Title: Clinical and cost-effectiveness of beta interferon and glatiramer acetate for treating multiple sclerosis (protocol for assessment report)

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2 Plain English summary

Multiple sclerosis (MS) is a complex, chronic and progressive disease, most commonly diagnosed in people between the ages of 40 and 45. About 100,000 people in the UK have MS, and around 2,500 new people are diagnosed each year. There are a wide range of symptoms that people with MS can suffer, including pain, muscle weakness, fatigue, speech problems and cognitive impairment. There are different ways that MS can progress over time, including progressively worsening disability and symptoms, as well short term relapses, after which individuals can either slowly recover to their previous condition or continue to get worse.

A number of different drugs, called disease modifying therapies, are used to treat patients with MS. The aim of these drugs is to reduce the speed at which an individual's disability increases, and/or to reduce the number or severity of the relapses they experience. Because individuals will often need to be treated with these drugs for a long period of time, they are expensive for the NHS, and hence it is important to make sure that the NHS is receiving value for money for the drugs it purchases.

In 2002, the National Institute for Health and Care Excellence looked at the value for money provided by a number of possible MS treatments (beta interferons and glatiramer acetate). It found that although there were benefits in the short term, not enough was yet known about the long term outcomes resulting from treatment with these drugs to recommend they should be widely used in the NHS.

In order to gather more evidence about the long term benefits, the UK MS risk-sharing scheme was set up, in which patients would be provided with the drugs for ten years whilst being closely

monitored over that period, with changes made to the price paid for the drugs by the NHS if the benefits in the long-term were different to those in the short-term. The final data from this 'risk-sharing' scheme have now been collected, and hence it is important to re-look at the initial question raised when these drugs first became available; do these drugs represent good value for money for patients and the NHS?

3 Decision problem

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

3.1 Background

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.

3.1.1 Types of MS

The disease can develop and progress in four major forms,: (i) relapsing remitting (RRMS); (ii) Primary progressive (PPMS); (iii) Secondary progressive (SPMS) and (iv) progressive relapsing (PRMS), all of which can originate 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 symptoms such as optic neuritis (in monofocal episodes) or optic neuritis and cerebellar or spinal syndromes, e.g. limb weakness (in multifocal episodes).

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 is characterised by at least two attacks of neurological dysfunction over the preceding two-year period. RRMS can be subtyped as

rapidly evolving or highly active MS, which are characterised by 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]

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

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]

Classically, the initial signs of MS follow a distinctive course, with the onset of fatigue or tiredness arising in patients around the 3rd decade of life. Symptoms can increase in severity and frequency as the disease develops, creating visual problems and pain associated with the eyes.[18] In most cases, the fifth decade of life witnesses disturbances in the sensory and motor neural networks, as the descending and ascending spinal tracts are affected, causing unsteadiness in balance and pain in limbs and the back during neck flexion (Lhermitte's sign).[19]

Within the first 10 years after a definitive diagnosis, there is a more prominent decline in physical functional systems than in social and cognitive systems.[20] Younger patients often have painful muscle spasms and back pain. Women are more likely to experience progressively worsening headaches than men.[21]

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).

3.1.2 Disease modifying therapies (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.[22] 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 (PEG-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 administrations (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.[23]

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 definitive MS. IFN-β-1b is also licensed for use in SPMS. IFN-β is not indicated for PPMS.

The most common reported adverse events of IFN-β are irritation at injection-site reactions and flu-like syndrome.[24] Other adverse events include hypersensitivity reactions, blood disorders (mainly leukopenia), menstrual disorders, and mood and personality changes. 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.[25]

3.1.3 Disease modifying therapies (glatiramer acetate)

There are two licensed formulations (Copaxone) of glatiramer acetate (GA). GA is the acetate salt of synthetic polypeptides, containing four naturally occurring amino acids. The mechanism(s) by which GA exerts its effects in patients with MS is (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 and anxiety.[26] 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.[25]

3.1.4 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 and of PEG-IFN-β-1a, which were released after the publication of TA 32. Within the risk-sharing scheme, 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.

