Published in final edited form as:
Pharmacoeconomics. 2013 June ; 31(6): 455–469. doi:10.1007/s40273-013-0063-4.

Modelling the Cost Effectiveness of Disease-Modifying Treatments for Multiple Sclerosis:

Issues to Consider

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Abstract

Several cost-effectiveness models of disease-modifying treatments (DMTs) for multiple sclerosis (MS) have been developed for different populations and different countries. Vast differences in the approaches and discrepancies in the results give rise to heated discussions and limit the use of these models. Our main objective is to discuss the methodological challenges in modelling the cost effectiveness of treatments for MS. We conducted a review of published models to describe the approaches taken to date, to identify the key parameters that influence the cost effectiveness of DMTs, and to point out major areas of weakness and uncertainty. Thirty-six published models and analyses were identified. The greatest source of uncertainty is the absence of head-to-head randomized clinical trials. Modellers have used various techniques to compensate, including utilizing extension trials. The use of large observational cohorts in recent studies aids in identifying population-based, 'real-world' treatment effects. Major drivers of results include the time horizon modelled and DMT acquisition costs. Model endpoints must target either policy makers (using cost-utility analysis) or clinicians (conducting cost-effectiveness analyses). Lastly, the cost effectiveness of DMTs outside North America and Europe is currently unknown, with the lack of country-specific data as the major limiting factor. We suggest that limited data should not preclude analyses, as models may be built and updated in the future as data become available. Disclosure of modelling methods and assumptions could improve the transferability and applicability of models designed to reflect different healthcare systems.

1 Introduction

Until the 1990s, there was no specific therapy for the treatment of multiple sclerosis (MS). Management consisted of symptom control, physiotherapy, psychiatric and social support, and disability aids. In the USA, there are currently six products that are licensed as disease-modifying treatments (DMTs) in relapsing-remitting MS (RRMS): interferon beta-1a intramuscular (IM) [Avonex], interferon beta-1a subcutaneous (SC) [Rebif], interferon beta-1b (Betaseron, Extavia), glatiramer acetate (Copaxone), natalizumab (Tysabri), and the more recently approved fingolimod (Gilenya)[1–9]. In addition, mitoxantrone (Novantrone) is

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Author Contributions Joel Thompson contributed to the concept and design, the acquisition of data, the analysis and interpretation of data, drafting the manuscript, critical revision of the manuscript, and study supervision. Amir Abdolahi contributed to the acquisition of data, drafting the manuscript, and critical revision of the manuscript. Katia Noyes contributed to the concept and design, the acquisition of data, the analysis and interpretation of data, drafting the manuscript, critical revision of the manuscript, and study supervision, and obtained funding for the study. Joel Thompson acts as guarantor for the overall content of this article.

US FDA approved as a DMT for secondary progressive MS (SPMS). Interferons and glatiramer acetate are typically used as first-line DMTs. Natalizumab and fingolimod are more potent immunomodulators but carry additional risks and are typically reserved for MS refractory to first-line treatments. The use of mitoxantrone is even more limited by its potential for cardiac toxicity and leukaemia. These second-line DMTs can effectively reduce relapse rates but may impose additional costs due to monitoring for and treating their complications.

Models to assess the cost effectiveness of MS DMTs have been developed for various populations in the USA, Canada, the UK and many countries in Europe. However, the use of models for the assessment of the cost effectiveness of MS DMTs has been the subject of considerable debate, both because of the data used (or not used) and because of the methodology chosen for modelling and parameter estimation[10–15]. A recent review of cost-of-illness studies and cost-effectiveness analyses is available elsewhere, including a breakdown of results by DMT type[16]. In this review, we will discuss the methodological challenges in modelling the cost effectiveness of treatments for MS. Our approach consisted of identifying previously published models, analysing the approaches taken to date, identifying the assumptions and parameters likely to have the greatest influence on cost effectiveness, and discussing where the major areas of uncertainty lie.

2 Approach

We searched Ovid MEDLINE (keywords “multiple sclerosis” and “costs and cost analysis”, including all subheadings) on 26 April 2012, which resulted in 386 studies. PubMed was also used (("multiple sclerosis"[Title/Abstract]) AND (cost[Title/Abstract]) searched on 30 April 2012), which resulted in 443 publications. Titles and abstracts were reviewed and 31 analyses were identified that reported cost plus a quality-of-life metric or measure of disease activity as a combined outcome. Four additional studies were identified by reviewing the references of published studies, resulting in a total of 35 studies identified (summarized in Table 1).

3 Study Characteristics

The majority of the studies used a Markov model approach, which allows for the transfer between different health states over a period of time (e.g. progression of disability or presence of relapses). Only two models used non-Markov approaches, such as individual patient-level simulation[17] or direct costs and effects estimation[18]. The length of the model cycle varied from 1 month[15] to 3 years[10].

The country with the most studies was the USA (11 studies), followed by the UK (10 studies), even though US-based models were not published until 2003 or later. The time horizon used in models ranged from 2 years to a patient’s lifetime. The majority of the studies reported base-case results from a societal perspective. We recognize that a cost-effectiveness analysis from the societal perspective may not seem practical in countries that have numerous healthcare stakeholders with conflicting agendas (like the USA) and that many high-quality cost-effectiveness evaluations from a non-societal perspective have been published[19, 20]. However, the societal perspective is the only approach that allows decision makers to make cross-country comparisons and to incorporate consequences to all conceivable stakeholders[21].

For modelling treatment effects, most studies used natural history of disease data combined with treatment effects from randomized clinical trials (RCTs) and extension studies, although two recent studies also utilized large MS patient registries[46,47]. Outcomes included incremental cost per QALY gained (the cost-utility endpoint), as well as cost-effectiveness

outcomes such as cost per relapse avoided. Outcomes varied widely between countries and also between studies within the same country. In general, outcomes were sensitive to the DMT acquisition cost, the time horizon of the analysis, and the estimation of the treatment effects. Studies with longer treatment duration reported worse (higher) incremental cost-effectiveness ratios (ICERs)[28]. Lastly, there is a trend towards industry-sponsored studies (Fig. 1), especially in the USA where eight of eleven published studies were industry sponsored. There is also a trend towards cost-effectiveness endpoints (i.e. cost per relapse avoided).

