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Convergence yet Continued Complexity: A Systematic Review and Critique of Health Economic Models of Relapsing-Remitting Multiple Sclerosis in the United Kingdom

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ABSTRACT

Objectives: Several disease-modifying therapies have marketing authorizations for the treatment of relapsing-remitting multiple sclerosis (RRMS). Given their appraisal by the National Institute for Health and Care Excellence, the objective was to systematically identify and critically evaluate the structures and assumptions used in health economic models of disease-modifying therapies for RRMS in the United Kingdom. **Methods:** Embase, MEDLINE, The Cochrane Library, and the National Institute for Health and Care Excellence Web site were searched systematically on March 3, 2014, to identify articles relating to health economic models in RRMS with a UK perspective. Data sources, techniques, and assumptions of the included models were extracted, compared, and critically evaluated. **Results:** Of 386 results, 26 full texts were evaluated, leading to the inclusion of 18 articles (relating to 12 models). Early models varied considerably in method and structure, but convergence over time toward a Markov model with states based on disability score, a 1-year cycle length, and a lifetime time horizon was apparent. Recent models also allowed for disability improvement within the natural history of the condition. Considerable variety remains, with increasing numbers of comparators, the need for treatment sequencing, and different assumptions around efficacy waning and treatment withdrawal. **Conclusions:** Despite convergence over time to a similar Markov structure, there are still significant discrepancies between health economic models of RRMS in the United Kingdom. Differing methods, assumptions, and data sources render the comparison of model implementation and results problematic. The commonly used Markov structure leads to problems such as incapability to deal with heterogeneous populations and multiplying complexity with the addition of treatment sequences; these would best be solved by using alternative models such as discrete event simulations.

Keywords: cost-effectiveness, health economics, multiple sclerosis, systematic review.

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disease characterized by inflammation in the central nervous system [1]. It affects more than 100,000 people in the United Kingdom and is the most common cause of disability in working-age adults [2]. For most of the patients, symptoms such as movement problems and sensory disturbances initially follow a relapsing-remitting pattern (relapsing-remitting multiple sclerosis [RRMS]), but over time disability progresses until the disease enters the secondary-progressive phase (secondary-progressive multiple sclerosis [SPMS]) [3]. MS has a significant impact on patients' health-related quality of life [4]. The economic burden of the disease is also substantial and increases with disease severity and during relapses [5]. A number of immunomodulatory drugs are now available for the treatment of RRMS. Because these reduce the number of relapses, and may reduce disability progression and/or slow down the observed changes on magnetic resonance imaging scans, these are collectively referred to as disease-modifying therapies (DMTs) [6].

A number of DMTs have marketing authorizations in the European Union for the treatment of RRMS, and the National Institute for Health and Care Excellence (NICE) in the United Kingdom has undertaken health technology appraisals of beta interferons and glatiramer acetate (2002), natalizumab (2007), fingolimod (2012), teriflunomide (2014), alemtuzumab (2014), and dimethyl fumarate (2014). NICE prefers that technology appraisals be conducted from the cost perspective of the National Health Service (NHS) and Personal Social Services (PSS), so the economic benefits of DMTs should be balanced against their direct costs. In

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addition, long-term clinical benefits in terms of health-related quality-of-life improvements over a patient's lifetime need to be taken into account by decision makers when deciding whether each DMT is to be reimbursed. The NICE appraisal process for beta interferons and glatiramer acetate in MS ran from August 1999 to February 2002, leading to controversy because NICE found all the economic models presented unsatisfactory. Appeals against the initial draft guidance were upheld, prompting NICE to commission a satisfactory model to inform its reconsideration of the initial proposed guidance. In the published final guidance, NICE was unable to recommend beta interferons and glatiramer acetate but these were subsequently made available on the NHS under a risk-sharing scheme. Natalizumab, fingolimod, teriflunomide, alemtuzumab, and dimethyl fumarate all received positive recommendations in the RRMS population, or subgroup(s) thereof.

Considerable complexity in modeling is required to adequately capture the natural history of MS, and, as such, models presented to decision makers to this point have been highly variable in their characteristics. Four recent review articles have considered aspects of economic modeling in RRMS. Guo et al. [7] reviewed the methodological challenges of modeling the cost-effectiveness of DMTs in MS, focusing on long-term ($\geq$10 years) cost-effectiveness analyses with homogeneous contexts of analysis, published over the previous decade. They included 12 studies and identified several major issues associated with the included studies, including great variations in model designs and assumptions; repetitive use of an old data source for the natural history of disease progression; infrequent use of comparative efficacy data from head-to-head clinical trials or network meta-analyses; and no consideration of switching to other DMTs after initial treatment discontinuation. Thompson et al. [8] discussed the methodological challenges in modeling the cost-effectiveness of treatments for MS. Their review included 36 published models and analyses and found that the greatest source of uncertainty was the absence of head-to-head randomized controlled trials (RCTs). Major drivers of results included the time horizon modeled and DMT acquisition costs. Hawton et al. [9] conducted a review to identify all published economic evaluations of MS treatments to suggest practical recommendations for future research to aid decision making. They included 37 articles; estimates for utilities, costs, and impact of treatment on the course of MS varied considerably between studies. They identified issues concerning the wide variation in costs and outcomes from different sources, from potentially unrepresentative samples, and the modeling of disease progression from natural history data from over 30 years ago. Yamamoto and Campbell [10] evaluated the quality of recent cost-effectiveness studies. They included 22 articles in their review and found that most studies (68%) achieved the highest quality category. To continue to improve the cost-effectiveness evidence for DMTs, several recommendations were made, including using lifetime horizons; the development of modeling and input standards for comparability; head-to-head RCTs between DMTs and long-term prospective studies; and comprehensive cost-effectiveness studies that compare all appropriate DMTs.

