and consultation with clinical expert; Curtis and Burns 2015[260]
Estimated initial cost for monitoring people receiving DMTs (Avonex/plegridy, Betaferon and Copaxone) in first year				**£553.20**
Estimated initial cost for monitoring people receiving Rebif in first year (includes thyroid function test)				**£560.33**

[1]We assumed a nurse specialist (community) employed on the NHS scale agenda for change Band 6 would require 15 minutes of contact time with a patient receiving disease modifying treatment. £75 per hour of patient-related work (see Table 10.4, p172 in Curtis and Burns 2015[260])

Table 99: Subsequent resource use and costs for monitoring DMTs

Resource use	Quantity	Description	Unit costs (£,2015)	Source
Investigations				
Full blood counts	2	DAPS05-haematology	3.01	Assumptions and consultation with clinical expert on the number of FBC, LFTs and renal function tests NHS reference costs 2014/15[275]
Liver function tests	2	DAPS04-clinical biochemistry	1.19	
Renal function tests	2	DAPS04-clinical biochemistry	1.19	
MRI	1	RD01A	137.23	NHS reference costs 2014/15
Neurologist visit	1	Outpatient attendance, Neurology 400	175.76	Assumption and consultation with clinical expert (Prof. Olga Ciccarelli, University College London, 2016, personal communication)
Subsequent annual cost for monitoring people receiving DMTs				**£323.77**

27 Appendix 9: Additional analyses undertaken by the assessment

27.1 *Time-varying model*

In Table 100 the results are presented in terms of cost per QALY for the time varying model. These results showed that the disease modifying strategy was more costly and more effective than best supportive care alone. Disease modifying strategy was approximately £25,400 more costly than best supportive care and produced 1.461 more QALYs, which equated to an ICER of approximately £17,400 per QALY. This indicates that for every additional QALY from disease modifying treatments there is an incremental cost of £17,400.

Table 100: Results based on cost per QALY, time-varying model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
Disease modifying treatments	387,500	25,400	10.125	1.461	17,400
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years;					

SA 2a: Individual drugs from assessment group review, progression confirmed at 3 months and individual drug annualised relapse rate

Results based on the time varying model by individual drug showed that best supportive care was the least costly and least effective strategy (see Table 101). Glatiramer acetate treatment strategy was approximately £26,300 more expensive than the best supportive care treatment strategy and produced 1.105 more QALYs with an ICER of approximately £2700 per QALY. IFN β-1b 250µg every other day (Betaferon) and IFN β-1a 125µg (Plegridy) were both shown to be cost-effective with ICERs of approximately £5700 and £9900 per QALY, respectively. Both IFN β-1a 30 µg IM (Avonex) and IFN β-1a 44 µg SC (Rebif) were dominated by IFN β-1a 125 µg (Plegridy).

Table 101: Results based on the time-varying model, SA 2a

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
Glatiramer acetate 20mg (Copaxone)	388,400	26,300	9.770	1.105	2,700
IFN β-1b 250 µg every other day (Betaferon)	390,500	2100	10.139	0.369	5700
IFNβ-1a 125µg (Plegridy)	395,500	5,000	10.642	0.503	9,900
IFNβ-1a 30µg IM (Avonex)	415,900	20,400	9.994	-0.648	Dominated

SC INFβ-1a 44µg (Rebif)	416,100	20600	10.420	-0.222	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; SC, subcutaneous					

SA 2b: Individual drugs from AG review, progression confirmed at 6 months, and individual drug annualised relapse rate

In Table 102, we report the results based on the time varying model. These results show that IFNβ-1a 125µg (Plegridy) dominated all other disease modifying treatment strategies. When compared to best supportive care, IFN β-1a 125 µg (Plegridy) was more expensive and effective and had an ICER of approximately £3200 per QALY.

Table 102: Results based on the time-varying model, SA 2b

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
IFNβ-1a 125µg (Plegridy)	371,500	9400	11.608	2.944	3200
SC INFβ-1a 44µg (Rebif)	395,700	24,200	11.290	-0.318	Dominated
Glatiramer acetate 20mg (Copaxone)	396,500	25000	9.485	-2.123	Dominated
IM IFNβ-1a 30µg (Avonex)	409,200	37700	10.267	-1.341	Dominated
BSC, best supportive care; IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

27.2 ***Incorporating carers' disutilities***

We present analyses below relating to the base run model.