4 Discussion

Overall, we identified the following major sources of variation and uncertainty: (1) uncertainty in the estimation of DMT effectiveness in the absence of head-to-head high-quality RCTs, including the modelling of long-term treatment effects; (2) variation in the characteristics of the included populations (age, gender, country); (3) variations in modelling assumptions (definition of health states, choice and duration of treatment, time horizon); (4) differences in the perspective and the target audience; (5) and wide disparities in the acquisition costs of DMTs between countries. An additional area of uncertainty is the cost effectiveness of DMTs outside North America and Europe.

4.1 The Importance of Head-to-Head RCTs of MS DMTs

The greatest source of bias and uncertainty in earlier models comparing DMTs was the absence of head-to-head RCTs[23]. Comparison across clinical trials may lead to errors and incorrect conclusions due to differences in study populations (due to varying inclusion and exclusion criteria), definitions of disease activity (e.g. relapse) and a shift towards recruitment of subjects with more benign disease in more recent clinical trials[24]. Early models projected treatment effects from pivotal RCTs onto natural history data, but implicit in this approach is the comparison of risk ratios, absolute treatment effects or relative treatment effects between DMTs and clinical trials. Additional drawbacks to this method include the reliance on assumptions for the durability of treatment effects after 2 years and assumptions on the applicability of treatment effects to populations not studied in the RCT. Furthermore, due to the wide acceptance of DMTs (about 50 % of all MS patients in the USA take at least one DMT in any given month)[25], treatment-naïve (previously untreated) patients selected for RCT inclusion no longer represent the general population[1–9].

Due mainly to the uncertainty of treatment effects after 2 years, modellers began to supplement pivotal RCT treatment effects with data from extension studies. Extension studies may be open label, non-randomized and un-blinded, which may limit the interpretation of results. However, well-designed observational studies can produce results that match those from pivotal clinical trials[26, 27]. Data from observational studies are currently most available for glatiramer acetate and interferons, and data for natalizumab will likely be made available in the future due to the increased surveillance associated with its use (due to the risk of progressive multifocal leukoencephalopathy [PML]). One approach to reduce the differences between RCT designs was published by Bell et al.[28] in 2007, in which all treatments modelled were given identical treatment effects for the first 2 years. However, this assumption is not in line with results from the head-to-head trials that have been conducted (as explained further on in this section).

Another model by Earnshaw et al.[29] compared glatiramer acetate and natalizumab utilizing RCT data for the first 2 years, followed by available trial extension data for glatiramer acetate. The treatment effects for both glatiramer acetate and natalizumab were adjusted in parallel fashion for the remainder of the model (the lifetime of a patient). However, while the incremental QALYs gained compared with supportive care were about equal for these

DMTs, the results were very sensitive to changes in disability progression when tested using sensitivity analysis. Of note, the results were not sensitive to adding in the incidence of neutralizing antibodies associated with natalizumab.

There are four trials comparing interferons and glatiramer acetate directly[30–33], although most trials had small cohorts (fewer than 250 participants) and not all trials reported primary results in terms of disease activity (i.e. relapse rate reduction). The EVIDENCE (EVidence of Interferon Dose-response: European North American Comparative Efficacy) trial is the largest randomized, controlled, single-blinded trial to date, and compared brands of interferon beta-1a[34]. The only model to utilize only data from a head-to-head trial (the EVIDENCE trial) was published by Guo et al.[35] and compared SC with IM interferon beta-1a. While this approach removes the biases of comparing across clinical trials, there was no placebo arm in the EVIDENCE trial, so the cost per relapse prevented was only available for SC interferon beta-1a (since IM interferon beta-1a was the comparator). Tappenden et al.[36] utilized all available trial data and combined the data with placebo-controlled RCT treatment effects using mixed-treatment comparison models. The re-calculated treatment effects on Expanded Disability Status Scale (EDSS) progression differed from the RCT-derived treatment effects, but relative risks of relapse were unchanged due to a lack of published evidence outside the RCTs.

4.2 The Role of Observational Data

An emerging potential solution to the comparison of treatment effects from different RCTs is the incorporation of data from observation cohorts, which enables generalizing results to a broader population outside clinical trial monitoring and to real-life clinical practice settings[37,38]. A pivotal example was recently published, bringing into question DMT effects on MS disability progression[39]. Another advantage is that observational data are likely to be more timely, decreasing the need to compare studies that may have been conducted almost a decade apart. However, determination of the natural history of disease progression (i.e. untreated population or control) with observational data is often complicated by concerns of selection bias, if those progressing the fastest are most likely to be treated, and the fact that there may be few remaining untreated subjects. While several analytic techniques have been developed to minimize the error of estimation due to selection bias, they are complex and not without limitations[40–45].

Kobelt et al.[46] published a recent model utilizing mixed-treatment effects of interferons and glatiramer acetate from a Swedish MS registry. Disease progression rates for the combined treatment population were then compared with both a natural history cohort and a clinical trial population. The combined treatment population results were compared with clinical trial results for natalizumab under the assumption that new treatments should be compared with current standard treatment. In order to place the registry patient cohort in context, a third patient cohort was modelled using RCT data for the first 2 years, followed by disease activity from a natural history patient cohort. However, the patient registry differs from the natalizumab RCT population in both known and unknown characteristics, with known variables including differing patient populations (inclusion of SPMS patients in the registry and not in the RCT) and a decreased level of monitoring in the registry (and thus likely underestimating the relapse rate and increasing the likelihood of capturing early effects on disease progression)[46]. Consequently, the comparison between these different patient groups likely does not decrease errors associated with comparing across clinical trials.

In a recently published analysis, Noyes et al.[47] also utilized data from an observational cohort in the attempt to reduce the impact of some of the biases associated with using RCT data for cost-effectiveness assessment. Untreated progression rates were developed by using data from a national observational cohort (Sonya Slifka Longitudinal MS study[48]), and by

correcting for the expected effects of patients' DMTs as reported by the pivotal trials. Using a heterogeneous sample of MS patients representative of the entire US population of MS patients, rather than RCT subjects only, improved the generalizability of the study results by reducing selection bias[47]. An overview of the iterative approach for estimating DMT effects used by Noyes et al.[47] is shown in Fig. 2. This approach may provide a wide application for population-based comparative effectiveness studies and economic policy assessments.

