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SYSTEMATIC REVIEW

Disease-Modifying Therapies for Multiple Sclerosis: A Systematic Literature Review of Cost-Effectiveness Studies

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Abstract

Introduction and objective Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system. MS is considered incurable; however, disease treatment has advanced significantly over the past several decades with the introduction of disease-modifying therapies (DMTs). The current study reviewed the cost-effectiveness analyses of DMTs in relapsing–remitting MS (RRMS) patients.

Methods A systematic literature search of bibliographic databases was conducted to identify economic evaluations published after 2007. The relevant population, intervention, comparators, outcomes, and study design (PICOS) were considered. The outcomes of interest were incremental cost-effectiveness ratios (ICERs), net monetary benefits, incremental benefits, and incremental costs. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement was used to assess the reporting quality of published studies.

Results A total of 1370 potentially relevant citations were identified, of which 33 published articles and four Health Technology Assessment (HTA) reports prepared for the UK were included in the final analysis. Almost all studies were based on a health economic model and considered RRMS as the phase of disease at study entry. The studies were conducted in 10 different countries, with approximately 50% based in the US. Study outcomes were rarely comparable due to the different settings, input data, and assumptions. Even within the same country, the discrepancy between study criteria was considerable. The compliance with reporting standards of the CHEERS statement was generally high.

Conclusions Internationally, a large number of health economic assessments of DMTs in RRMS were available, yielding difficult to compare, and at times conflicting, results.

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Key Points for Decision Makers

The level of compliance in the identified cost-effectiveness papers with reporting standards of the CHEERS statement was generally high.

The outcomes of the studies were difficult to compare due to the different settings, input data, and assumptions; a high level of heterogeneity and sometimes conflicting results were observed even between studies conducted in the same country.

While few conclusions can be drawn due to the variance in study inputs, the following general trends were of interest:

Pegylated interferon (pegIFN) and dimethyl fumarate (DMF) were mostly cost effective in all studies in which they were analyzed.

With the exception of three US studies, oral treatments were cost effective when compared with injection treatments.

The main drivers of the incremental cost-effectiveness ratios (ICERs) were treatment effectiveness and direct treatment costs.

1 Introduction and Objective

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system, in which the protective myelin layer covering the nerve cells in the brain and spinal cord are damaged, resulting in progressive disability [1, 2].

MS takes several forms, with new symptoms either occurring in isolated attacks (relapsing form) or building up over time (progressive form) [3]. Between attacks, symptoms may disappear completely; however, permanent neurological problems often remain, especially as the disease advances [3]. In 85% of patients with MS, the onset form is relapsing–remitting MS (RRMS) [4].

MS affects approximately 2.3 million people all over the world, with a ratio of about 2:1 women to men. The prevalence of the disease is estimated to be > 100 per 100,000 in North America and across most of Europe [4]. The disease onset occurs when patients are of working age, and therefore, the chronicity and progression of the disease heavily impacts on patients' quality of life (QoL) and, more broadly, on societal costs. MS is currently considered incurable [5]; however, treatment has advanced significantly over the past several decades [6–11]. Disease-modifying therapies (DMTs) can reduce the frequency and severity of clinical relapses, reduce the development of new lesions within the brain and spinal cord, and delay the progression of disability [12]. As is the case in many different therapeutic areas, clinical progress in treating the disease has accompanied a rise in costs to purchase biologic products [13]. DMTs have experienced a swift rise in acquisition costs over the last 15 years, despite the ongoing approval of novel DMTs as well as the recent introduction of the first generic in the US. Ultimately, a consequence of high drug prices for patients with MS in the US is the potential for reduced access to DMTs, and costs to major payers (i.e., Medicare) although often discounted, must be considered in the context of value [13]. Value for cost is a concept not limited to the US. In 2002 the NHS in the UK initiated a risk access scheme for interferon-beta (IFNβ) and glatiramer acetate (GA) that closely monitored patient outcomes in an attempt to confirm the cost effectiveness of the DMTs [14]. In this light, economic evaluations are key elements for healthcare decision making [13, 15]. Recently, cost-effectiveness studies of DMTs have been the subject of systematic literature reviews. Yamamoto and Campbell [16] conducted a general review of the literature with the aim of providing a comprehensive understanding of the cost effectiveness of DMTs for the treatment of MS, including the evaluation of the quality of recent cost-effectiveness studies through the use of the 16-item Quality of Health Economic Studies (QHES) instrument [17]. Koeser and McCrone [18] conducted a limited cost-effectiveness analyses review of a single specific DMT (natalizumab [NTZ]). Hawton et al. [19] analyzed the methodological challenges and suggested practical recommendations for future research, providing a statement on the scope and characteristics of the cost-effectiveness literature. Similarly, Thompson et al. [20] focused on the methodological challenges of modeling the cost effectiveness of MS treatments. They identified the key parameters influencing the cost effectiveness of DMTs and described the approaches taken including the major areas of weakness and uncertainty. Guo et al. [21] limited the review of cost-effectiveness analyses to studies published over the last decade that had a long-term time horizon ($\geq$ 10 years), and homogeneous contexts of analysis (i.e., similar study objectives, comparators, and target populations). A recent review by Allen et al. [22] focused on modeling methods and analyzed data sources, techniques, and assumptions of health economic models of DMTs for RRMS in the UK. Unlike the previous reviews discussed, Allen et al. included the website of the UK's National Institute for Health and Care Excellence (NICE) and in doing so added to their analysis the health economic evidence available from the process of Health Technology Assessment (HTA)

submissions. Overall, most of the recent systematic literature reviews of health economic evidence for DMTs in MS focused on aspects related to modeling techniques, while only Yamamoto and Campbell reviewed the quality of reporting in the analyzed studies [16]. Despite a lack of review of the quality of reporting in the field, several new biologic DMTs have been presented to the market in recent years, and the pharmacoeconomic value of these newer DMTs have been assessed in HTA submissions as well as in the general literature. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement has been developed and accepted by the scientific community and was produced by a dedicated task force on good reporting practice from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [23].

The objective of the present work was to conduct a systematic literature review of economic evidence from cost-effectiveness analyses of MS treatment to (i) summarize the evidence on cost effectiveness of the different treatments; (ii) provide an assessment of the quality of the studies (i.e., using the CHEERS checklist); and (iii) identify and discuss the main drivers of cost effectiveness.