Taking these reviews as a whole, several clear topline themes emerge, especially around the variety in model structure, the problems of comparability of results, the limited data available with a lack of head-to-head RCTs, and the repeated use of a natural history data set from many decades ago. One specific complication that was not extensively considered in these reviews is that in the European Union some DMTs have different licensed indications and are used in specific patient subpopulations; the available RCT data, however, do not always reflect these licensed indications. Since 2013, the launch and economic appraisal of teriflunomide, alemtuzumab, and dimethyl fumarate has resulted in further proliferation of models and data sources. The availability of manufacturers' submissions to NICE provides a rich set of contemporaneous, detailed, model reports in English, all taking a UK perspective. However, none of the reviews discussed above included NICE submissions within their remit or identified any other published reports of the cost-effectiveness of teriflunomide, alemtuzumab, or dimethyl fumarate. Therefore, there is a need to consider how models have further developed in the light of these significant new therapeutic options.

Exploration of how the techniques used in modeling RRMS in the United Kingdom have evolved over time, and critically evaluating these techniques with a focus on methodology, is important to inform the methodological development of future models. This will allow these future models to address issues and meet the challenges facing decision makers appraising DMTs. By restricting the perspective to one health system, problems of comparability are reduced and it becomes clearer which methodological points need to be addressed by the model builder and considered by the decision maker for any new DMT. Furthermore, given the globally influential nature of NICE and the impact of its decisions as one of the leading health technology appraisal bodies, a review focused on UK models will draw out modeling insights of global relevance. Therefore, this review seeks to systematically identify and critically evaluate the model structures and assumptions used to date in health economic models of DMTs for RRMS from a UK perspective. The review also aims to propose practical recommendations for future modeling that address the underlying drawbacks of models to date, with the recommendations being of particular interest to both model developers and decision makers.

Methods

A systematic review was conducted following the Cochrane Handbook for Systematic Reviews of Interventions for methods and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting, where appropriate [11,12]. The protocol for the systematic review was developed by the authors and is described fully in this article. The inclusion/exclusion criteria are listed in Table 1, along with the rationale for how each relates to the objectives stated above.

Information Sources and Search Strategy

Literature searches were carried out using both MeSH/Emtree and free text terms for MS, terms relating to treatment, terms relating to economic models, and terms relating to the United Kingdom. MEDLINE, MEDLINE In-Process, and Embase databases were searched on March 3, 2014, *via* OVID. The Cochrane Library platform was used to search the following databases: Cochrane Database of Systematic Reviews, NHS Economic Evaluation Database, and Health Technology Assessment database. Full details of all search terms and time periods used for each database are provided in Supplemental Material found at http://dx.doi.org/10.1016/j.jval.2015.05.006. The NICE Web site was also searched to identify economic models used in manufacturers' submissions of MS treatments. In addition, reference lists of relevant systematic reviews were checked to identify any further publications of interest.

Initially, a single reviewer screened the title and abstract of each result against predefined eligibility criteria. This was followed by the same reviewer assessing potentially relevant full texts against inclusion and exclusion criteria; decisions on full texts were then checked by a second reviewer. A full list of excluded full-text articles is given in Supplemental Material found at http://dx.doi.org/10.1016/j.jval.2015.05.006.

Changes Made during the NICE Appraisal Process

An inherent part of the NICE appraisal process is that manufacturers' models are critiqued and changes are often requested. For the included NICE submissions, the changes made during the process

Table 1 – The inclusion/exclusion criteria applied.

Inclusion criteria	Rationale
• The participants had a diagnosis of RRMS.	• No DMTs are licensed for other forms of MS.
• The intervention was any DMT authorized for use in the United Kingdom to treat RRMS.	• To reflect all current DMT options.
• An analysis from a UK perspective was presented.	• To maximize comparability.
• A comparison was made with any other treatment or no treatment; the outcomes included both costs and clinical outcomes.	• To ensure models are relevant to the decision maker and those building models to influence decision makers.
• The study design was any form of economic evaluation (cost-consequence, cost-minimization, cost-effectiveness, cost-utility, or cost-benefit analysis).	• To capture all model types relevant to decision makers.
Exclusion criteria	**Rationale**
• Publications that were not full original reports	• Full reports required for sufficient detail
• Publications that were not in the English language	• Unlikely that UK models would be published in other languages

DMT, disease-modifying therapy; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

were also extracted and those affecting model structure or assumptions are noted where relevant in the Results and Discussion sections.