4.3 Time Horizon Modelled

Cost-effectiveness analysis based on the in-trial information alone has limited usefulness for health policy and decision making because of its relatively short duration compared with the length of life with MS[49]. For this reason, the Panel on Cost-Effectiveness in Medicine recommends using a lifetime horizon for cost-effectiveness evaluations[19]. However, growing healthcare costs, the fast pace of technology development and innovation, and limited societal resources have shifted the priorities of the cost-effectiveness research paradigm in favour of pragmatic studies and a 'value-of-information' approach[50–52]. For this purpose, many studies present cost-effectiveness trends by presenting several ICERs for different time horizons (Fig. 3)[53], in addition to the pattern of healthcare use associated with the DMT (high costs in the earlier years and benefits acquired over time). The time horizon of a model will also affect the cost-effectiveness ratio, with longer time horizons producing more favourable ICERs and greater sensitivity to treatment effects on disease progression[28, 47]. Shorter time horizons show greater sensitivity to treatment effects on relapse reduction[46, 54, 55]. Changes in medical technology, its diffusion over time, and increases in the co-morbidities in an ageing population also raise a number of significant methodological challenges for lifelong cost-effectiveness assessment[52, 56–58].

4.4 Perspective and Audience

Despite the large body of research focusing on comparative effectiveness, methodologies of decision analysis and economic evaluation, the question that concerns most providers involved with MS patients is 'what, if any, relevance does this research have for clinical practice?'[59, 60]. Many clinicians in the USA would say it has none[61]. However, in the current US marketplace, cost-effectiveness and comparative effectiveness evaluations may benefit as well as harm providers (by reducing revenue and requiring behaviour or organizational change), depending on whether these studies confirm the appropriateness of current practice (i.e. start DMT early vs. later) or indicate a need for a major change (i.e. the risks of natalizumab or superiority of comprehensive MS care vs. single neurologist-driven care). Hence, rather than ignoring or discounting the results of cost-effectiveness studies, clinicians who are truly interested in providing a high quality of care to their patients may take an active interest in the design, interpretation and application of cost-effectiveness and comparative effectiveness evaluations[61]. At the organizational level, aligning provider reimbursement incentives and performance incentives (like in some dual-capitated long-term care programmes)[62] has a potential for achieving this goal.

Our results suggest a trend towards the greater prevalence of positive industry-sponsored cost-effectiveness studies in the USA, likely in order to improve the market share of their products (Table 1)[63, 64]. Industry-sponsored studies have previously been associated with more favourable ICERs[22].

4.5 Drug Pricing and Prescription Medication Coverage Policies

Making decisions based on the comparative value of prescription drugs, whether or not they formally incorporate the results of cost-effectiveness research or not, is something managed care pharmacists do every day[65]. For MS DMTs in particular, the greatest driver of the ICER is likely to be the drug acquisition cost, which varies greatly between countries. For

instance, the annual cost of interferon beta-1a IM in the UK is about £8,000 (US$12,000) compared with ~US$25,000 (US$34,000 in 2010 values) in the USA[66]. Drug acquisition costs are also on the rise, with a compounded annual growth rate of 8.2 % in the USA between 2006 and 2009[67]. Noyes et al.[47] recently demonstrated that if current DMT costs in the USA were reduced by two-thirds (which would match the prices in other industrialized countries), the cost effectiveness of DMTs would become comparable with the cost effectiveness of other accepted interventions[20]. Studies outside the USA have also shown that drug prices are a key driver of total costs[69].

We also would like to highlight the fact that the additional risks of the newer DMTs may impose a great deal of extra cost due to monitoring for and treating complications[70]; for example, in the USA, MRI scans for PML surveillance are required for all natalizumab patients in the higher risk groups for PML at least every 3 months, not to mention the very high costs of treating natalizumab-induced PML (long hospitalizations, plasmapheresis and severe long-term disability in many cases). These adverse events and increased clinical vigilance are currently not included in the cost-effectiveness studies of natalizumab[29, 46]. Extra testing also needs to be carried out for fingolimod (ophthalmological and dermatological screening) and mitoxantrone (serial ECGs). The associated expenses might still be a small fraction of the drug acquisition costs, but with the ever-increasing trend in utilization and focus on patient safety, it is an important category to account for. While in the USA the main focus of cost-containment activities has traditionally been on quality improvement and waste reduction[71], other countries (e.g. Australia, Canada, Sweden and the UK) have appropriately and advantageously incorporated cost effectiveness into the coverage decision-making process at the regional and national level. This decision-making process includes pre- and post-marketing authorization by implementing risk-sharing schemes (not only ‘yes’ and ‘no’ but also ‘yes, but …’[72]). Such an approach informs research priority decisions using a value-of-information approach,[73] while also changing providers’ and consumers’ perceptions from ‘rationing’ healthcare (a tool to restrict freedom) to an approach for fair prioritization[74].

4.6 Country-Specific Models Outside North America and Europe

A major area of uncertainty also lies in the need for country-specific models in areas outside Europe and North America. Our literature review revealed no studies in countries outside Europe and North America and only one study in a country in socio-economic transition[75]. In many countries or regions, cost data from national health systems or government contracts with pharmaceutical companies are available, and at least one cost-of-illness study has already been conducted in South America[76]. The prevalence of MS may also be obtained. However, quality-of-life data, the prevalence of MS disability states and healthcare utilization within MS disability states are likely not known.

There is one currently published cost-effectiveness analysis in a country in socio-economic transition that we are aware of[75]. In their analysis, Jankovic and colleagues[75] utilized a previously published model from the USA[28], supplemented with Serbian healthcare utilization by EDSS score (obtained from a retrospective chart review of randomly selected patients in a clinical centre), Serbian healthcare costs, drug acquisition costs and wages for lost productivity calculation. The unfavourable ICER in this analysis was driven by high drug acquisition costs and a low QALY gain from disease-modifying agents.