4 Clinical Effectiveness methods

4.1 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 have been identified. [27-31]

The following search strategy has been 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.[27-32] Clinical searches will be restricted to RCT evidence. The included and excluded study lists from previous Cochrane systematic reviews will be checked.[29, 30] The main search of databases will be limited by date from 2012 (the date the searches were undertaken for the broad review and network meta-analysis (NMA) by Filippini, et al., 2013[30]) to the present day. This review was chosen because of the breadth of its scope, search strategy and eligibility criteria. Other more recent reviews are 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, will be undertaken. The search terms that are likely to be used in the major databases are provided in Appendix A. These searches were developed for MEDLINE and will be adapted as appropriate for other databases.

The search strategy will comprise 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

Databases will include:
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.

The following trial databases will also be searched: WHO ICTRP; Current Controlled Trials; ClinicalTrials.gov.

All bibliographic records identified through the electronic searches will be collected in a managed reference database. Citation searches of included studies will be undertaken using the Web of Science citation search facility. The reference lists of included studies and relevant review articles will also be checked and the companies' websites will be screened for relevant publications. Grey literature searches will be undertaken using the online resources of various regulatory bodies, health service research agencies, professional societies and patient organisations. Any relevant unpublished data in company submissions will be included, and the reference lists of company submissions will be checked for additional relevant studies.

4.2 Study selection

4.2.1 Inclusion of relevant studies

We will include studies meeting the following criteria.

- The **study design** is a randomised controlled trial, a systematic review, or a meta-analysis
- The **population** is people diagnosed with RRMS, SPMS, or CIS
- The **intervention** is one of the following drugs, when used within indication:
    - Interferon beta 1a
    - Peginterferon beta 1a
    - Interferon beta 1b
    - Glatiramer acetate
- The **comparator** is best supportive care without DMT
- The reported **outcomes** include at least one of the following:
    - Relapse rate
    - Severity of relapse
    - Disability, including as measured by the Expanded Disability Status Scale

- Multiple sclerosis symptoms, such as fatigue, cognition and visual disturbance
- Freedom from disease activity
- Mortality
- Health-related quality of life (HRQoL)
- Treatment-related adverse events
- Discontinuation (any cause)
- Discontinuation due to loss of effectiveness attributed to neutralising antibody formation
- Progression to multiple sclerosis (for patients with CIS)

The study must be **reported** as a full-text report in English.

We will exclude:

- Studies that compare an eligible intervention against an irrelevant comparator;
- Studies that only examine MS subtypes other than those in the eligible population;
- Studies that only examine 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.

4.2.2 Study selection process

First, we will examine the relevant past systematic reviews (including Filippini, et al., 2013[30]) and the original MTA report for studies meeting the inclusion criteria. We will verify inclusion of these studies by examining their full text.

For updated and new searches (including for studies addressing CIS), we will collect all retrieved records in a specialised database and duplicate records will be identified and removed. The reviewers will pilot-test a screening form based on the predefined study inclusion and exclusion criteria. Subsequently, two reviewers will apply inclusion/exclusion criteria and screen all identified bibliographic records for title/abstract (level I) and then for full text (level II). Any disagreements over eligibility will be resolved through consensus or by a third party reviewer. Reasons for exclusion of full text papers will be documented. The study flow will be documented using a PRISMA diagram.[33]

4.3 Data extraction and quality appraisal

4.3.1 Data extraction

For all included studies, the relevant data will be extracted independently by two reviewers using a data extraction form informed by the NHS Centre for Reviews and Dissemination (CRD).[34] Uncertainty and/or any disagreements will be crosschecked with another reviewer and will be

resolved by discussion. Where studies do not report summary statistics (e.g., mean score, standard deviation, standard error), we will attempt to calculate these parameters if individual participant data or related effect size-level statistics are provided. If a study reports only a standard error of the mean response, we will convert it into a standard deviation. Where several types of MS are treated in one trial, we will extract information for relevant MS subtypes. The extracted data will be entered into summary evidence tables (see Appendix B). The extracted information will include:

- 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 will also be extracted (standard deviation, 95% CI, standard error, p-values).