Data Extraction, Quality Assessment, and the Development of Recommendations for Future Models

For each included study, one reviewer extracted prespecified data on the decision problem, model structure, and data sources; this extraction was checked by a second reviewer. Data were tabulated, and model characteristics and data sources of individual studies were compared. First, to provide an external anchor for the assessment of the models, each included study was assessed by one reviewer against the Drummond criteria [13] (which are used by NICE in its submission template) and this rating was checked by a second reviewer. The consideration of the risk of bias to model results was not considered relevant to this systematic review of economic modeling methodology.

Second, in seeking to identify the most important future considerations for model developers and decision makers, comparisons were made between the included models over time, with special focus on areas in which convergence was not observed. Furthermore, model capabilities and limitations were considered with respect to the increasing complexity of treatment options for DMT usage, and areas in which converged model assumptions have ceased to be appropriate were identified. From this, recommendations were developed as to how best to capture this complexity efficiently in future models.

Results

In line with previous reviews in this area [7,9], the most relevant considerations for model developers and decision makers did not emerge directly from the formal assessment of models against published assessment criteria but rather from examining the evolution of models over time and considering how the growing complexity of DMT options has affected the continued appropriateness of the model structures used. The results of the systematic review process are first presented below, followed by the formal quality assessment of the included studies against the Drummond criteria [13]; this is then followed by our substantive critical review of the main modeling decisions arising from the included models and our proposals on how these are best addressed in modeling the current range of DMTs.

Systematic Review Results

The database search process returned 397 results, of which 20 were found to be duplicates. Nine records were identified through hand-searching; these included five manufacturer submissions to NICE, one commissioned academic report to NICE, and its addendum, all found by searching the NICE Web site, and two articles identified by searching review articles' bibliographies. Figure 1 shows as a flow diagram the articles identified, screened, retrieved, excluded, and included.

Eleven articles from peer-reviewed journals met the inclusion criteria [14–24]. The one commissioned academic report to NICE [25], its addendum [26], and all five submissions to NICE [27–31] were also identified as relevant. Three articles by Parkin et al. [14], McNamee and Parkin [15], and Parkin et al. [16] described the same underlying model and because the article published in 2000 [16] provided a less detailed summary, the primary reports used for data extraction were the original publication from 1998 [14] and the update incorporating new data published in 1999 [15]. Two articles by Bose et al. [19,20] were found to describe the same model, and data were initially extracted from the 2001 article [19] and then checked against the 2002 article [20]. An article by Gani et al. [24] was found to be based on a manufacturer's submission to NICE [27], and once again the more detailed version (the NICE submission) was used as the primary report for data extraction. The article by Chilcott et al. [23] was found to be based on the original School of Health and Related Research (ScHARR) report commissioned by NICE [25] and its addendum [26], which were available in full on the NICE Web site and therefore these were also considered together; the term "the ScHARR model" is used for these reports hereafter. Therefore, 18 reports on 12 models were identified for inclusion and data extraction. All models were based on the Kurtzke Expanded Disability Status Scale (EDSS) [32], an ordinal scale describing the severity of disability in patients with MS. The full data extracted are presented in Tables 2 and 3.

Quality Assessment of Included Reports

The quality assessment against the Drummond criteria [13] rated results for all models in the "Study Design" section as good but revealed deficiencies in some of the early models in the "Data Collection" and "Analysis and Interpretation" sections. Two reports did not clearly describe the model used or the currency and inflation adjustments made [17,18]. Most reports up to 2003 did not report quantities separately to unit costs [17–23,25,26]. Likewise, none of the models before the ScHARR model reported probabilistic sensitivity analyses [14–22].

Technical Comparison of Models

The model summaries provided in Tables 2 and 3 show a clear pattern over time, with the ScHARR model commissioned by