2 Methods

2.1 Data Sources and Search Strategy

A systematic literature search of bibliographic biomedical and economic databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials [CENTRAL], the Centre for Reviews and Dissemination [CRD] HTA database, the National Health System Economic Evaluations Database [NHS EED] and Econlit) was conducted on December 22, 2016. Results were limited to economic evaluations published after the year 2007, in order to limit the analysis to the most recent evidences developed in the past 10 years. The search strategy comprised both selected subject headings and keywords relating to MS and relevant treatments. In addition, a search for grey literature, including HTAs, was undertaken. For a full description of the search strategy and resources used please see the electronic supplementary materials. The search was conducted in accordance with the requirements of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24].

2.2 Selection Criteria

To address the research question, criteria were developed to describe the relevant population, intervention, comparators, outcomes, and study design (PICOS). Publications identified in the search of the different databases were combined and duplicates were removed.

Population The population of interest was adults (aged $\geq$ 18 years) diagnosed with MS.

Interventions All the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) authorized DMTs, including IFNβ-1a, IFNβ-1b, pegylated interferon (pegIFN) β-1a, GA, mitoxantrone, teriflunomide, NTZ, dymethilfumarate (DMF), fingolimod hydrochloride (FGM), alemtuzumab, and daclizumab were included in the search.

Comparators No restriction by comparator was applied.

Outcomes of interest Comparative outcomes from economic analyses, such as incremental cost-effectiveness ratios (ICERs), net monetary benefits (NMBs), incremental benefits, and incremental costs were considered.

Study design of interest Fully published economic analyses that considered costs and benefits, while simultaneously comparing the results in more than two interventions, such as cost-effectiveness, cost-utility, and cost-benefit analyses were included.

The first step of the screening process involved study selection based on title/abstract, followed by full-text screening for articles that were not definitively categorized via title/abstract. Two independent reviewers (SI and CI) simultaneously screened all abstracts and articles for inclusion/exclusion. A third reviewer (LP) was available to resolve disagreements. No limitation by language was applied in the searches. However, studies in languages other than English were excluded during screening.

2.3 Data Extraction and Quality Assessment

A comprehensive data extraction form was created in Microsoft Excel and used to compile the data. The study characteristics included type of economic analysis, geographic region, evidence base (i.e., model or real-world evidence), type of model, time horizon, disease phase at study entry (i.e., RRMS, primary-progressive or secondary-progressive MS), treatment and doses, use of network meta-analysis (NMA) for effectiveness inputs, and base-case results. Data were extracted by one researcher (CI) and validated by a second researcher (SI). A third researcher (LP) performed a random control on 50% of the selected papers. For all studies not reporting values in US dollars ($US), both original and converted values (listed in square brackets if different from the original value) were reported in the text. The following conversion rates were used, as of May 2017: $US1 = $Can1.346 = €0.895 = £0.782 = Kr8.688.

The CHEERS statement was used to assess the reporting quality of published studies. Quality of reporting control was not applied to HTA reports. The CHEERS criteria

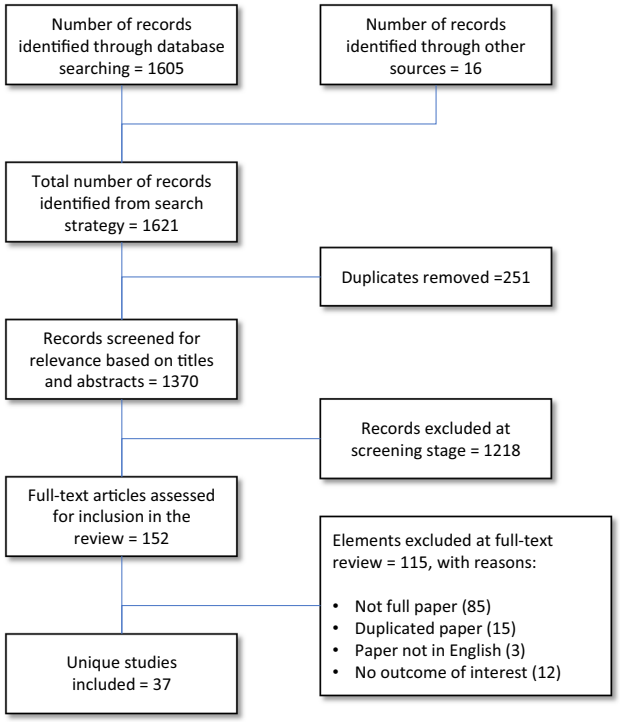

Fig. 1 PRISMA flow diagram

were checked for reporting in each selected paper, and when positive, page numbers were noted.

3 Results

The search strategy provided a total of 1370 potentially relevant citations, of which 33 published articles [6, 7, 10, 11, 25–53] and four HTA reports [8, 9, 54, 55] were included in the final analysis. A flow diagram of the search and selection strategy is shown in Fig. 1.

3.1 Modeling Approach

In the majority of cases ($n = 33$), the analysis was based on a health economic model. In three studies, the evidence base was mixed (i.e., a model and real-world data [30, 47, 51]), and in one case the study was completely based on observational data [45]. Among the model-based studies, ten analyses were simple decision trees that measured the economic value of DMTs in terms of cost per relapse avoided over a limited time horizon of between 2 and 4 years [25–28, 30, 32, 37, 48–50]. Twenty-four analyses employed a Markov technique, with a longer time horizon variable of between 5 years and lifetime, and two made use of more sophisticated dynamic modeling techniques [38, 47]. The ten studies based on a decision tree did not adjust effectiveness data to account for the heterogeneity of sources (naïve comparison), and as such sourced input data directly from published randomized clinical trials. The other 26 studies were based on more sophisticated modeling techniques (i.e., Markov or dynamic simulations). Of these, ten cases made use of published or unpublished mixed treatment comparisons (MTC) [6, 8–10, 31, 39, 40, 53–55], five cases were directly based on head-to-head trials [7, 33, 38, 51] or real-world efficacy data [47], and 11 cases used a naïve comparison [11, 29, 34–36, 41–44, 46, 52] (Table 1).