4.3.2 Quality appraisal

Systematic reviews used to locate primary studies will be appraised using the AMSTAR checklist.[35] All primary studies will be appraised using the Cochrane risk of bias assessment tool.[36] Appraisal will be undertaken by two reviewers. Uncertainty and/or any disagreements will be crosschecked with a second reviewer and will be resolved by discussion.

4.4 Synthesis

Studies will be narratively synthesised, organised hierarchically: first by MS subtype, then by intervention-comparator contrast, and finally by each outcome for which data are available. If deemed appropriate, outcome data for studies in each intervention-comparator contrast will be pooled by MS subtype using random effects meta-analysis in Stata v14. Where conceptually related outcomes are measured on different scales (e.g. different scales for the presence or severity of fatigue as a symptom), effect sizes will be converted to standardised mean differences and meta-analysed. For each meta-analysis, heterogeneity statistics (i.e. Cochran's Q, I^2, and significance test) will be presented.

It is unlikely that subgroup analysis on individual treatment-comparator contrasts will be possible, given the expected numbers of studies.

If studies are similar enough, we will combine studies using a network meta-analysis model estimated in WinBUGS with vague prior distributions. We will considering estimating separate models by MS subtype. We will consider undertaking a robustness check on this model by specifying a prior distribution using treatment effects estimated from the MS risk-sharing scheme cohort evaluation.

5 Cost-effectiveness methods

5.1 Identification of existing evidence

A comprehensive search of the health economic literature will be undertaken to identify existing economic evaluations of disease modifying therapy for RRMS, SPMS and CIS. The purpose of this search is to identify existing cost-effectiveness model designs and identify parameter values suitable for use in the cost-effectiveness model (e.g. health state utilities, costs etc.). Scoping searches undertaken in October 2015 have identified several systematic reviews of cost-effectiveness studies in MS.[37, 38]

5.1.1 Objectives

- Provide an overview of systematic reviews, published in the last five years, of studies that assess the cost-effectiveness of treating RRMS, SPMS and CIS.
- Systematically review recent primary health economic studies in RRMS, SPMS and CIS.

5.1.2 Overview of systematic reviews

The search terms that are likely to be used in the major databases are provided in Appendix A. These searches were developed for MEDLINE and will be adapted as appropriate for other databases.

The search strategy will comprise the following main elements:

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

The following electronic databases will be 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.

All bibliographic records identified through the electronic searches will be collected in a managed reference database. The reference lists of included studies and relevant review articles will also be

checked. Grey literature searches will be undertaken using the online resources of various regulatory bodies, health service research agencies, professional societies and patient organisations.

5.1.3 Recent primary studies

We will search for primary studies from the search date used in the most suitable systematic review identified in the overview of systematic reviews (see section 5.1.2). Suitability will be assessed through the use of a quality checklist, by comparing the scope of each included systematic review against our decision problem and by considering publication date. The same sources and the same search terms for MS, CIS, cost-effectiveness and HRQoL as for the overview of systematic reviews (see section 5.1.2 and Appendix A) will be used in the search for primary studies, but the systematic review filter will not be applied.

5.1.4 Additional searches

We will check primary studies and systematic reviews identified through the searches described in sections 5.1.2 and 5.1.3 for studies on the natural history of people with multiple sclerosis and MS patient registries. We will also undertake targeted database searches to identify any additional multiple sclerosis patient registries that include data from before 1995 (see Appendix A). Citation searches on any included studies will be undertaken to identify more recent literature. Additional searches may be undertaken to identify relevant information to support the development of the economic model.