Converting a model from one country to another requires more than changing the costs. Jankovic et al.[75] were able to introduce Serbian healthcare utilization into the model to more accurately identify cost savings or expenditures in that country. However, other model assumptions should also be considered when a model is tailored for another country. Initial patient distribution among health states would ideally also use country-specific data; this

would account for any differences between countries in MS stage at the time of diagnosis, which is more likely to occur earlier in areas where advanced MRI techniques are available[77]. In addition, differences between countries in patient disability states when initiating or terminating treatment with a DMT should also be reflected in the model. Later diagnosis of MS or initiation of treatment would decrease potential health gains realized by DMTs.

The applicability of transporting utility values for health states between countries or sub-populations is another area that should be considered. The vast majority of models for MS group disability states by EDSS score and assign utilities to each score or score grouping. It is generally thought that tariffs should be used when transferring utility values from one country to another. Tariffs reflect both differences in methodology when measuring EQ-5D states between studies and cultural differences between countries or populations[78, 79]. Cultural differences include the willingness to trade quantity for quality of life and the weight communities place on each of the dimensions of the EQ-5D (mobility, self-care, usual activities, pain/discomfort and anxiety/depression)[79]. However, tariffs for the EQ-5D are available for only 17 countries, and many other survey instruments have not had tariffs calculated.

There are three potential solutions to this problem for countries for which no original survey data or tariffs are available. The first is to use the utilities incorporated into the original model, with the limitation that differences between countries and cultures are not being incorporated into the analysis. As stated in the 2003 ISPOR guidelines, “a model should not be faulted because existing data fall short of ideal standards of scientific rigor”[59]. One benefit of a model is that it can be updated as new data become available. A second solution is to perform a survey to collect data on quality of life and resource utilization. Early cost-effectiveness analysis studies used small surveys of 60–400 patients[80–82]. Over the past decade, sample sizes have increased to over 2,000 patients in the US-based Sonya Slifka database[48]; over 1,800 patients in France’s European Database for MUltiple Sclerosis (EDMUS) cohort[83]; and almost 7,000 patients in the Swedish MS registry[46]. A third potential solution is to forgo quality-of-life assessment and report cost-effectiveness endpoints. The earliest MS cost-effectiveness analysis identified reported ‘normalized disability years avoided’[84]. Recent studies have also reported endpoints such as cost per relapse avoided, cost per relapse-free years gained, and cost per years of an EDSS score of 0–5.5 gained. These endpoints are increasingly being utilized by industry-sponsored studies, likely due to the small QALY gains associated with DMT use reported in many studies.

One last difficulty faced by modellers outside North America and Europe is that there is little opportunity for cross-validation of results due to a lack of previous country-specific models. Therefore, increased testing to ensure internal validity (model structure and calculations are correct), calibration (inputs are consistent with available data) and face validity (results make intuitive sense) should be used[59, 60].

5 Conclusion

With the growing focus on evidence-based medicine and on enhancing the quality and efficiency of healthcare delivery systems, the need for information about comparative effectiveness of alternative treatment strategies is increasing[74, 86, 87]. However, with the increase in the number of available treatments in the market as well as the growing cost of clinical trials designed to test health interventions, more researchers turn to decision analytic modelling to make decisions in the presence of uncertainty[21]. Our review summarized the key issues regarding modelling disease and treatment progression in MS, in particular, for the purpose of economic evaluation. We also try to provide practical solutions to some of

these problems, such as combining several sources of data when calculating DMT effectiveness to improve the inherent weaknesses of each individual data source. We also emphasize that the lack of a perfect available dataset should not be used as an excuse for avoiding decisions about the costs and benefits of health interventions. Instead, we encourage investigators and decision makers to provide a complete disclosure of modelling methods and assumptions and a careful discussion of the study limitations and implications in the face of patient and physician preferences.

Acknowledgments

The authors would like to express sincere gratitude and appreciation to Dr. Matthew Bellizzi for his clinical consultations and thoughtful suggestions. In the past, Joel Thompson and Katia Noyes have received research grants from Biogen Idec for updating a previously published risk-benefit assessment of natalizumab.

Funding Contract HC 0103 from the National Multiple Sclerosis Society (Programme Officer: Nicholas LaRocca, PhD); Clinical and Translational Science Award (CTSA) [UL1 RR024160] from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH) and the NIH Roadmap for Medical Research.

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Key Points for Decision Makers

- While data on multiple sclerosis (MS) disease-modifying treatments (DMTs) that are currently available to decision makers have substantial limitations, this should not preclude clinicians, healthcare administrators and payers from incorporating this information into decision making, as decisions made based on real evidence tend to be more comprehensive and better reflect the stakeholder's perspective
- Researchers and decision makers could substantially improve the transferability and applicability of models designed to reflect different healthcare systems by providing complete disclosure of modelling methods and assumptions
- The greatest source of uncertainty is the absence of head-to-head randomized clinical trials. Modellers have used various techniques as well as non-randomized data, such as extension trials and observation data, to compensate
- The use of large observational cohorts in recent studies aids in identifying population-based, 'real-world' treatment effects
- The major drivers of DMT cost effectiveness include time (time of DMT initiation, duration of DMT and overall study time horizon) and DMT acquisition costs
- The cost effectiveness of DMTs outside North America and Europe is currently unknown, with the lack of country-specific data as the major limiting factor