3.2 Economic Value of Disease-Modifying Therapies (DMTs)

Most of the studies were performed in North America ($n = 19$) or Europe ($n = 15$). The remaining three studies were performed in Iran [41, 45, 46]. The included studies used a cost-effectiveness or cost-utility analysis. Only one study added the cost-benefit technique to the standard cost effectiveness and thus reported results also in terms of net-monetary benefit [11]. About 62% of the studies ($n = 23$) performed the economic evaluation from a third-party payer cost perspective, while the remaining 14 also considered a societal perspective in their evaluation. All studies included in the review considered RRMS as the phase of the disease at study entry, with the only exception being the model developed by Noyes at al. [47], who considered both patients in RRMS and in secondary-progressive MS (SPMS). The cost-effective treatment was defined as the one with the lowest ICER, the dominant treatment, or the treatment with an ICER below a willingness-to-pay threshold cited by the authors. Given the lack of transferability of economic analysis results between different geographic locations [56], the results reported by the studies included in the review in the remainder of this section were grouped by country (Table 2).

3.2.1 Analysis in the Canadian Setting

Su et al. [10] performed a cost-utility analysis that compared DMF with GA and IFNβ-1a 44 μg from the Canadian healthcare system perspective, reporting an ICER of $Can44,118 [$US32,767]/quality-adjusted life-year(-QALY) and of $Can10,672 [$US7926]/QALY, respectively. At a threshold range of $Can50,000–$Can60,000 [$US37,150–$US44,580], DMF was cost effective [10].

3.2.2 Analysis in the French Setting

Chevalier et al. [31] analyzed the cost effectiveness of DMF to other DMTs from both the perspective of the French healthcare system and of the broad society. From both perspectives, DMF and IFNβ-1a 44 μg were the two

Table 1 Model characteristics of the included studies

Study	Evidence base	Model type	Time horizon	Use of NMA for effectiveness inputs	Drivers of the cost effectiveness
Bozkaya et al. [6]	HE model	Markov	10 years	Published NMA	Drug prices Tx duration Effectiveness
Hernandez et al. [40]	HE model	Markov	30 years	Published NMA	Tx duration Effectiveness
Su et al. [10]	HE model	Markov	20 years	Unpublished NMA	Tx duration Long-term effect QoL utilities
Hernandez et al. [39]	HE model	Markov	10 years	Published NMA	Drug prices Effectiveness
Nikfar et al. [46]	HE model	Markov	Lifetime	Naive comparison	QoL utilities
Imani and Golestani [41]	HE model	Markov	Lifetime	NR	NR
Chevalier et al. [31]	HE model	Markov	30 years	Published NMA	Drug prices Effectiveness Direct costs
Maruszczak et al. [44]	HE model	Markov	Lifetime	Naive comparison	Drug prices Effectiveness
Najafi et al. [45]	RWE	NA	NA	NA	Drug prices
O'Day et al. [50]	HE model	Decision tree	2 years	Naive comparison	NR
Zhang et al. [11]	HE model	Markov	5 years	Naive comparison	Drug prices Tx duration QoL utilities
Dembek et al. [34]	HE model	Markov	30 years	Naive comparison	Drug prices Effectiveness QoL utilities
Darbà et al. [33]	HE model	Markov	10 years	Head-to-head trial	NR
Brandes et al. [30]	HE model + RWE	Decision tree	2 years	Naive comparison	Drug prices Effectiveness
Lee et al. [7]	HE model	Markov	10 years	Head-to-head trial	Drug prices QoL utilities
Pan et al. [51]	HE model	Markov	Lifetime	Head-to-head trial	Time horizon Social costs Baseline characteristics
Agashivala and Kim [25]	HE model	Decision tree	2 years	Head-to-head trial	Drug prices Effectiveness Direct costs
Sánchez-de la Rosa et al. [52]	HE model	Markov	10 years	Naive comparison	Time horizon Social costs NAbs
Noyes et al. 2011 [47]	HE model + RWE	Monte Carlo simulations	10 years	Efficacy based on regression analyses on Sonya Slifka Longitudinal Multiple Sclerosis study	Drug prices Tx duration
O'Day et al. [49]	HE model	Decision tree	2 years	Naive comparison	Drug prices Effectiveness
Becker and Dembek [28]	HE model	Decision tree	2 years	Naive comparison	Effectiveness
Nuijten and Mittendorf [48]	HE model	Decision tree	4 years	Naive comparison	Effectiveness

Table 1 continued

Study	Evidence base	Model type	Time horizon	Use of NMA for effectiveness inputs	Drivers of the cost effectiveness
Tappenden et al. [53]	HE model	Markov	50 years	Published NMA	Effectiveness
Goldberg et al. [37]	HE model	Decision tree	2 years	Naive comparison	Drug prices
					Effectiveness
					Baseline characteristics
Earnshaw et al. [35]	HE model	Markov	Lifetime	Naive comparison	Drug prices
					Effectiveness
					QoL utilities
Jankovic et al. [42]	HE model	Markov	40 years	Naive comparison	QoL utilities
					Social costs
Chiao and Meyer [32]	HE model	Decision tree	2 years	Naive comparison	Effectiveness
					Baseline characteristics
Kobelt et al. [43]	HE model	Markov	20 years	Naive comparison	Drug prices
					Long-term effect
					Time horizon
Gani et al. [36]	HE model	Markov	30 years	Naive comparison	Time horizon
Bell et al. [29]	HE model	Markov	Lifetime	Naive comparison	Drug prices
					Effectiveness
					QoL utilities
					Time horizon
Agashivala et al. [26]	HE model	Decision tree	2 years	Naive comparison	Drug prices
					Effectiveness
					Baseline characteristics
Guo et al. [38]	HE model	Discrete event simulation	4 years	Head-to-head trial	Drug prices
					Tx duration
					Effectiveness
					Time horizon
Bakhshai et al. [27]	HE model	Decision tree	2 years	Naive comparison	Effectiveness
					Baseline characteristics
NICE TA127 [54]	HE model	Markov	20 years	Published NMA	Drug prices
					Effectiveness
					Time horizon
					Baseline characteristics
NICE TA254 [8]	HE model	Markov	50 years	Published NMA	Effectiveness
					Long-term effect
					Time horizon
NICE TA320 [9]	HE model	Markov	30 years	Published NMA	Tx duration
					Effectiveness
					QoL utilities
					Direct costs
					Baseline characteristics
NICE TA312 [55]	HE model	Markov	Lifetime	Published NMA	Drug prices
					Tx duration
					Effectiveness
					Long-term effect
					Direct costs

HE health economic, *NA* not available, *NAbs* neutralizing antibodies, *NMA* network meta-analysis, *NR* not reported, *QoL* quality of life, *RWE* real-world evidence, *Tx* treatment