5.2 Study selection

Published economic evaluations including a decision analytical model will be included in the review. Studies presenting information on costs and outcomes related to the natural history of or disease modifying therapy for people with RRMS, SPMS and/or will be reviewed in detail. Systematic reviews of economic evaluations that involve the use of economic models in RRMS/SPMS/CIS will be included and appraised separately.

5.3 Quality appraisal and data extraction

Critical appraisal will be undertaken using the following tools:

- Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (adapted from Husereau et al., 2013[39]) [Appendix C] for economic evaluations.
- The Philips checklist (Philips et al., 2004[40]) [Appendix D] for decision analytical models.
- The AMSTAR checklist for systematic reviews.

Data will be extracted by one reviewer and cross-checked by a second reviewer. Any disagreements will be resolved by discussion or by recourse to a third-party reviewer. A data extraction sheet is provided in Appendix E. Reviewers will extract relevant information on resource use and costs, time horizon, perspective of the analysis and utility information.

5.4 Economic modelling

5.4.1 RRMS/SPMS

Economic modelling undertaken by the assessment group will be based on the structure of the model built for analysing the MS risk sharing scheme (RSS),[41] including data from the ten year follow up, where available. The RSS compares the cohort of UK patients from the RSS with a historical, pre-treatment cohort from British Columbia. The effect of treatment is modelled through reductions in relapse rates and slower progression to higher EDSS scores. When appropriate, additional analyses will be undertaken to account for uncertainties in the original modelling. These include:

- Comparison and synthesis of the results from the RSS with available RCT data, as identified by and synthesised from the clinical effectiveness review.
- Inclusion of those drugs now licensed but which were not part of the RSS.
- An update of cost, utility, adverse event and natural history parameters in the model, informed by both the clinical and cost-effectiveness searches undertaken.
- The inclusion of a probabilistic sensitivity analysis, undertaken as a Monte Carlo simulation, sampling from the distributions of each of the parameter inputs in the model.

The particular sensitivity and scenario analyses undertaken will be informed by the list of those already conducted or planned to be conducted as part of the Department of Health evaluation of the risk sharing scheme, when this information becomes available.

5.4.2 CIS

A de novo economic model will be constructed to evaluate the costs and benefits of treating individuals diagnosed with CIS. This will be based on the clinical, cost and quality of life evidence identified by the systematic reviews undertaken, and will estimate differences in costs and benefits between treated and untreated individuals whilst they remain in the CIS state, as well as any differences in transitions from CIS to MS. If changes to the rate of progression from CIS to MS are found (either individuals who, once treated, do not progress to MS, or a delay in the rate of progression from CIS to MS), the impact of these changes will be assessed using the MS RSS model (e.g. comparing cohorts with different ages of onset of MS.)

5.5 Company submission(s)

Company submissions received by the assessment group before the submission deadline specified by NICE will be appraised, with those submitted after not considered unless they are specifically requested from the Company by either NICE or the assessment group. The model structures, assumptions and parameter values from models submitted will be critiqued and the results compared to the equivalent results from the main RSS model. Where there are differences between the results obtained, an effort will be made to provide a justification for the key driving factors influencing these differences.

6 Competing interest of authors

None of the authors have any competing interests.

7 Timetable/milestones

Final protocol	12/01/2016
Draft assessment report	04/07/2016
Final assessment report	01/08/2016

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9 Appendices

9.1 Appendix A. Search strategies

9.1.1 Clinical effectiveness: main search

MEDLINE (Ovid) 1946 to November Week 2 2015, searched 24/11/2015

1	exp Multiple Sclerosis/	49039
2	multiple sclerosis.tw.	51161
3	1 or 2	59541
4	randomized controlled trial.pt.	416592
5	controlled clinical trial.pt.	92207
6	clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/	37175
7	(random* or "controlled trial*" or "clinical trial*" or rct).tw.	897584
8	4 or 5 or 6 or 7	1095462
9	Animals/	5651921
10	Humans/	14563331
11	9 not 10	4055381
12	8 not 11	993120
13	3 and 12	5105
14	(metaanalys* or "meta analys*" or "meta-analys*").tw.	71524
15	"systematic* review*".mp.	62791
16	meta analysis.pt.	62260
17	14 or 15 or 16	126543
18	3 and 17	651
19	13 or 18	5495