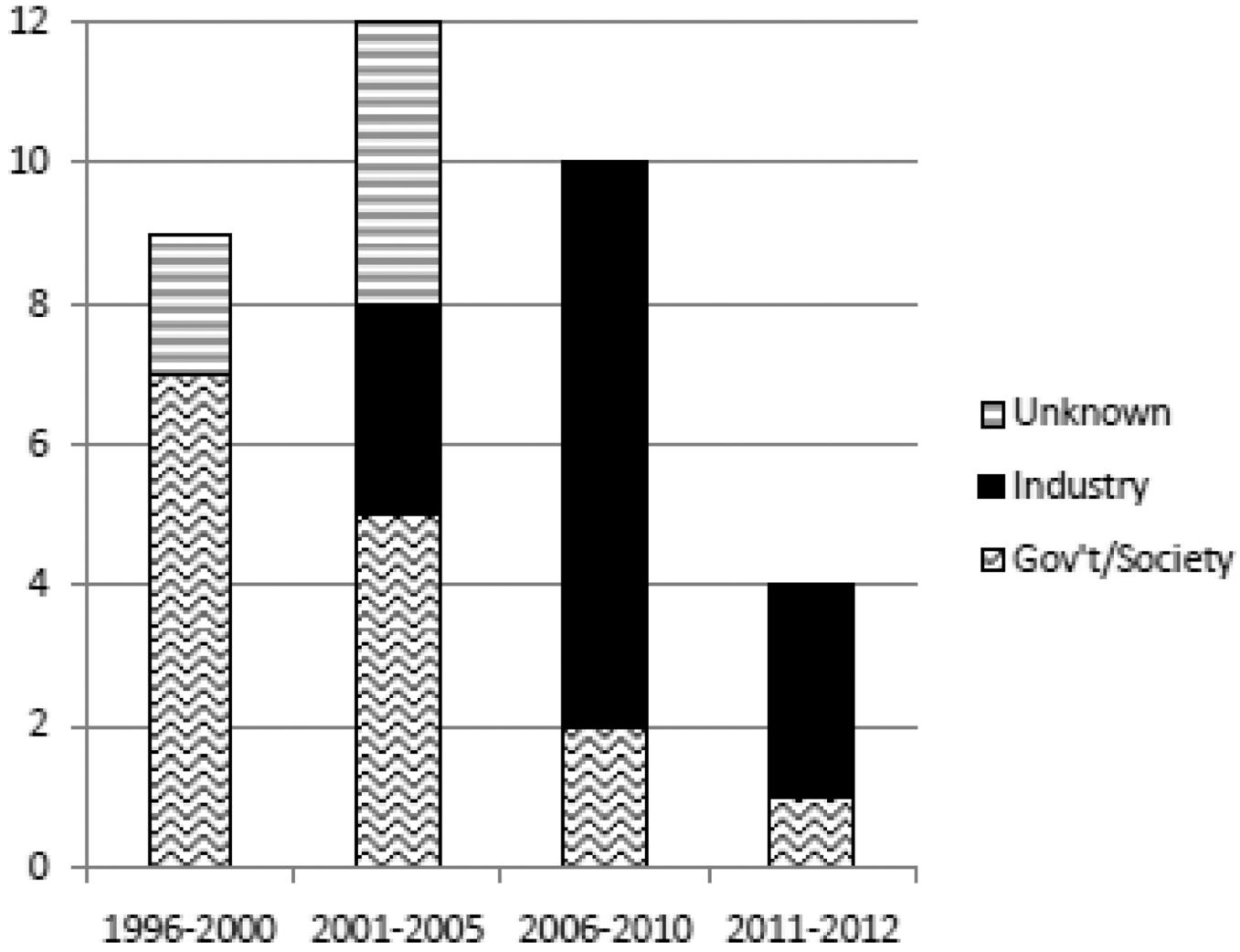

Fig. 1. Number of published studies on Cost-Effectiveness Modeling Studies of MS DMTs by year of publications and by sponsor

The number of published studies on the cost-effectiveness modelling of multiple sclerosis disease-modifying treatments by year of publication and by sponsor, 1996–2012. *Gov't* government