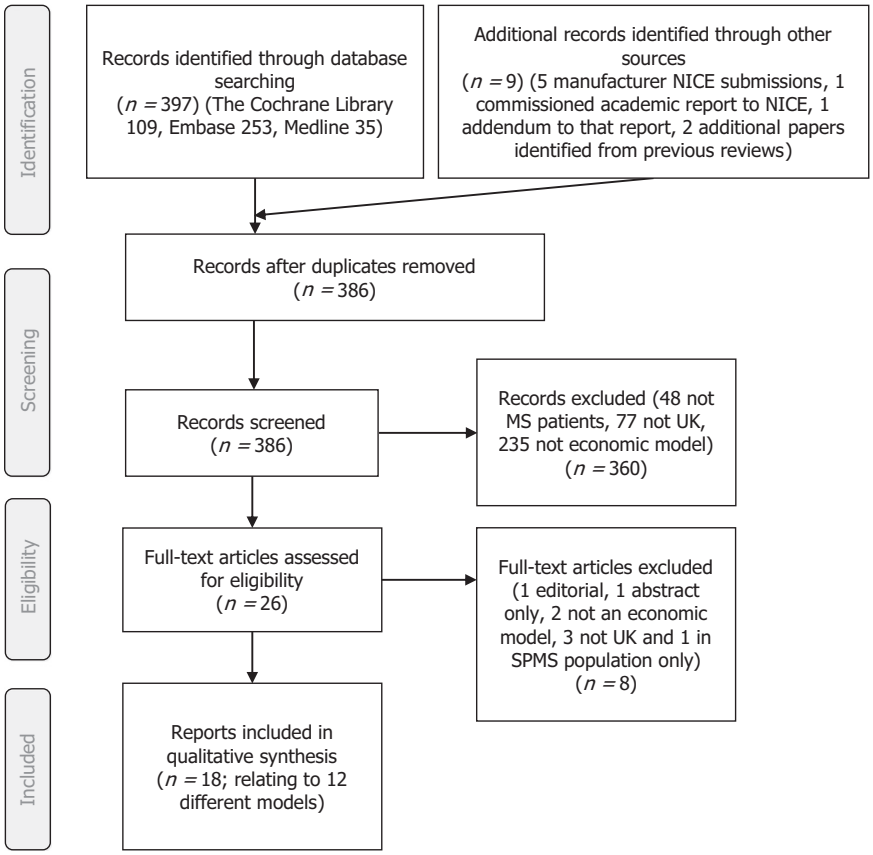

Fig. 1 – Flow diagram of the identification, screening, and inclusion process.

NICE [23,25,26] clearly a pivotal point in model evolution. There is diversity in modeling technique, model structure, input data, and assumptions across the six models developed before the ScHARR model [14–22]. In contrast, models developed after the ScHARR model converge with respect to the technique and basic structure. In line with other recent reviews [7,9], one feature common to all included models was the use of EDSS to model disability progression, in spite of criticism of this instrument for its inability to capture relevant clinical milestones [34]. As one would expect in a review of models taking a UK perspective, the impact of changes in guidance issued by NICE over time is also apparent, both in terms of the recommended discount rates for costs and utilities and also in terms of the balance between the risks of extrapolation of limited clinical effectiveness data versus the desire for a lifetime horizon. Time horizons varied, with 5, 8, 10, 20 years, and lifetime (represented as 50 years in two models) all used; more recent models have used longer time horizons. Short-term studies would have a tendency to underestimate the cost-effectiveness of DMTs because the main advantage of using DMTs is to postpone the development of severe MS, which occurs after a longer time period.

Of the models published before the ScHARR model in 2003 [23], two appeared to be decision tree models (though were not explicit in stating their model type) [14–16,18], one described itself as semi-Markov [21], one simulated individual patients [19,20], whereas two used forms of regression analysis [17,22]. The decision tree and Markov-type models [14–16,18,21] used various cohort structures based on different subsets of EDSS scores. The regression models attempted to consider the area under the EDSS score–time curve, in spite of the EDSS score being a series of ordered categories rather than a cardinal number amenable to such analysis [17,22]. Only one of the early models attempted to incorporate progression from RRMS to SPMS into its structure in any form [21]. This model applied inputs from the SPMS population to all patients with an EDSS score of 4.5 or above [21], which is not consistent with disease progression in clinical practice [35]. This same model was also the only early example to incorporate death and treatment withdrawal [21]. None of the early models reported incorporating the disutility or costs of adverse events (AEs), subgroup analyses, or probabilistic sensitivity analysis. All early studies provided results from an NHS and PSS perspective, though it was not the primary perspective for all the studies—MS has considerable effects on productivity for both patients and carers; therefore, some models provided results from a societal perspective [17,18,21]. NICE, however, specifies an NHS and PSS perspective as the basis for decision making, and UK models tend therefore to follow this approach; greater variation in perspective would be expected had other countries been included in this review. Costs were all discounted by the then-standard 6%, but utilities were not consistently discounted by the then-standard 1.5%.

As discussed in the Introduction, the controversy surrounding the first NICE appraisal of beta interferons and glatiramer acetate led to the commissioning of a new economic model by NICE. The commissioned model was produced by a consortium led by ScHARR and is available on the NICE website [25] along with a short addendum addressing new utility data that became available after the main report had been submitted but before the appraisal process was completed [26]. The effect of this process on those modeling DMTs in MS from a UK perspective is apparent from the results presented in Tables 2 and 3, and after the ScHARR model all models describe themselves explicitly as being based on the ScHARR model. This new model defined a Markov structure based on the full set of EDSS scores (including

Table 2 – Summary of the included models—authors, funders, and basic model structure.