27.2.1 Cost-effectiveness analysis results: base case and sensitivity analyses

Base Case

In Table 103, we present the findings from our base case analysis with the inclusion of carers' disutilities. The results showed that the disease modifying treatment strategy was more costly and more effective than best supportive care. The expected mean costs per person for the disease modifying treatment strategy were approximately £25,700 more costly than the best supportive care strategy and produced 1.046 more QALYs with an ICER of approximately £24,600 per QALY.

Table 103: Base case results based cost per QALY

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)

Best supportive care	362,100	-	7.148	-	-
Disease modifying treatments	387,800	25,700	8.194	1.046	24,600
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

SA 1: Pooled on-scheme DMTs from assessment group review

We used two key estimates of treatment effectiveness from our clinical effectiveness review: the aggregated hazard ratio for disability progression confirmed at 3 months and the aggregated annualised relapse rate.

In Table 104, the results show that disease modifying treatment strategy was more costly and more effective than best supportive care alone. The disease modifying treatment strategy was approximately £10,200 more costly than best supportive care and produced 2.201 more QALYs, which equated to an ICER of approximately £4600 per QALY.

Table 104: Cost per QALY, SA 1

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
Disease modifying treatments	372,300	10,200	9.349	2.201	4600
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

SA 2a Individual drugs from AG review, progression confirmed at 3 months (preferred analysis)

Table 105: Cost per QALY, SA 2a (assessment group estimates of relapse rate and disability progression confirmed at 3 months)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
IFN β-1a 125µg (Plegridy)	379,900	17,800	10.016	2.868	6200
Glatiramer acetate 20mg (Copaxone)	381,000	1100	8.646	-1.552	Dominated
IFN β-1b 250 µg every other day (Betaferon)	393,400	13,500	8.556	-1.46	Dominated
INF β-1a 44µg SC (Rebif)	404,800	24,900	9.614	-0.402	Dominated
IFNβ-1a 30µg IM	406,100	26,200	9.027	-0.989	Dominated

(Avonex)					
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

The results in Table 105, were robust to the inclusion of carers' disutilities. These results showed that IFN β-1a 125 µg (Plegridy) remained dominant over all other disease modifying treatment strategies. When compared to best supportive care, IFN β-1a 125 µg (Plegridy) was approximately £17,800 more costly and was more effective by expected mean gains of QALYs, with an ICER of £6200 per QALY.

SA 2b: Individual drugs from AG review, progression confirmed at 6 months

Likewise, these results were robust when we included carers' disutilities in the analysis. Results showed that IFN β-1a 125 µg SC every two weeks (Plegridy) remained dominant over all other strategies included in this analysis (see Table 106).

Table 106: Cost per QALY, SA 2b (assessment group estimates, disability progression confirmed at 6 months)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
IFN β-1a 125 µg SC every two weeks (Plegridy)	347,000	-	11.584	-	-
Best supportive care	362,100	15,100	7.148	-4.436	Dominated
IFN β-1a 44 µg SC three times a week (Rebif)	377,600	30,600	10.966	-0.618	Dominated
Glatiramer acetate 20 mg SC daily (Copaxone)	391,900	44,900	8.236	-3.348	Dominated
IFN β-1a 30 µg IM once weekly (Avonex)	396,900	49,900	9.446	-2.138	Dominated
BSC, best supportive care; IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

SA 3: Hazard ratios from company submissions

When we used the estimates for treatment effectiveness (annualised relapse rate and disability progression) reported by each company and included carers' disutilities, these results showed that IFN β-1a 125 µg (Plegridy) dominated all other disease modifying treatment strategies (see Table 107). When compared to best supportive care, IFN β-1a 125 µg (Plegridy) resulted in an ICER of £3000 per QALY.

Table 107: Cost per QALY, SA 3 (company estimates of effectiveness)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive	362,100	-	7.148	-	-

care					
IFN β-1a 125 µg SC every two weeks (Plegridy)	366,300	4200	8.566	1.418	3000
Glatiramer acetate 40 mg SC three times weekly (Copaxone)	387,000	20,700	7.971	-0.775	Dominated
IFN β-1a 30µg IM once weekly (Avonex)	387,600	21,300	8.149	-0.417	Dominated
IFN β-1a 44µg SC three times a week (Rebif)	412,900	46,600	8.318	-0.248	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

SA 4: Time horizon changed from 50 years to 20 and 30 years

Table 108 and Table 109 show the results based on a 20-year and 30-year time horizon, respectively. Findings showed that the glatiramer acetate treatment strategy continued to be extendedly dominated by IFN β-1a 125 µg (Plegridy) in both analyses, with the inclusion of carers' disutilities. Additionally, IFN β-1a 125 µg (Plegridy) dominated both IFN β-1a 30 µg IM (Avonex) and IFN β-1a 44µg SC (Rebif) treatment strategies. Excluding all dominated strategies, IFN β-1a 125 µg (Plegridy) when compared to best supportive care had an ICER of approximately £ and £ per QALY for the 20-year and 30-year time horizon, respectively.