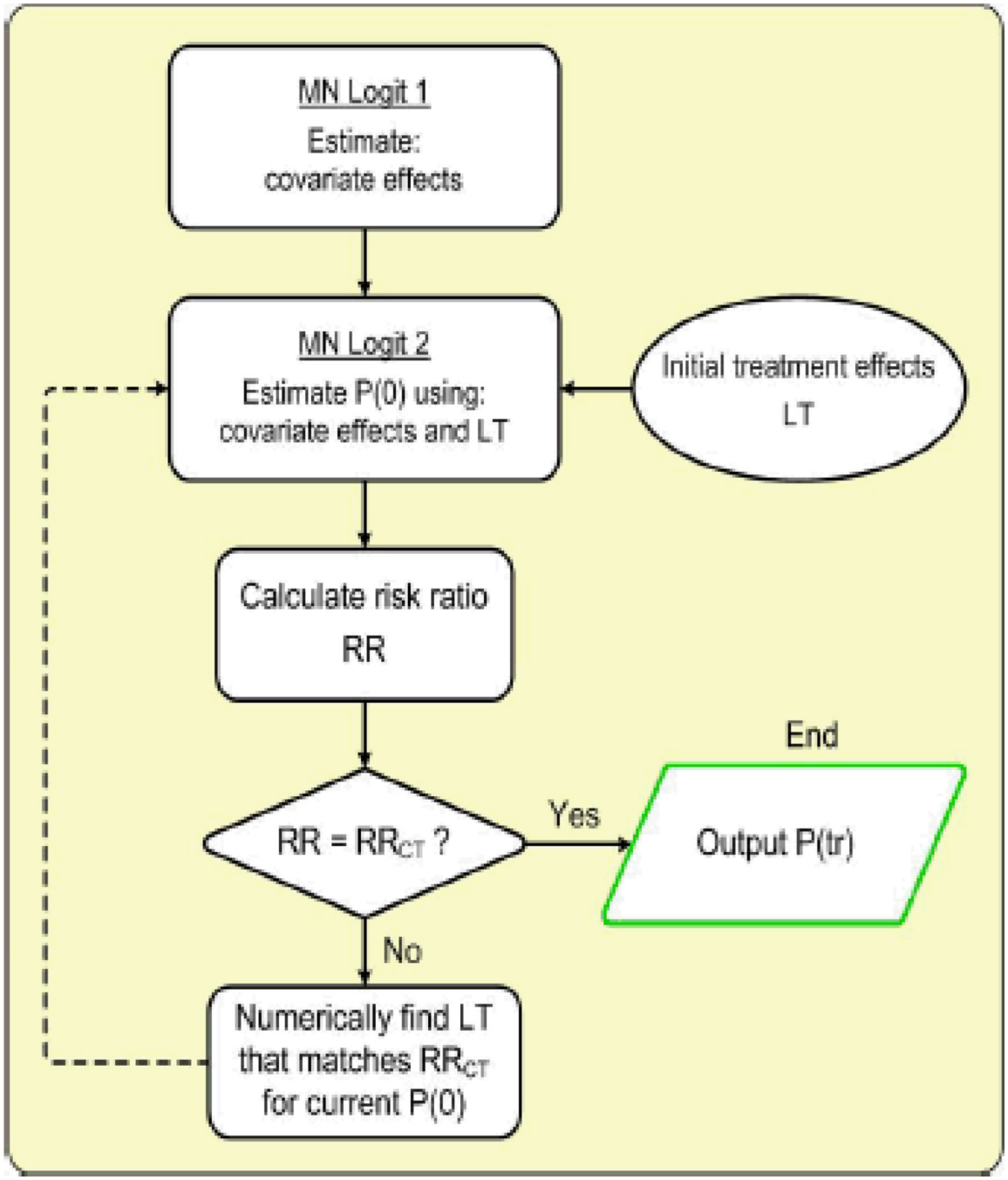

Fig. 2. Algorithm for estimating the disease state transition probabilities

To estimate the multiplicative treatment effect coefficients [P(tr)] that would produce the same RR ratios of progression probabilities as reported by pivotal RCTs (RR_{CT}), we kept the progression probabilities without DMT constant (MN Logit 1) while modifying the treatment factors (LT, individual dummy variable for each specific DMT). We implemented an iterative approach by using a numerical grid search algorithm to find a new set of treatment factors that match the published RRs. Next, we re-estimated no DMT transition probabilities using an MN logit model (MN Logit 2) with new treatment effects, calculated post-estimation RR ratios and modified the treatment effects if necessary. By iteratively adjusting transition probabilities (in MN Logit 2) without DMT and treatment effects, we

eventually approached the values that best match the RRs of disease progression from the literature ($e < 0.001$). *DMT* disease-modifying treatment, *LT* treatment effect, *MN* multinomial, *P(O)* probability of progressing from current disease state, *RCT* randomized clinical trial, *RR* relative risk

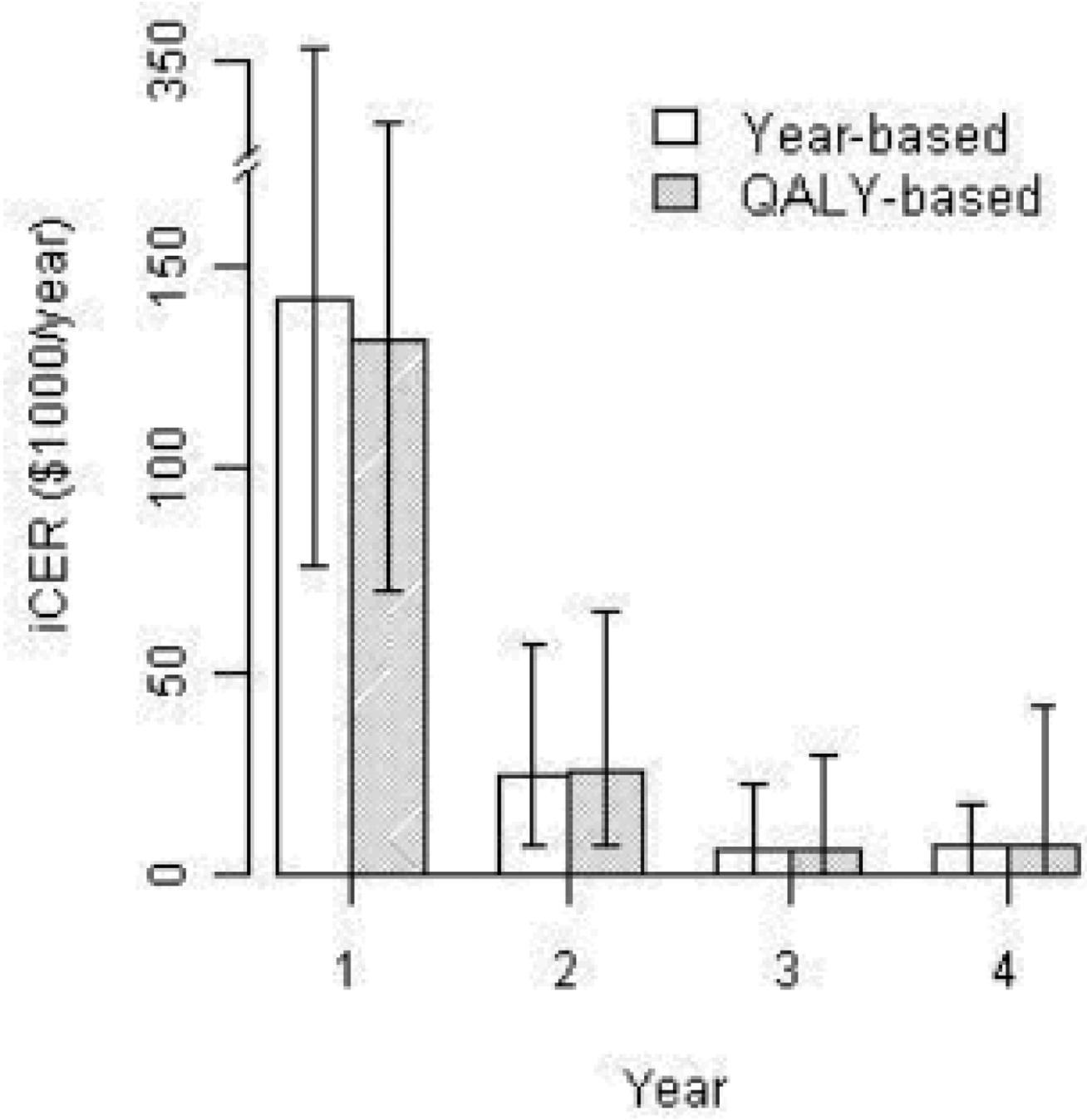

Fig. 3. ICERs presented by the length of the time horizon modelled
Reproduced from Noyes et al.[53], with permission. *ICER* incremental cost-effectiveness ratio