Study	Author and funding	Model type	Drugs compared	Time horizon	Cycle length	Perspective
Parkin et al. [14], McNamee and Parkin [15], and Parkin et al. [16]	NHS Health Technology Assessment programme	Decision tree	• IFN-β-1b (Betaferon) • s.c. IFN-β-1a 44/22 μg (Rebif 44/22 μg) (1999 article only) • Best supportive care	5 and 10 y	NA	NHS & PSS; 6% discount rate
Kendrick and Johnson [17]	Biogen; Source of funding was not reported within the article, but is identified in NICE TA32	Regression analysis	• i.m. IFN-β-1a 30 μg (Avonex) • Best supportive care	20 y	NA	UK societal and NHS perspectives both reported; 6% discount rate
Phillips et al. [18]	Schering—author affiliation; Source of funding was not explicitly reported within the article	Decision tree	• IFN-β-1b 250 μg (Betaferon) • Best supportive care	10 and 20 y	NA	NHS and UK societal perspectives both presented; discount rate 6% for costs only
Bose et al. [19,20]	Aventis and Teva—author affiliations; Source of funding was not explicitly reported within the article	Individual patient simulation	• Glatiramer acetate (Copaxone) • Best supportive care	8 y	Not reported	NHS; no discounting in the base case but 6% for both and 6% costs/1.5% for life benefits were both also reported
Nuijten and Hutton [21]	MEDTAP International (a health economics consultancy)	Semi-Markov process	• IFN-β-1b 250 μg (Betaferon) • Best supportive care	Lifetime	3 y	NHS and UK societal perspectives both presented; 6% discount rate
Lepen et al. [22]	Funded by Serono	Time series regression model	• IFN-β-1a 44/22 μg (Rebif 44/22 μg) • Best supportive care	10 and 20 y	NA	6% discount for cost, no discount for effectiveness mentioned; therefore, none assumed
ScHARR report to NICE [25], ScHARR addendum [26], and Chilcott et al. [23]	ScHARR funded by NICE	Markov	• Glatiramer acetate (Copaxone) • IFN-β-1a (Avonex) • IFN-β-1b (Betaferon) • IFN-β-1a (Rebif 22 and 44 μg)	20 y	1 y	NHS; costs discounted at 6%, life benefits at 1.5%, but results at 6% discount for both are also presented
Natalizumab manufacturer's NICE STA submission [27] and Gani et al. [24]	Biogen, model developed by Heron Evidence Development on their behalf	Markov	• Best supportive care • Natalizumab (Tysabri) • Glatiramer acetate (Copaxone) • Blended comparator: interferons (Avonex, Betaferon, Rebif 22 and 44 μg) • Best supportive care	20 y (NICE submission) 30 y (Gani et al. article)	1 y	UK societal, UK governmental, and NHS & PSS perspectives all reported; 3.5% discount rate

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Table 2 – *continued*

Study	Author and funding	Model type	Drugs compared	Time horizon	Cycle length	Perspective
Fingolimod manufacturer's NICE STA submission [28]	Novartis	Markov	Initial submission: • Fingolimod (Gilenya) • i.m. IFN-β-1a 30 μg (Avonex) Added during appraisal: • s.c. IFN-β-1b 250 μg (Betaferon/ Extavia) • s.c. IFN-β-1a 44/22 μg (Rebif 44/22 μg) • Blended comparator: best supportive care and interferons (Avonex, Betaferon, Extavia, Rebif 22 and 44 μg)	50 y	1 y	NHS & PSS; 3.5% discount rate
Teriflunomide manufacturer's NICE STA submission [29]	Genzyme	Markov	• Teriflunomide (Aubagio) • Blended comparator: interferons and glatiramer acetate • Glatiramer acetate (Copaxone) • i.m. IFN-β-1a 30 μg (Avonex) • s.c. IFN-β-1b 250 μg (Betaferon/ Extavia) • s.c. IFN-β-1a 44/22 μg (Rebif 44/22 μg) • Fingolimod (Gilenya) (HA subgroup only) • Natalizumab (Tysabri) (RES subgroup only)	50 y	1 y	NHS & PSS; 3.5% discount rate
Alemtuzumab manufacturer's NICE STA submission [30]	Genzyme	Markov	• Alemtuzumab (Lemtrada) • Fingolimod (Gilenya) • Natalizumab (Tysabri) • Glatiramer acetate (Copaxone) • i.m. IFN-β-1a 30 μg (Avonex) • s.c. IFN-β-1b 250 μg (Betaferon/ Extavia) • s.c. IFN-β-1a 44/22 μg (Rebif 44/22 μg)	50 y	1 y	NHS & PSS; 3.5% discount rate

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Dimethyl fumarate manufacturer's NICE STA submission [31]	Biogen	Markov	• Dimethyl fumarate (Tecfidera) • Fingolimod (Gilenya) • Natalizumab (Tysabri) • Glatiramer acetate (Copaxone) • i.m. IFN-β-1a 30 μg (Avonex) • s.c. IFN-β-1b 250 μg (Betaferon/ Extavia) • s.c. IFN-β-1a 44/22 μg (Rebif 44/22 μg)	30 y	1 y	NHS & PSS; 3.5% discount rate