20	limit 19 to yr="2012 -Current"	1455

9.1.2 Clinical effectiveness: additional search for CIS

MEDLINE (Ovid) 1946 to November Week 2 2015, searched 24/11/2015

1	Demyelinating Diseases/	10467
2	Myelitis, Transverse/	1134
3	exp Optic Neuritis/	6750
4	Encephalomyelitis, Acute Disseminated/	1614
5	Demyelinating Autoimmune Diseases, CNS/	322
6	demyelinating disease*.tw.	4823
7	transverse myelitis.tw.	1372
8	neuromyelitis optica.tw.	1749
9	optic neuritis.tw.	3929
10	acute disseminated encephalomyelitis.tw.	1102
11	devic.tw.	107
12	ADEM.tw.	587
13	demyelinating disorder.tw.	343
14	clinically isolated syndrome.tw.	637
15	first demyelinating event.tw.	72
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	24883
17	randomized controlled trial.pt.	416592
18	(random* or "controlled trial*" or "clinical trial*" or rct).tw.	897584

19	17 or 18	1000543
20	(metaanalys* or "meta analys*" or "meta-analys*").tw.	71524
21	"systematic* review*".mp.	62791
22	meta analysis.pt.	62260
23	20 or 21 or 22	126543
24	16 and 19	686
25	16 and 23	75
26	24 or 25	738

9.1.3 Cost-effectiveness: search for systematic reviews of health economic literature

MEDLINE (Ovid) 1946 to November Week 2 2015, searched 24/11/2015

1	exp Multiple Sclerosis/	49039
2	multiple sclerosis.tw.	51161
3	1 or 2	59541
4	Demyelinating Diseases/	10467
5	Myelitis, Transverse/	1134
6	exp Optic Neuritis/	6750
7	Encephalomyelitis, Acute Disseminated/	1614
8	Demyelinating Autoimmune Diseases, CNS/	322
9	demyelinating disease*.tw.	4823
10	transverse myelitis.tw.	1372
11	neuromyelitis optica.tw.	1749

12	optic neuritis.tw.	3929
13	acute disseminated encephalomyelitis.tw.	1102
14	devic.tw.	107
15	ADEM.tw.	587
16	demyelinating disorder.tw.	343
17	clinically isolated syndrome.tw.	637
18	first demyelinating event.tw.	72
19	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 or 18	24883
20	3 or 19	75441
21	exp Economics/	522541
22	exp "Costs and Cost Analysis"/	195680
23	Health Status/	65149
24	exp "Quality of Life"/	133903
25	exp Quality-Adjusted Life Years/	8138
26	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.	483075
27	(health state* or health status).tw.	41760
28	(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.	144762
29	(markov or time trade off or TTO or standard gamble or hrql or hrqol or disabilit* or disutilit*).tw.	136495
30	(quality adj2 life).tw.	158010

31	(decision adj2 model).tw.	4170
32	(visual analog* scale* or discrete choice experiment* or health* year* equivalen* or (willing* adj2 pay)).tw.	33513
33	("resource use" or resource utili?ation).tw.	9794
34	(well-being or wellbeing).tw.	47197
35	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34	1349509
36	20 and 35	9804
37	(metaanalys* or meta analys* or meta-analys*).tw.	71524
38	(systematic* and review*).mp.	96817
39	meta analysis.pt.	62260
40	(literature and review*).mp.	319194
41	37 or 38 or 39 or 40	433318
42	36 and 41	494
43	limit 36 to systematic reviews	428
44	42 or 43	655
45	limit 44 to yr="2010 -Current"	332