Table 2 Setting and results presented by the studies included in the review

Study	Country	Perspective	Base-case ICERs	Year of valuation	Source of funding
Su et al. [10]	Canada	NHS	DMF vs comparator: GA: $Can44,118 [$US32,767]/QALY IFNβ1a 44 μg: $Can10,672 [$US7,926]/QALY	2013	Pharma
Chevalier et al. [31]	France	Payer and societal perspectives	From both perspectives, DMF and IFNβ-1a 44 μg dominated all other comparators on the efficiency frontier. From the societal perspective, DMF vs IFNβ-1a 44 μg had an ICER of €13,110 [$US14,655]/QALY, while from the payer perspective the ICER was €29,047 [$US32,474]/QALY	2013	Pharma
Nuijten and Mittendorf [48]	Germany	Societal	Comparator vs no active treatment (societal): IFNβ-1a 30 μg: €133,770 [$US149,583]/relapse avoided GA: €71,416 [$US79,858]/relapse avoided IFNβ-1b 250 μg: €54,475 [$US61,918]/relapse avoided IFNβ-1a 44 μg: €51,250 [$US57,280]/relapse avoided Comparator vs no active treatment (statutory health insurance): IFNβ-1a 30 μg: €140,728 [$US157,287]/relapse avoided GA: €73,385 [$US82,065]/relapse avoided IFNβ-1 250 μg: €57,034 [$US63,791]/relapse avoided IFNβ-1a SC: €54,244 [$US60,636]/relapse avoided	2008	Pharma
Nikfar et al. [46]	Iran	Societal	Comparator vs placebo: IFNβ-1a 30 μg: $US19,954/QALY IFNβ-1a 44 μg: $US11,850/QALY IFNβ-1b 250 μg: $US16,864/QALY IFNβ-1a 30 μg(biopharmaceutical copy): $US904/QALY IFNβ-1a 44 μg(biopharmaceutical copy): $US6,975/QALY IFNβ-1b 250 μg(biopharmaceutical copy and biosimilar): $US12,740/QALY	2012	Academic or Government
Imani and Golestani [41]	Iran	NHS	Comparator vs placebo: IFNβ-1a 30 μg: $US607,397/QALY IFNβ-1b 250 μg: $US1,374,355/QALY IFNβ-1a 44 μg: $US1,166,515/QALY IFNβ-1a 30 μg(biopharmaceutical copy): $US1,010,429/QALY	2011	Academic or Government
Najafi et al. [45]	Iran	Third-party payer	IFNβ-1a 30 μg(biopharmaceutical copy) dominant over IFNβ-1a 30 μg	2011	Academic or Government
Hernandez et al. [40]	Scotland	NHS PSS	pegIFNβ-1a vs comparator: IFNβ-1a 30 μg: dominant IFNβ-1a 22 μg: dominant IFNβ-1a 44 μg: dominant IFNβ-1b: dominant GA: £5773[$US7382]/QALY	NR	Pharma
Jankovic et al. [42]	Serbia	Societal	Comparator vs symptom management: GA: 1240 M RSD [$US1,129,660]/QALY IFNβ-1a 44 μg: 4520 M RSD [$US41,194,769]/QALY IFNβ-1a 30 μg: 4527 M RSD [$US41,258,566]/QALY IFNβ-1b 250 μg: 4022 M RSD [$US36,656,053]/QALY	2008	Academic or Government
Sánchez-de la Rosa et al. [52]	Spain	Societal	IFNβ-1a 30 μg vs: IFNβ-1a 44 μg: dominant IFNβ-1b 250 μg: dominant GA: €117,914 [$US131,771]/QALY	2010	Pharma

Table 2 continued

Study	Country	Perspective	Base-case ICERs	Year of valuation	Source of funding
Dembek et al. [34]	Spain	Societal	Comparator vs BSC: IFNβ-1a 30 μg: €168,629 [$US188,505]/QALY IFNβ-1a 44 μg: €231,853 [$US259,117]/QALY IFNβ-1b 250 μg: €295,638 [$US330,409]/QALY GA: €318,818 [$US356,298]/QALY	2010	Pharma
Darbà et al. [33]	Spain	NHS PSS	GA vs: IFNβ-1a: dominant IFN + GA: dominant	2013	Pharma
O'Day et al. [50]	Sweden	NHS	NTZ vs FGM: All patients: Kr25,448 [$US2,929]/ relapse avoided Rapidly evolving severe disease: NTZ dominant	2011	Pharma
Kobelt et al. [43]	Sweden	Societal	NTZ dominant vs all comparators	2005	Pharma
NICE TA127 [54]	UK	NHS PSS	NTZ vs comparator (Rapidly Evolving Severe subgroup) IFNβ: £27.0 K [$US34,521]/QALY GA: £27.4 K [$US35,032]/QALY BSC: £34.9 K [$US44,621]/QALY NTZ vs comparator (Sub-Optimal Therapy subgroup) IFNβ: £44.1 K [$US56,384]/QALY GA: £45.0 K [US$57,535]/QALY BSC: £57.0 K [US$72,878]/QALY	2006	Academic or Government
NICE TA254 [8]	UK	NHS PSS	FGM vs IFNβ-1a 30 μg: £55,634 [$US71,131]/QALY	2010	Academic or Government
NICE TA320 [9]	UK	NHS PSS	List price DMF vs comparator: IFNβ-1a 22 μg: £142,283 [$US182,328]/QALY GA: £159,295 [$US204,128]/QALY IFNβ-1a 30 μg: £136,452 [$US174,825]/QALY IFNβ-1b 250 μg: £106,127 [$US135,972]/QALY IFNβ-1a 44 μg: £122,105 [$US156,443]/QALY NTZ: dominant FGM: £173,745 [$US222,590]/QALY	2012	Academic or Government
NICE TA312 [55]	UK	NHS PSS	Alemtuzumab strongly or extendedly dominated IFNs, NTZ and FGM. The ICER of alemtuzumab compared with GA was £8924/QALY	2012	Academic or Government
Gani et al. [36]	UK	Societal	NTZ vs comparator: IFNβ: £2300 [$US2946]/QALY GA: £2000 [$US2562]/QALY BSC: £8200 [$US10,508]/QALY	2006	Pharma
Maruszczak et al. [44]	UK	NHS PSS	FGM vs DMF: £12,528 [$US16,014]/QALY	2013–2014	Pharma
Zhang et al. [11]	USA	Societal	IFNβ-1a 30 μg vs comparator: Teriflunomide: $US7115/QALY FGM: $US46,328/QALY DMF: dominated	2012	None
Lee et al. [7]	USA	Societal	FGM vs IFNβ-1a 30 μg: $US73,975/QALY	2011	None
Pan et al. [51]	USA	Societal	Interferon β-1b vs placebo: $US46,357/QALY	2011	Pharma