HA, highly active; IFN, interferon; i.m., intramuscular; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services; RES, rapidly evolving severe; s.c., subcutaneous; STA, single technology appraisal; TA, technology appraisal.

the half-number scores as well as the whole-number scores) incorporating RRMS EDSS states 0–10, SPMS EDSS states 2–10, and a general death state. Mortality was modeled either as disease progression to EDSS state 10 (MS death), or as a result of other causes at any model stage (general death). Patients could transition from RRMS to SPMS at any point, and adverse effects and withdrawal from treatment were explicitly considered. Extrapolation of the short-term clinical efficacy data available at the time was balanced with the long-term nature of the disease through the choice of a 20-year time horizon. Comprehensive scenario analyses and probabilistic sensitivity analyses were also reported, addressing a criticism of many of the previously submitted models that had presented limited uncertainty analyses. Subsequent models have clearly converged to a standardized structure based on that used in the ScHARR model, but with two modifications. First, the number of states has been reduced from the full EDSS set used in the ScHARR model down to a set based on whole-number states, with each half-number state grouped with the one above. The exception to this is the EDSS 9.5 state, which is grouped in with EDSS state 9 (and 8.5). Second, the separate MS death (EDSS state 10 in each of RRMS and SPMS) and general death states have been combined into a single absorbing state. In all the models developed after the ScHARR model, costs and utilities were both discounted by the current UK standard of 3.5%. In spite of the adoption of this standardized structure, variation has been apparent in the model assumptions, as will be discussed below, and also with respect to some aspects of the data in which there are problems with lack of consensus and openness of data, with consequences for replicability.

Comparators, the Use of a Blended Comparator, and Sequencing

The ScHARR model [23,25,26] sought to compare the first DMTs to be made available, that is, the various beta interferons and glatiramer acetate, with the then-standard best supportive care. Best supportive care remained a comparator at the time of the natalizumab and fingolimod NICE appraisals [24,27], alongside the first DMTs, but as can be seen in Table 2, it was removed from the scope for subsequent NICE appraisals [28–31]. The fingolimod submission did not consider best supportive care alone, only as part of a blended comparator. This reflects the evolution of the treatment algorithm for RRMS in the United Kingdom over recent years, with few patients now receiving best supportive care alone. In line with the findings of previous reviews, there is a lack of head-to-head studies in RRMS and models therefore were informed by indirect comparisons and network meta-analyses.

Several models designed for NICE included a blended comparator that was based on a meta-analysis of the efficacy of various different therapies and assigned a single weighted cost [24,27,29]; this was also added in response to appraisal committee requests during the appraisal process for fingolimod [36]. The agents included in the blended comparator have changed over time (see Table 2). Using a blended comparator can appear advantageous because it simplifies comparisons when there are many similar agents available. A comparator that would be considered cost-effective in a pairwise comparison against a new intervention, however, could be concealed within a non–cost-effective blended comparator when combined with cost-inefficient drugs. NICE now does not support the use of a blended comparator and did not take into account the blended comparator presented in the teriflunomide submission [37].

As the number of DMTs available has increased, the need to consider sequences of treatment with sequential DMTs has become important; this evolution can be seen in Table 3. From the ScHARR model onwards, a number of models [23–28,30,31] have analyzed two lines of treatment, in which a patient can be

Table 3 – Summary of data extracted from included articles—details of model structure and assumptions.

Study	Description and number of health states	Whether transition to death is treated separately to EDSS transitions	No. of lines of treatment	Any changes in withdrawal with time	Any changes in efficacy with time	Criteria for inclusion of adverse events	Whether improvement in patients' conditions was allowed	Subgroups investigated
Parkin et al. [14], McNamee and Parkin [15], and Parkin et al. [16]	5 states (whole-number RRMS EDSS states 3–7) in IFN-β-1b; unclear but more for IFN-β-1a	Death not included	1	NR	No	NR	No	No
Kendrick and Johnson [17]	Simple regression model based on the EDSS score, no discrete health states	NR	1	NR	No	NR	No	No
Phillips et al. [18]	Uncertain, at least Parkin's 5 states (whole-number RRMS EDSS states 3–7); probably higher states as well	NR, not included in the analysis	1, because BSC after Betaferon is not analyzed	NR	No	NR	No	No
Bose et al. [19,20]	No Markov states because it is not a Markov model but patient can be in 1 of the 10 EDSS states for RRMS, no SPMS analyzed	NR, death means exclusion from the sample, which is already incorporated in the model	1, because BSC after GA is not analyzed	Purely driven by individual patient data, so probably yes but not specified	Purely driven by individual patient data, so probably yes but not specified	NR	Probably yes because it is an IPD-driven model and they mention this possibility in the real setting, but not stated explicitly	No
Nuijten and Hutton [21]	9 Markov states (whole-number intervals RRMS EDSS states 2.5–3.5; SPMS EDSS states 4.5–9.5; EDSS state 10 = death)	Yes	1	Yes, applied only in the first cycle	No	SAE excluded from the analysis	No	No
Lepen et al. [22]	NR, not a Markov model, but there are 10 EDSS states of RRMS	NR, death means exclusion from the sample, which is already incorporated in the model	1, because BSC after Rebif is not analyzed	Purely driven by individual patient data, so probably yes but not specified	Purely driven by individual patient data, so probably yes but not specified	NR	Probably yes because it is an IPD-driven model and they mention this possibility in the real setting, but not stated explicitly	No