9.1.4 Cost-effectiveness: search for studies on multiple sclerosis patient registries

Ovid MEDLINE(R) 1946 to November Week 3 2015, searched 06/01/2016

1	exp Multiple Sclerosis/	49495
2	multiple sclerosis.tw.	51625
3	1 or 2	60044

4	exp Registries/	66038
5	(registry or registries).tw.	67517
6	(register or registers).tw.	44760
7	4 or 5 or 6	136343
8	3 and 7	728
9	limit 8 to yr="1902 - 2005"	182

9.2 Appendix B: Draft data extraction and appraisal form for primary studies

Name of the reviewer:

Study details
Study ID (Endnote):
First author surname:
Year of publication:
Country:
Study setting:
Number of centres:
Duration of study:
Follow up period:
Funding:
Subtypes of MS included:
Definition of CIS used:
Aim of the study
Participants
Inclusion criteria:
Exclusion criteria:
Subtypes of MS in the trial:
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:
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: Timing of assessment: Study end point: Adverse event: Yes/No Health related quality of life: Yes/No; which measures used? Length of follow up:

Number of participants	**Intervention**	**Comparator, if present**
Screened		
Randomised/Included		
Excluded		
Missing participants		
Withdrawals		
Patient baseline characteristics	**Intervention**	**Comparator, if present**
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	**Intervention**	**Comparator, if present**

(add rows as necessary)		
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

9.3 Appendix C: Critical appraisal of the economic evaluation studies using the CHEERS checklist (adapted from Husereau et al., 2013[39])

CHEERS criteria	Study			
Title and abstract				
1 Title: Identify the study as an economic evaluation, or use more specific terms such as ``cost-effectiveness analysis``, and describe the interventions compared.				
2 Abstract: Provide a structured summary of objectives, methods including study design and inputs, results including base case and uncertainty analyses, and conclusions.				
Introduction				
3 Background & objectives: Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.				
Methods				
4 Target Population and Subgroups: Describe characteristics of the base case population and subgroups analysed including why they were chosen.				
5 Setting and Location: State relevant aspects of the system(s) in which the decision(s) need(s) to be made.				
6 Study perspective: Describe the perspective of the study and relate this to the costs being evaluated.				
7 Comparators: Describe the interventions or strategies being compared and state why they were chosen.				
8 Time Horizon: State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.				
9 Discount Rate: Report the choice of discount rate(s) used for costs and outcomes and say why				

CHEERS criteria	Study			
appropriate.				
10 Choice of Health Outcomes: Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.				
11a Measurement of Effectiveness - Single Study-Based Estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.				
11b Measurement of Effectiveness - Synthesis-based Estimates: Describe fully the methods used for identification of included studies and clinical effectiveness data synthesis of clinical effectiveness data.				
12 Measurement and Valuation of Preference-based Outcomes: If applicable, describe the population and methods used to elicit preferences for health outcomes.				
13a Estimating Resources and Costs - Single Study-based Economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.				
13b Estimating Resources and Costs - Model-based Economic Evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.				

CHEERS criteria	Study			
14 Currency, Price Date and Conversion: Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.				
15 Choice of Model: Describe and give reasons for the specific type of decision-analytic model used. Providing a figure to show model structure is strongly recommended.				
16 Assumptions: Describe all structural or other assumptions underpinning the decision-analytic model.				
17 Analytic Methods: Describe all analytic methods supporting the evaluation. This could include methods for dealing with skewed, missing or censored data, extrapolation methods, methods for pooling data, approaches to validate a model, and methods for handling population heterogeneity and uncertainty.				
Results				
18 Study parameters: Report the values, ranges, references, and if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. We strongly recommend the use of a table to show the input values.				
19. Incremental costs and outcomes: For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.				
20a Characterizing Uncertainty - Single study-based economic evaluation: Describe the effects of				