Table 2 continued

Study	Country	Perspective	Base-case ICERs	Year of valuation	Source of funding
Earnshaw et al. [35]	USA	Societal Healthcare payers	Comparator vs symptom management (without productivity loss): GA: $US496,222/QALY NTZ: $US606,228/QALY Comparator vs symptom management (with productivity loss): GA: dominant NTZ: dominant	2007	Pharma
Noyes et al. [47]	USA	Societal	Comparator vs BSC: IFNβ-1a 30 μg: $US901,319/QALY IFNβ-1b 250 μg: $US1,123,162/QALY GA: $US2,178,555/QALY IFNβ-1a 44 μg: $US1,487,306/QALY	2005	Academic or Government
Bell et al. [29]	USA	Societal	Comparator vs symptom management: GA: $US258,465/QALY IFNβ-1a 30 μg: $US337,968/QALY IFNβ-1a 44 μg: $US416,301/QALY IFNβ-1b 250 μg: $US310,691/QALY	2005	Pharma
Hernandez et al. [39]	USA	Managed care organization	PegIFNβ-1a vs comparator: IFNβ-1a 44 μg: dominant GA 20 mg: dominant	2014	Pharma
Tappenden et al. [53]	USA	US healthcare payer Medicaid Services	Comparator vs BSC: IFNβ-1a 6 MIU (physician administered): $US233,967/QALY IFNβ-1a 6 MIU (self-administered): $US218,206/QALY; IFNβ-1a 22 μg: $US189,174/QALY IFNβ-1a 44 μg: $US172,438/QALY IFNβ-1b 8 MIU: $US91,515/QALY GA: $US309,173/QALY	2005	Academic or Government
Agashivala and Kim [25]	USA	Managed care organization	Cost-effectiveness ratio: Early FGM: $US83,125 per relapse avoided Delayed FGM: $US103,624 per relapse avoided	2011	Pharma
Brandes et al. [30]	USA	Managed care organization	Cost-effectiveness ratios: FGM: $US74,843 per relapse avoided IFNβ-1b 250 μg (Extavia): $US94,423 per relapse avoided IFNβ-1b 250 μg (Betaferon): $US102,530 per relapse avoided IFNβ-1a 44 μg: $US108,940 per relapse avoided GA: $US124,512 per relapse avoided IFNβ-1a 30 μg: $US197,073 per relapse avoided	2011	Pharma
Agashivala et al. [26]	USA	Managed care organization	FGM vs comparator: IFNβ-1b 250 μg [Extavia): $US19,579/relapses avoided IFNβ-1b 250 μg [Betaseron): $US27,686/relapses avoided GA: $US49,668/relapses avoided IFNβ-1a 30 μg: $US122,230/relapses avoided IFNβ-1a 44 μg: $US34,097/relapses avoided	2010	Pharma
Bakhshai et al. [27]	USA	Third-party payer	NTZ vs comparator: IFNβ-1a 30 μg: $US23,029/relapses avoided IFNβ-1b 250 μg: $US24,452/relapses avoided GA: $US20,671/relapses avoided IFNβ-1a 44 μg: $US20,403/relapses avoided	NR	None

Table 2 continued

Study	Country	Perspective	Base-case ICERs	Year of valuation	Source of funding
Chiao and Meyer [32]	USA	Managed care organization	NTZ vs comparator: IFNβ-1a 30 μg: $US23,029/relapses avoided IFNβ-1b 250 μg: $US24,452/relapses avoided GA: $US20,671/relapses avoided IFNβ-1a 44 μg: $US20,403/relapses avoided	2008	Pharma
O'Day et al. [49]	USA	Managed care organization	Cost-effectiveness ratio: NTZ: $US117,164 per relapse avoided FGM: $US168,754 per relapse avoided	NR	Pharma
Goldberg et al. [37]	USA	Managed care organization	Comparator vs no DMT treatment: GA: $US88,310 per relapse avoided IFNβ-1a 30 μg: $US141,721 per relapse avoided IFNβ-1a 44 μg: $US80,589 per relapse avoided IFNβ-1b 250 μg: $US87,061 per relapse avoided	2008	Pharma
Becker and Dembek [28]	USA	Managed care organization	Cost-effectiveness ratio: IFNβ-1a 30 μg: $US77,980 per relapse avoided IFNβ-1a 44 μg: $US80,121 per relapse avoided IFNβ-1b 250 μg: $US86,572 per relapse avoided GA: $US87,767 per relapse avoided	NR	Pharma
Guo et al. [38]	USA	Managed care organization	IFNβ-1a 44 μg vs IFNβ-1a 30 μg: $US10,755/relapses avoided	2006	Pharma
Bozkaya et al. [6]	USA	Third-party payer	NTZ dominant over FGM DMF dominant over GA pegIFNβ-1a dominant over IFNβ-1a 44 μg	NR	Pharma

Cost-effective treatments were those resulting in the lowest ICER or were dominant over the comparator

BSC best supportive care, *DMF* dimethyl fumarate, *DMT* disease-modifying therapies, *FGM* fingolimod, *GA* glatiramer acetate, *ICER* incremental cost-effectiveness ratio, *IFN* interferon, *IM* intramuscular, *MIU* million international units, *NHS* National Health Service, *NR* not reported, *NTZ* natalizumab, *PSS* personal social services, *QALY* quality-adjusted life year, *RSD* Serbian Dinar, *SC* subcutaneous, *UK* United Kingdom, *USA* United States

optimal treatments, as they dominated the other comparative treatments (IFNβ-1a 30 μg, IFNβ-1b 250 μg, teriflunomide, GA, and FGM) on the efficiency frontier. From the societal perspective, DMF versus IFNβ-1a 44 μg had an ICER of €13,110 [$US14,655]/QALY, while from the payer perspective the ICER was €29,047 [$US32,474]/QALY.