Table 1

Summary of the cost-effectiveness modelling studies of multiple sclerosis DMTs

Study	Country	Population	Base year	Time horizon	Perspective	DMT	Treatment effects source data	Health outcome	Base-case result[a]	Sensitivity (improving cost-effectiveness ratio)
Otten[84]	Canada	RRMS, SPMS	1992	40 years	Healthcare system[g]	IFNβ-1b	RCT	Cost per DYA	Can$219,000 per normalized DYA	Increased treatment efficacy, higher compliance
Brown et al.[88]	Canada	RRMS	Not reported	40 years	Healthcare system[g]	IFNβ-1b	RCT	Cost per relapse avoided, cost per DYA	Can$31,000+ per relapse avoided Can $306,000 per normalized EDSS DYA	Increased treatment efficacy, higher compliance, lower treatment cost
Parkin et al.[80]	UK	RRMS (IFNβ-1b, IFNβ-1a and GA)	1996	2, 5 and 10 years	Societal[g]	IFNβ-1a, IFNβ-1b, GA	RCT	QALY	2 years: £327,000 (IFNβ-1b) to £434,000 (GA) per QALY gained 5 years: £328,000 (IFNβ-1b) per QALY gained 10 years: £228,000 (IFNβ-1b) per QALY gained	Increased number of relapses, decreased drug costs
Otten[85]	Canada	RRMS, SPMS	1996	2 years	Healthcare system[g]	IFNβ-1a	RCT	QALY	Can$406,000 per QALY gained	Increased disease progression
Forbes et al.[89]	UK	SPMS	1995	3 years	Healthcare system[n]	IFNβ-1b	RCT	QALY	£1,025,000 per QALY gained	Not sensitive to changes in drug cost
Brown et al.[17]	Canada	RRMS	1997	40 years	Healthcare system[g]	IFNβ-1b	RCT	Cost per DYA	Can$275,000 per DYA	Treatment efficacy
Kobelt et al.[90]	Sweden	SPMS	2000	10 years	Societal[g]	IFNβ-1b	RCT	QALY	SEK343,000 per QALY gained	Lower utility for severe disability state, longer relapse duration, exclusion of extra monitoring costs of treatment
Kendrick and Johnson[11]	UK	RRMS	1995	20 years	Healthcare system and societal[n]	IFNβ-1a	RCT	QALY	Healthcare system: £27,000 (2 years' treatment) to £38,000 (20 years' treatment) per QALY gained Societal: cost saving	Not done
Parkin et al.[91]	UK	RRMS	1997	5 and 10 years	Societal[g]	IFNβ-1b	RCT	QALY	£328,300 (5 years) and £228,300 (10 years) per QALY gained	Change in range of conditions
Bose et al.[92] *b*	UK	RRMS	2000	8 years	Unknown[n]	GA	RCT	Cost per relapse avoided, cost per disability unitavoided, QALY	£11,000 per relapse avoided, £9,000 per disability unit avoided, and £23,000–65,000 per QALY gained	Unknown

Study	Country	Population	Base year	Time horizon	Perspective	DMT	Treatment effects source data	Health outcome	Base-case result[a]	Sensitivity (improving cost-effectiveness ratio)
									(depending on relapse disutility)	
Phillips et al.[93] *b*	UK	RRMS	1999	10 and 20 years	Societal[n]	IFNβ-1b	RCT	QALY	£8,000 per QALY gained.	Unknown
Kobelt et al.[94]	Sweden	SPMS	2000	10 years	Societal[n]	IFNβ-1b	RCT	QALY	SEK257,000 per QALY gained	None reported
Nuijten and Hutton[10]	UK	Initial RRMS (allowing for development of SPMS) vs. usual care	1998	Pt's lifetime	Insurer[n]	IFNβ-1b	RCT	QALY	£52,000 per QALY gained	Inclusion of relapses, decreased drug cost, increased disability progression
Chilcott et al.[64]	UK	RRMS, SPMS	2001	20 years	Healthcare system[g]	IFNβ-1a, IFNβ-1b, GA	RCT, commercial in-confidence data	QALY	£42,000–98,000 per QALY gained.	Longer time horizon, incorporating disability progression after stopping treatment, decreased drug cost
Lepen et al.[95]	UK and France	RRMS	2000	10 and 20 years	Societal[i]	IFNβ-1a	RCT, prospective extension study	Cost per EDSS-month saved	UK: £453 per EDSS-month saved over 10 years; £222 per EDSS-month saved over 20 years France: €712 per EDSS-month saved over 10 years; €374 per EDSS-month saved over 20 years	None reported
Kobelt at al.[14]	Sweden	RRMS, SPMS	1999	10 years	Societal[g]	IFNβ-1b	RCT, prospective extension study	QALY	€7,800 (over 36 months of treatment) and €38,700 (over 54 months of treatment) per QALY gained	Longer time horizon, increased MS mortality, treatment at higher disability levels (SPMS)
Rubio-Terres et al.[12]	Spain	RRMS	2001	Pt's lifetime	Societal[g]	IM IFNβ-1a, SC IFNβ-1a, SC IFNβ-1b, GA	RCT	Average lifetime cost per pt	Dominant (GA)	Increased disability progression, increased cost of disease
Touchette et al.[96]	USA	SPMS	2000	10 years	Insurer and societal[i]	IFNβ-1b	RCT	QALY	US$395,000 (insurer) and US$86,000 (societal) per QALY gained	Decreased drug cost, increased treatment efficacy
Prosser et al.[15]	USA	RRMS, SPMS	1999	10 years	Societal[g]	IFNβ-1a, IFNβ-1b, GA	RCT	QALY	US$1,838,000 per QALY gained (men taking IFNβ-1a) to dominated (IFNβ-1b, GA)	Shorter treatment duration, starting treatment earlier, increased disease progression, decreased drug costs
Iskedjian et al.[97]	Canada	Pts who experienced a single demyelinating event	2002	15 years	Healthcare system[i]	IFNβ-1a	RCT	QAMLY	Can$189,000 (IFNβ-1a) per QAMLY gained	Longer time horizon, increasing relapse disutility