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ScHARR report to NICE [25], ScHARR addendum [26], and Chilcott et al. [23]	38 Markov states (full RRMS EDSS states 0–10; SPMS EDSS states 2–10; general death)*	Both transitions to EDSS state 10 (×2) and all-cause death	2	Discontinuation 10% in first and second years; 3% thereafter	No	A general disutility for AEs based on Prosser [33] and CIC data is applied. No specific AEs modeled	No	No
Natalizumab manufacturer's NICE STA submission [27] and Gani et al. [24]	19 Markov states (whole-number RRMS EDSS states 0–9; SPMS EDSS states 2–9; EDSS state 10 = death)*	Yes	2, no evidence for more is given	Yes—withdrawal rates applied for the first 10 y only; rates applied to GA differ between NICE submission and Gani et al.'s article	No	A general disutility based on the ScHARR model is applied and in addition, for natalizumab only, specific AEs are included. The rationale for the choice of AEs is not specified explicitly	Yes	SOT and RES
Fingolimod manufacturer's NICE STA submission 2011 [28]	19 Markov states (whole-number RRMS EDSS states 0–9; EDSS 2–9; SPMS EDSS state 10 = death)*	Yes	2	No	Initial submission: No Added during appraisal: 50% at 5 y	General disutility model as per the ScHARR model for IFNs and GA. No general disutility for fingolimod but three specific SAEs modeled. The rationale for the choice of AEs is not specified explicitly	No	No
Teriflunomide manufacturer's NICE STA submission [29]	19 Markov states (whole-number RRMS EDSS states 0–9; SPMS EDSS states 2–9; EDSS state 10 = death)*	Yes	4	Yes, to 50% of the initial value after 2 y	Initial submission: Base case: No Scenario analyses: reduced by 25% or 50% from year 6 onwards Added during appraisal: reduced by 25% after 2 y and 50% after 5 y	AEs that had ≥4% probability of occurrence, compared with placebo	Initial submission: No Added during appraisal: Yes	HA RRMS and RES

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Table 3 – *continued*

Study	Description and number of health states	Whether transition to death is treated separately to EDSS transitions	No. of lines of treatment	Any changes in withdrawal with time	Any changes in efficacy with time	Criteria for inclusion of adverse events	Whether improvement in patients' conditions was allowed	Subgroups investigated
Alemtuzumab manufacturer's NICE STA submission [30]	19 Markov states (whole-number RRMS EDSS states 0–9; SPMS EDSS states 2–9; EDSS state 10 = death)*	Yes—probability of death higher with increasing EDSS score	2	No withdrawal for alemtuzumab. For other DMTs, after 2 y it is assumed that the probability of withdrawal will be 50% of the initial one	Initial submission: Base case: No Scenario analyses: reduced by 25% or 50% from year 6 onwards Added during appraisal: assume efficacy waning begins at 3 or 5 y	A difference of ≥4% in the probability of occurrence, compared with placebo. Where comparisons with placebo data were not available, adverse events with an incidence of >5% in the treatment arm were included; OR Included within section 4.4 of SmPC detailing special warnings and precautions for use	Initial submission: No Added during appraisal: Yes	RES and HA RRMS
DMF manufacturer's NICE STA submission [31]	19 Markov states (whole-number RRMS EDSS states 0–9; SPMS EDSS states 2–9; EDSS state 10 = death)*	Yes	2	No	The treatment effect wanes to 75% after 2 y and to 50% after 5 y	Most common AEs on DMF label (≥5% incidence in any treatment group in trials), common DMF AEs on label that have been extracted in the systematic review, or any AE occurring at	Yes	No

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an incidence of ≥3% higher in the total DMF group than in the placebo group, AEs included in the model were only those reported in DMF studies

AE, adverse event; BSC, best supportive care; CIC, commercial-in-confidence; DMF, dimethyl fumarate; EDSS, Extended Disability Status Scale; GA, glatiramer acetate; HA, highly active; IFN, interferon; IPD, individual patient data; NICE, National Institute for Health and Care Excellence; NR, not reported; RES, rapidly evolving severe; RRMS, relapsing-remitting multiple sclerosis; SAE, serious adverse event; SmPC, summary of product characteristics; SOT, suboptimally treated; SPMS, secondary-progressive multiple sclerosis; STA, single technology appraisal.
* Many of these models describe a larger structure for SPMS; however, the transition matrices preclude anyone from entering SPMS at an EDSS score of less than 2, so these are unused dummy states and have therefore been excluded from the description here to facilitate comparison.