3.2.3 Analysis in the German Setting

Nuijten and Mittendorf compared DMTs in terms of cost per relapse avoided [48]. From the perspective of society, the ICER of each DMT compared with no active treatment was IFNβ-1a 30 μg €133,770 [$US149,583]/relapse avoided; GA €71,416 [$US79,858]/relapse avoided; IFNβ-1b 250 μg €54,475 [$US61,918]/relapse avoided; IFNβ-1a 44 μg €51,250 [$US57,280]/relapse avoided. From the perspective of the third-party payer, the ICER was IFNβ-1a 30 μg €140,728 [$US157,287]/relapse avoided; GA €73,385 [$US82,065]/relapse avoided; IFNβ-1b 250 μg €57,034 [$US63,791]/relapse avoided; IFNβ-1a 44 μg €54,244 [$US60,636]/relapse avoided. Under both perspectives, IFNβ-1a 44 μg was the cost-effective therapy [48].

3.2.4 Analyses in the Iranian Setting

Two studies compared DMTs with placebo (symptom management alone) in the perspectives of society [46] and of the third-party payer [41]. Nikfar et al. found that the ICER ranged from a minimum of $US904/QALY for IFNβ-1a 30 μg(biopharmaceutical copy) to a maximum of $US19,954/QALY for IFNβ-1a 30 μg, showing the convenience and cost effectiveness of biopharmaceutical copies [46]. However, Imani and Golestani reported an almost opposite result, with a minimum ICER of $US607,397/QALY for IFNβ-1a 30 μg and a maximum ICER of $US1,010,429/QALY for IFNβ-1a 30 μg(biopharmaceutical copy). In this study, IFNβ-1a 30 μg was found to be the cost-effective therapy [41]. A more recent

Iranian analysis by Najafi et al. analyzed a head-to-head comparison between IFNβ-1a 30 μg and IFNβ-1a 30 μg(biopharmaceutical copy) and showed that, in the perspective of the third-party payer, the latter is dominant [45].

3.2.5 Analysis in the Scottish Setting

Hernandez et al. evaluated the cost effectiveness of pegIFNβ-1a when compared with IFNβ-1a, IFNβ-1b or GA in the perspective of the Scottish NHS [40]. According this analysis, pegIFNβ-1a was dominant over all the other IFNs, and had an ICER of £5773 [$US7382]/QALY versus GA [40].

3.2.6 Analysis in the Serbian Setting

Jankovic et al. compared the different IFNs and GA with placebo (symptom management) from the perspective of Serbian society [42]. The ICER for all DMTs considered exceeded a billion Serbian dinars (> $US90 million) per QALY gained, making each of the four immunomodulatory therapies not cost effective.

3.2.7 Analyses in the Spanish Setting

Two studies adopted the perspective of Spanish society and made a paired comparison of IFNs and GA [52] or compared them with best supportive care (symptomatic treatment and treatment of relapses) [34]. Sánchez-de la Rosa et al. found that none of the IFNs were cost effective when compared with GA as first-line therapy (ICERs ranging from €117,914 [$US131,827]/QALY of IFNβ-1a 30 μg vs GA to €618,146 [$US691,083]/QALY of IFNβ-1a 44 μg vs GA) [52]. In Dembek et al., none of the DMTs were shown to be cost effective; the best ICER (€168,629 [$US188,505]/QALY) was reported for IFNβ-1a 30 μg [34]. A third analysis by Darbà et al. considered the third-party payer perspective and based on the effectiveness data of the head-to-head CombiRX trial, showed that GA was dominant over IFNβ-1a 30 μg [33].

3.2.8 Analyses in the Swedish Setting

Two economic analyses studied DMTs for MS in the Swedish setting [43, 50]. The O'Day et al. analysis, based on a short-term decision tree, adopted the perspective of the Swedish healthcare system and showed that NTZ was cost effective when compared with FGM, with an ICER of Kr25,448 [$US2929]/relapse avoided. In the sub-population of patients with rapidly evolving, severe disease, NTZ dominated FGM [50]. The second analysis by Kobelt et al. was developed from the perspective of society and showed that NTZ was dominant over a 'standard therapy' defined as a mix of IFNs and GA [43].

3.2.9 Analyses in the UK Setting

Six studies from the UK setting were included in the systematic review, of which four were part of the NICE Technology Appraisal processes [8, 9, 54, 55] and two were journal publications [36, 44]. The four analyses that were part of a NICE process adopted the perspective of the UK NHS. The NICE analysis of NTZ was cost effective (i.e., with an ICER below the threshold of £30,000 [$US38,356]/QALY) versus IFNs and GA in the sub-group of patients with rapidly evolving severe disease, but not in the general population [54]. FGM was not cost effective and had an ICER of £55,634 [$US71,131]/QALY versus IFNβ-1a 30 μg [8]. DMF was not cost effective when compared with IFNs and GA (with ICERs above £100,000 [$US127,855]/QALY in all comparisons), but was dominant over NTZ [9]. Alemtuzumab strongly or extendedly dominated IFNs, NTZ, and FGM, and the ICER of alemtuzumab compared with GA was £8924 [$US11,408]/QALY [55]. Gani et al. adopted the perspective of UK society and showed that NTZ was cost effective, with ICERs of £2300 [$US2946]/QALY versus pooled IFN-β, £2000 [$US2562]/QALY versus GA, and £8200 [$US10,508]/QALY versus best supportive care [36]. Maruszczak et al. concluded that FGM was cost effective versus DMF in the perspective of the UK NHS and presented an ICER of £12,528 [$US16,014]/QALY [44].

3.2.10 Analysis in the US Setting

The majority of analyses were conducted in the US setting (18 studies). Among the studies that adopted the societal perspective (6 studies), a diverse set of conclusions were reported. Zhang et al. showed that DMF was the most cost-effective strategy among IFNβ-1a 30 μg, teriflunomide, and FGM [11]. Lee et al. found that FGM provided better outcomes at an increased cost when compared with IFNβ-1a 30 μg, with an ICER of $US73,975/QALY [7]. Pan et al. estimated the impact of early treatment with IFNβ-1b and concluded it was cost effective with an ICER of $US46,357/QALY vs placebo [51]. Earnshaw et al. found that GA and NTZ were dominant over symptom management alone [35]. Two analyses assessed IFNs and GA versus best supportive care with a different modeling approach and different input data, but came to the same conclusion that they were not cost effective (ICERs ranging from $US901,319/QALY to $US2,178,555/QALY in Noyes et al., [47] and above $US200,000/QALY in Bell et al. [29]).