Table 108: Cost per QALY, SA 3 (time horizon changed to 20 years)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	196,900	-	5.710	-	-
Glatiramer acetate 20mg (Copaxone)	220,500	23,600	6.628	0.918	Extendedly dominated
IFNβ-1a 125µg (Plegridy)	225,800	28,900	7.301	1.591	18,200
IFNβ-1a 30µg IM (Avonex)	242,600	16,800	6.789	-0.512	Dominated
IFN β-1a 44µg SC (Rebif)	245,200	19,400	7.156	-0.145	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; SC, subcutaneous					

Table 109: Cost per QALY, SA 3 (time horizon changed to 30 years)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)

Best supportive care	279,400	-	6.540	-	-
Glatiramer acetate 20mg (Copaxone)	298,900	19,500	7.790	1.25	Extendedly dominated
IFNβ-1a 125µg (Plegridy)	300,400	21,000	8.809	2.269	9300
INFβ-1a 44µg SC (Rebif)	322,900	22,500	8.551	-0.258	Dominated
IFNβ-1a 30µg IM (Avonex)	323,000	22,600	8.057	-0.752	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; SC, subcutaneous					

28 Appendix 10: Results by age of RRMS onset

Using the base run RSS model, we derived mean costs and mean QALYs for the best supportive care and disease modifying treatments arm, for various ages of onset of relapsing remitting multiple sclerosis.

Table 110: Mean costs and QALYs by age of onset of RRMS

Age	Mean costs (best supportive care) (£)	Mean QALYs (best supportive care)	Mean costs (DMTs) (£)	Mean QALYs (DMTs)
30	362,128	8.664	387,755	9.607
31	360,392	8.643	386,012	9.583
32	358,487	8.620	384,100	9.557
33	356,426	8.596	382,032	9.528
34	354,182	8.569	379,780	9.497
35	351,763	8.540	377,352	9.464
36	349,145	8.508	374,727	9.428
37	346,303	8.474	371,876	9.388
38	343,252	8.437	368,817	9.345
39	339,985	8.397	365,542	9.299
40	336,479	8.354	362,029	9.250
41	332,764	8.309	358,310	9.197
42	328,825	8.261	354,369	9.141
43	324,639	8.208	350,182	9.081
44	320,230	8.153	345,775	9.017
45	315,615	8.095	341,167	8.950
46	310,782	8.034	336,345	8.879
47	305,740	7.969	331,319	8.804
48	300,491	7.901	326,089	8.725
49	295,059	7.829	320,683	8.642
50	289,449	7.754	315,105	8.555
51	283,682	7.677	309,378	8.465
52	277,718	7.595	303,458	8.371
53	271,632	7.511	297,427	8.273
54	265,398	7.423	291,254	8.171
55	259,060	7.333	284,987	8.067
56	252,565	7.239	278,568	7.957
57	245,948	7.141	272,034	7.844
58	239,201	7.040	265,374	7.726
59	232,326	6.934	258,589	7.604
60	225,352	6.825	251,711	7.477
61	218,270	6.712	244,724	7.346
62	211,077	6.595	237,624	7.210
63	203,763	6.472	230,397	7.068
64	196,405	6.345	223,122	6.922
65	189,004	6.216	215,799	6.772
66	181,530	6.081	208,388	6.616
67	174,037	5.942	200,947	6.457
68	166,497	5.798	193,437	6.292
69	158,995	5.652	185,950	6.124
70	151,501	5.501	178,447	5.951
71	144,046	5.347	170,955	5.775
72	136,611	5.187	163,444	5.593
73	129,248	5.024	155,968	5.407
74	121,999	4.858	148,568	5.219
75	114,851	4.688	141,220	5.027

Age	Mean costs (best supportive care) (£)	Mean QALYs (best supportive care)	Mean costs (DMTs) (£)	Mean QALYs (DMTs)
76	107,837	4.515	133,956	4.833
77	101,019	4.342	126,843	4.637
78	94,362	4.165	119,833	4.440
79	87,944	3.989	113,014	4.243
80	81,775	3.814	106,399	4.048