Study	Country	Population	Base year	Time horizon	Perspective	DMT	Treatment effects source data	Health outcome	Base-case result[a]	Sensitivity (improving cost-effectiveness ratio)
Rubio-Terres and Dominguez-Gil[13]	Spain	RRMS	2003	Pt's lifetime	Societal[g]	Azathioprine, IM IFNβ-1a, SC IFNβ-1a, SC IFNβ-1b, GA	RCT	QALY	€413,000–1,308,000 (all interferons) per QALY gained compared with azathioprine	Increased cost of disease, increased disability progression, increased treatment efficacy
Bell et al.[28]	USA	RRMS	2005	Pt's lifetime	Societal[i]	IM IFNβ-1a, SC IFNβ-1a, SC IFNβ-1b, GA	RCT, prospective extension studies, long-term follow-up	QALY	US$258,000 (GA) to US$416,000 (SC IFNβ-1a) per QALY gained	Increased disease progression, larger range of health state utilities, decreased treatment costs, longer time horizon
Gani et al.[98]	UK	Highly active RRMS	2006	30 years	Societal[i]	NAT, GA, IFNβ (combined)	*Post hoc* analysis of RCT population subset	QALY for NAT	NAT: £2,000 (compared with GA) to £8,200 (compared with best supportive care) per QALY gained	Longer time horizon
Kobelt et al.[46]	Sweden	RRMS, SPMS	2005	20 years	Societal[i]	NAT, mixture of currently prescribed DMTs	RCT, observational cohort	QALY	Dominant (NAT)	Longer time horizon
Janković et al.[75]	Serbia	RRMS	2008	40 years	Societal[g]	GA, IM IFNβ-1a, SC IFNβ-1a, IM IFNβ-1b	RCT, prospective extension studies, long-term follow-up	QALY	>1 billion Serbian dinars (GA) to >4 billion Serbian dinars (all IFNβs) per QALY gained	Increased drug effectiveness, increased indirect costs (wages lost)
Guo et al.[35]	USA	RRMS	2006	4 years	Payer[i]	High-dose SC IFNβ-1a, low-dose IM IFNβ-1a	RCT, prospective extension study	Cost per relapse prevented; cost per relapse-free day gained	US$11,000 (SC IFNβ-1a) per relapse prevented and US$232 per relapse-free day gained compared with IM IFNβ-1a	Increased treatment efficacy, longer time horizon, lower drug costs
Chiao and Meyer[99]	USA	RRMS	2008	2 years	Payer[i]	NAT, IM IFNβ-1a, IFNβ-1b, GA, SC IFNβ-1a	RCT	Cost per relapse avoided	US$56,594 (NAT) to US$103,665 (GA) per relapse avoided	Increased treatment efficacy
Earnshaw et al.[29]	USA	RRMS	2007	Pt's lifetime	Societal[i]	GA, NAT	RCT, prospective extension studies	QALY	US$496,222 (GA) to US$606,228 (NAT) per QALY gained	Longer time horizon, increased disease progression, lower drug costs, increased treatment efficacy, higher compliance
Goldberg et al.[54]	USA	RRMS	2008	2 years	Payer[i]	IM IFNβ-1a, SC IFNβ-1a, SC IFNβ-1b, GA	RCT	Cost per relapse avoided	US$81,000 (SC IFNβ-1a) to US $142,000 (IM IFNβ-1a) per relapse avoided	Increased relapse rate, increased treatment efficacy, higher compliance
Tappenden et al.[36]	USA	RRMS, SPMS	2005	50 years	Payer[g]	INFβ-1a, INFβ-1b	RCT	QALY	US$104,000 (SC IFNβ-1a) to US $312,000 (IFNβ-1b) per QALY gained	Not including head-to-head trials, stopping treatment at an EDSS score of 7, including nursing home costs

Study	Country	Population	Base year	Time horizon	Perspective	DMT	Treatment effects source data	Health outcome	Base-case result[a]	Sensitivity (improving cost-effectiveness ratio)
Nuijten and Mittendorf[100]	Germany	RRMS	2008	4 years	Societal[i]	IM IFNβ-1a, SC IFNβ-1a, SC IFNβ-1b, GA	RCT	Cost per relapse avoided	€51,000 (SC IFNβ-1a) to €134,000 (IM IFNβ-1a) per relapse avoided	Increased treatment efficacy
Becker and Dembeck[101]	USA	RRMS	2008	2 years	Payer[i]	IM IFNβ-1a, SC IFNβ-1a, SC IFNβ-1b, GA	RCT	Cost per relapse avoided	US$78,000 (IM IFNβ-1a) to US $88,000 (GA) per relapse avoided	None
O'Day et al.[102]	USA	RRMS	2000	2 years	Payer[i]	NAT, fingolimod	RCT	Cost per relapse avoided	US$117,164 (NAT) and US$168,754 (fingolimod) per relapse avoided	Higher willingness-to-pay threshold
Noyes et al.[47]	USA	RRMS, SPMS	2005	10 years	Societal[g]	IM IFNβ-1a, SC IFNβ-1a, SC IFNβ-1b, GA	RCT, observational cohort	QALY	US$901,000 (IM IFNβ-1a) to US $2,179,000 (GA) per QALY gained	Lower drug cost, early treatment initiation
Sánchez-de la Rosa et al.[69]	Spain	RRMS	2010	10 years	Societal[i]	IM IFNβ-1a, SC IFNβ-1a, SC IFNβ-1b, GA	RCT	QALY	€118,000 (GA) to €1,005,194 (SC IFNβ-1a) per QALY gained	Decrease in NAbs, higher productivity loss, longer time horizon

[a]The cost per health outcome compared with supportive treatment only

[b]Based on abstracts only

Can$ Canadian dollars, *DMT* disease-modifying treatment, *DYA* disability year avoided, *EDSS* Expanded Disability Status Scale, [g] government/academic/agency sponsorship, *GA* glatiramer acetate, [i] industry sponsorship, *IFN*β interferon beta, *IM* intramuscular, [n] no sponsorship or sponsorship unknown, *NAb* neutralizing antibody, *NAT* natalizumab, *pt(s)* patient(s), *QAMLY* quality-adjusted monosymptomatic life-year, *RCT* randomized clinical trial, *RRMS* relapsing-remitting multiple sclerosis, *SC* subcutaneous, *SEK* Swedish kronor, *SPMS* secondary progressive multiple sclerosis