The other 12 studies adopted the cost perspective of the third-party payer. Among these, two studies assessed the economic value of DMTs in terms of cost per QALY [39, 53]: Hernandez et al. concluded that pegIFNβ-1a is an efficient option, being dominant over IFNβ-1a 44 μg and GA [39], while Tappenden et al. concluded that the ICER of IFNs and GA as compared with best supportive care was expected to be in excess of $US100,000 per QALY gained [53].

The remaining ten studies estimated the cost-effectiveness ratio mainly as cost per relapse avoided, and again presented a diverse set of results. Agashivala and Kim showed that the cost per relapse avoided improved if FGM was initiated early rather than late ($US83,125 and $US103,624 per relapse avoided, respectively) [25]. Two studies (Brandes et al. [30] and Agashivala et al. [26]) compared FGM with IFNs and GA and concluded that the drug presents a favorable economic profile measured as cost per relapse avoided. Three analyses assessed NTZ, the first two (Bakhshai et al. [27] and Chiao and Meyer [32]) came to the same conclusion that the cost per relapse avoided was lowest for NTZ at $US56,594, followed by $US87,791 for IFNβ-1b, $US93,306 for IFNβ-1a 30 μg, $US96,178 for IFNβ-1a 44 μg, and $US103,665 for GA. O'Day et al. compared NTZ with FGM and found that the first was dominant in the incremental cost-effectiveness analysis, as it was less costly and more effective in reducing relapses [49]. Goldberg et al. [37] and Becker and Dembek [28] assessed the cost per relapse avoided ratio of IFNs and GA, using the same model but effectiveness data from a different selection of clinical trials, and reported similar results ($US88,310 and $US87,767 for GA, $US80,589 and $US80,121 for IFNβ-1a 44 μg, and $US87,061 and $US86,572 for IFNβ-1b 250 μg), with the exception of IFNβ-1a 30 μg ($US141,721 in the first study and $US77,980 in the second). Guo et al. [38] compared IFNβ-1a 44 μg with IFNβ-1a 30 μg sourcing most of the effectiveness data from the EVIDENCE head-to-head trial, and finding that the first IFNβ-1a 44 μg was more expensive but more effective in reducing relapses, with an ICER of $US10,755/relapses avoided. Bozkaya et al. compared the cost effectiveness of NTZ versus FGM, DMF versus GA, and pegIFNβ-1a versus IFNβ-1a 44 μg, showing that the first DMT in each comparison was dominant over the second DMT in each comparison in terms of cost per relapse avoided [6].

3.3 Funding Sources

Funding sources were categorized as from pharmaceutical companies (pharma), academic or governmental sources, or no external source of funding. Ten studies from the US, UK, Serbia, and Iran were funded from academic or governmental agencies. Three studies from the US received no external funding and the remaining 24 studies from Western Europe, the UK, and the USA identified pharma sources of funding. Overall, the source of funding did not impact the results of the cost-effective analyses and the drug of interest in most cases was determined to be cost effective.

3.4 Drivers of the Cost Effectiveness

An analysis was conducted to identify the most important drivers of the cost effectiveness in the studies included in the review. These were identified by analyzing the reported results and the parameters that most influenced the sensitivity analysis results of the different papers, following the discussion and the ranking of importance (i.e., tornado diagram) presented by the authors. Moreover, the discussion section was reviewed for reports of the main drivers of the cost effectiveness. The drivers were then grouped into ten categories, as reported in Table 3. Three studies did not report information on the drivers of the ICERs and were therefore not included in this analysis [33, 41, 50]. The driver that was most cited was 'Effectiveness' [23/37 papers, corresponding to 62% of the cases) followed by 'Drug prices' ($n = 20$, 54%), 'QoL utilities' ($n = 9$, 24%), 'Tx duration' and 'Time horizon' ($n = 8$, 22%), 'Baseline characteristics' ($n = 7$, 19%), 'Long-term effect' and 'Direct costs' ($n = 4$, 11%), 'Social costs' ($n = 3$, 8%), and 'NAbs' ($n = 1$, 3%).

3.5 Quality of Reporting

We assessed the reporting quality of 33 studies using the CHEERS statement (Table 4). In general, the level of compliance with reporting standards was high. All studies were identifiable as economic evaluations based on the title, presented a structured abstract, and an explicit statement of the broader context for the study. Studies generally reported the target population and subgroups well ($n = 26$ of 33, 79%). In most analyses with a time horizon longer than 2 years, a statement on the choice of discount rate was reported ($n = 23$ of 24, 96%). The description of the sources for effectiveness was generally sufficiently detailed ($n = 30$ of 33, 91%). The information on the population and methods used to elicit preferences for outcomes was available in almost all the cost-utility analyses ($n = 16$ of 18, 89%). The year of costing was available in all but five studies ($n = 28$ of 33, 85%). In almost all studies, conflicts of interests were reported ($n = 30$ of 33, 91%).

4 Discussion and Conclusions

We systematically reviewed the literature with the objective of assembling and analyzing recent published evidence on cost effectiveness of DMTs in MS patients. The strength

Table 3 Categories of main drivers of the ICER

Category	Description
Drug prices	DMT acquisition costs
Tx duration	Parameters affecting drug cost accrual, such as discontinuation rates, drop out after conversion to SPMS, time to treatment initiation
Effectiveness	Parameters related to the effectiveness of the study drug such as the annualized relapse rate and the disability progression hazard ratio
Long-term effect	Waning effect of treatments, different hypothesis on treatment's long-term effectiveness
QoL utilities	Utility of EDSS states, utilities linked to treatments, disutilities due to relapse
Direct costs	Periodic management costs defined as a function of EDSS states, cost of management for an event of relapse
Time horizon	Time horizon of the economic analysis
Social costs	Social cost parameters, such as productivity loss
Baseline characteristics	Baseline characteristics such as initial EDSS distribution, baseline number of relapses, baseline progression of disease
NAbs	Incidence of neutralizing antibodies

DMT disease modifying therapies, *EDSS* Expanded Disability Status Scale, *ICER* incremental cost-effectiveness ratio, *NAbs* neutralizing antibodies, *QoL* quality of life, *SPMS* secondary-progressive multiple sclerosis, *Tx* treatment

Table 4 Assessment of the reporting quality of $n = 33$ included studies using CHEERS statement