CHEERS criteria	Study			
sampling uncertainty for the estimated incremental cost and incremental effectiveness, parameters together with the impact of methodological assumptions.				
20b Characterizing Uncertainty - Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.				
21 Characterizing Heterogeneity: If applicable, report differences in costs, outcomes or in cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.				
Discussion				
22 Study Findings, Limitations, Generalizability, and Current Knowledge: Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.				
Other				
23 Source of Funding: Describe how the study was funded and the role of the funder in the identification, design, conduct and reporting of the analysis. Describe other non-monetary sources of support.				
24 Conflicts of Interest: Describe any potential for conflict of interest among study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors'				

CHEERS criteria	Study			
recommendations				

*Key: Y = yes, No = no, N/A = not applicable and * = partially completed*

9.4 Appendix D: Critical appraisal of the economic models using an adapted Philips checklist[40]

Philips criteria		Response	Comments
STRUCTURE			
1	Is there a clear statement of the decision problem?		
2	Is the objective of the model specified and consistent with the stated decision problem?		
3	Is the primary decision maker specified?		
4	Is the perspective of the model stated clearly?		
5	Are the model inputs consistent with the stated perspective?		
6	Has the scope of the model been stated and justified?		
7	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?		
8	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?		
9	Are the sources of the data used to develop the structure of the model specified?		
10	Are the causal relationships described by the model structure justified appropriately?		
11	Are the structural assumptions transparent and justified?		
12	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?		
13	Is there a clear definition of the options under evaluation?		
14	Have all feasible and practical options been evaluated?		
15	Is there justification for the exclusion of feasible options?		
16	Is the chosen model type appropriate given the decision problem and specified casual relationships within the model?		
17	Is the time horizon of the model sufficient to reflect all		

Philips criteria		Response	Comments
	important differences between the options?		
18	Are the time horizon of the model, the duration of treatment 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?		
20	Is the cycle length defined and justified in terms of the natural history of disease?		
DATA			
21	Are the data identification methods transparent and appropriate given the objectives of the model?		
22	Where choices have been made between data sources are these justified appropriately?		
23	Has particular attention been paid to identifying data for the important parameters of the model?		
24	Has the quality of the data been assessed appropriately?		
25	Where expert opinion has been used are the methods described and justified?		
26	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?		
27	Is the choice of baseline data described and justified?		
28	Are transition probabilities calculated appropriately?		
29	Has a half-cycle correction been applied to both costs and outcomes?		
30	If not, has the omission been justified?		
31	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?		

Philips criteria		Response	Comments
32	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?		
33	Have alternative extrapolation assumptions been explored through sensitivity analysis?		
34	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?		
35	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis		
36	Are the costs incorporated into the model justified?		
37	Has the source for all costs been described?		
38	Have discount rates been described and justified given the target decision maker?		
39	Are the utilities incorporated into the model appropriate?		
40	Is the source of utility weights referenced?		
41	Are the methods of derivation for the utility weights justified?		
42	Have all data incorporated into the model been described and referenced in sufficient detail?		
43	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate?)		
44	Is the process of data incorporation transparent?		
45	If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?		
46	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?		
47	Have the four principal types of uncertainty been addressed?		

Philips criteria		Response	Comments
48	If not, has the omission of particular forms of uncertainty been justified?		
49	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?		
50	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?		
51	Has heterogeneity been dealt with by running the model separately for different sub-groups?		
52	Are the methods of assessment of parameter uncertainty appropriate?		
53	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?		
54	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?		
55	Are any counterintuitive results from the model explained and justified?		
56	If the model has been calibrated against independent data, have any differences been explained and justified?		
57	Have the results been compared with those of previous models and any differences in results explained?		
N- No; N/A- Not Applicable; Y- Yes; UNC-Unclear			

9.5 Appendix E: Data extraction sheet for included cost-effectiveness studies

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	
Target population and subgroups	
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	
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	