	Reported *n* (%)	Not reported *n* (%)
Title	33 (100)	0 (0)
Abstract	33 (100)	0 (0)
Background and objectives	33 (100)	0 (0)
Target population and subgroups	26 (79)	7 (21)
Setting and location	33 (100)	0 (0)
Study perspective	33 (100)	0 (0)
Comparators	33 (100)	0 (0)
Time horizon	32 (97)	1 (3)
Discount rate (on analyses with a time horizon longer than 2 years; $n = 24$)	23 (96)	1 (4)
Choice of health outcomes	33 (100)	0 (0)
Measurement of effectiveness	30 (91)	3 (9)
Measurement and valuation of preference based outcomes (on cost-utility analyses; $n = 18$)	16 (89)	2 (11)
Estimating resources and costs	32 (97)	1 (3)
Currency, price date, and conversion	28 (85)	5 (15)
Choice of model (on analyses based on a model; $n = 32$)	31 (97)	1 (3)
Assumptions	26 (79)	7 (21)
Analytical methods	29 (88)	4 (12)
Study parameters	30 (91)	3 (9)
Incremental costs and outcomes	33 (100)	0 (0)
Characterizing uncertainty	32 (97)	1 (3)
Characterizing heterogeneity	0 (0)	33 (100)
Study findings, limitations, generalizability, and current knowledge	32 (97)	1 (3)
Source of funding	33 (100)	0 (0)
Conflicts of interest	30 (91)	3 (9)

of the systematic review is to provide a replicable overview of the state of research in a particular field and to enable an assessment of the quality of individual studies [57]. As such, the main focus of the systematic review was the assessment of the quality of the studies, using the CHEERS checklist, and on the identification of the main drivers for cost effectiveness. Among the 33 papers and four HTA reports that were included in the review, almost all were

based on a health economic model, with only one study that was completely based on observational data. Modeling studies broadly belonged to two main groups: the first applied a simple approach to estimate a short-term measure of cost consequence (mostly cost per relapse avoided), while the second group relied on a more standard cost per QALY estimate over patients' lifetime. The conclusions reported in the reviewed studies were difficult to classify and synthesize, for the most part due to the different geographic areas covered.

It is widely recognized that cost-effectiveness results are rarely transferable between different countries [56]. The 37 studies included for review were developed in 10 different countries, including seven European countries, Canada, the US, and Iran. However, about half of the studies were in the US setting. Even within the same country, the level of discrepancy between results was high. For example, in Iran, three separate analyses compared the same set of treatments and arrived at contradictory conclusions. It was thus not possible to summarize the results of all the analyses, providing a clear indication on what group of DMTs could be considered more cost effective in MS.

Although a summary of overall analysis was not possible due to the variance in study inputs, general trends of interest were identified. Overall, pegIFN and DMF were almost always cost effective in studies in which they were analyzed. With the exception of three US studies, oral treatments were generally cost effective when compared with injection treatments.

The studies' category of funding (i.e., pharma, academic/governmental, and no funding) did not seem to have an impact on the results of the individual analyses and the drugs of interest were mostly determined to be cost effective.

More informative was the analysis of the drivers of the cost effectiveness. Not surprisingly, the most cited driver was the effectiveness of the treatment, encompassing all parameters related to the effectiveness of the study drug such as the annualized relapse rate and the disability progression hazard ratio. The second parameter that was cited by more than 50% as a key driver of the cost effectiveness was the price of the drugs involved. Efficacy is always of utmost importance in patient care; however, it is not surprising that the second most cited driver was the drug cost. Drug acquisition costs vary greatly between countries. For instance, in Serbia, no DMTs were found to be cost effective [42]. Noyes et al. found that DMTs represent a considerable fraction of health-related costs for patients with MS in the US [47]. While there is no uniform threshold in the US, some studies found the estimated ICER(s) higher than many accepted cost-effectiveness thresholds for chronic diseases, but comparable to some other immunomodulatory therapies [29, 47]. The variation in ICERs for DMTs indicates the field would benefit from further analyses of drivers both within countries and internationally.

An important consideration was the analysis of the quality of reporting in the primary studies. Unlike clinical studies that report only the efficacy and safety of an intervention, economic evaluations require many additional inputs including resource use, direct and indirect costs, treatment preference information, and treatment effectiveness. The magnitude and complexity of model inputs create a challenge for journal editors, peer reviewers, and anyone who wishes to evaluate the findings of a cost-effectiveness study. As such, the quality of reporting of economic evaluations has been shown to vary [58]. Transparency of reporting on inputs and model structure is of utmost importance with health economic evaluations, as there are significant implications from policy decisions which may be based on misleading study findings. As the number of published economic evaluations continues to increase, the lack of systemic accountability makes it especially important to assess the quality of reporting in a systematic fashion [23]. The CHEERS statement checklist developed by the ISPOR Health Economic Evaluation Publication Guidelines Task Force provides recommendations in a checklist to evaluate reporting in health economic evaluations [23]. The included studies were checked against the CHEERS statement. In general, the level of compliance with reporting standards was very high, with only a limited amount of the prescribed information missing. We believe this could be to the result of a general improvement in the quality of reporting in health economics papers seen in the recent years.

In an effort to capture the maximum available HTA (unpublished) results, the systematic literature review (SLR) included HTA reports for all agencies which disclosed the full data set for each input that was considered and details on the methods and analyses that were performed. This limited the inclusion of reports from agencies/countries that only publish the results of the cost-effectiveness analysis and at the end only the reports from the UK's NICE met the criteria and were included. This, however, represents a limit to our analysis. In addition to HTA reports, the SLR was limited to full, published journal articles in English and excluded abstracts or other unpublished results.

In conclusion, recent years have seen the publication of a large number of health economic assessments of DMTs in RRMS in several different countries. While the methods employed were not dissimilar and the quality of the reporting was generally high, the conclusions reached were not homogeneous and in some cases even conflicting. These discrepancies were likely due to different input data or to non-homogeneous assumptions. This study provides a

valuable analysis of the primary literature to identify and review the main drivers, recognize trends in cost effectiveness of DMTs, and a systematic evaluation of the quality of primary studies identified in the review. As such, the paper provides an important essential base for policymakers and stakeholders when considering the quality of results. As well, it provides a strong repository of information on the main drivers and trends in cost effectiveness of DMTs in RRMS that can be drawn on for comparison or to fuel in-depth research with a narrower scope to answer questions on the effect of driver variance.

Data Availability Statement The evidence abstraction database synthesizing the information from the papers included in the review is made available as electronic supplementary material.

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Compliance with Ethical Standards

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