moved from the initially assigned active treatment to best supportive care. With some patients experiencing highly active disease and requiring second-line treatments, however, modeling a single active treatment line no longer accurately represents clinical practice. Only models incorporating three or more lines of treatment [29] are able to accurately reflect the current treatment pathway. Sequencing is particularly important in this disease area given the differences in licensed indications between comparators and the effect that previous treatments can have on eligibility for future treatments or the risk of AEs even after switching treatment. Furthermore, given that the potential comparators and sequences available vary depending on the disease severity experienced by the patient, it is important to be able to take this into account. Future models need to be able to allow for such effects methodologically, although direct head-to-head evidence is likely to be limited for many treatment sequences.

To incorporate each additional line of treatment into a Markov model requires the creation of all model states and transition matrices separately for each treatment line. This adds a large amount of computational intensity to the deterministic model, with each additional treatment line effectively adding the equivalent of a whole single-treatment-line model. The relative effect on computational intensity for probabilistic modeling is equivalent, but the absolute increase is greater by several orders of magnitude. This inherent limitation of Markov models is not present in some other well-established health economic modeling methods such as discrete event simulation (DES) models, which track each simulated patient individually, yet in a computationally efficient manner. Such models are capable of making use of all available data on the effect of both baseline covariates and the consequences of any modeled events, including patient eligibility for, and the outcome of, specific treatment sequences.

Constant or Waning Efficacy and Discontinuation Rate Over Time

Because clinical trials do not usually cover the whole of the time horizon relevant to the decision maker, it is necessary to make assumptions about the efficacy and withdrawal rate of the treatments in the extrapolated period. The ScHARR model [23,25,26] and the ScHARR-derived models in the natalizumab, fingolimod, teriflunomide, and alemtuzumab NICE submissions [24,27–30] assumed constant efficacy of DMTs in the base case, whereas the dimethyl fumarate manufacturer's NICE submission [31] assumed that efficacy would fall to 75% of the initial value after 2 years of treatment and to 50% after 5 years. The teriflunomide and alemtuzumab submissions included waning as a scenario analysis. Waning assumptions were added to the base case in response to appraisal committee requests during the appraisal process for fingolimod, teriflunomide, and alemtuzumab. All waning assumptions were arbitrary and were applied equally to all comparators even though the comparators have differing propensities to cause neutralizing antibodies [38] and long-term observational data have been published for some comparators [39–42]. Similar variation in assumptions was found in the probabilities of treatment discontinuation: the ScHARR model [23,25,26] and the natalizumab, teriflunomide, and alemtuzumab manufacturers' NICE submissions [24,27,29,30] all made differing assumptions of changes in discontinuation rates over time, whereas the fingolimod and dimethyl fumarate manufacturers' NICE submissions [28,31] assumed a constant probability of discontinuation. This disparity in assumptions makes it difficult to compare results from different models, and furthermore the implications of these assumptions are not necessarily straightforward. For example, applying a percentage decrease in efficacy to all comparators could actually favor less effective therapies when incremental differences are compared.

Modeling assumptions related to changing efficacy or discontinuation rate over time imply knowledge of the number of years a patient has been receiving a given treatment. For first-line treatment, this is simply the number of cycles elapsed; however, as patients enter subsequent lines of treatments at different times, it becomes necessary to add tunnel states to create "memory" within the Markov model framework. Such tunnel states multiply the model size for each additional year of memory required, introducing considerable complexity and computational intensity. As noted above with respect to treatment sequencing, use of DES models would remove such difficulties by allowing the efficient incorporation of changing efficacy and discontinuation rates into subsequent treatment lines.

Improvement in the EDSS Score

Patients with MS experience, on average, a deterioration in their EDSS score over time, leading to death. It is important to note, however, that some patients experience spontaneous improvements in condition [43]. The ScHARR model [23,25,26] assumed that patients cannot be transferred to a lower EDSS score, that is, their condition cannot improve, and the same assumption was made in the fingolimod, teriflunomide, and alemtuzumab models [28–30]. Revised natural history data to allow for improvement in the EDSS score were added to the base case in response to appraisal committee requests during the appraisal process for teriflunomide and alemtuzumab. Censoring improvement in the EDSS score could make MS appear more severe than it is; therefore, the more recent models allow improvement in disability levels within the natural history progressions [24,27,31].

An additional complication is that a substantial amount of the information used in the models submitted to NICE has been marked as confidential by the submitting manufacturer, making it impossible to compare and replicate some aspects of these models; for example, the exact transition probabilities for the natural history of patients with RRMS in those models that allow improvement in disability [27,31]. Thus, there are limitations in the data available to inform other models, even though it is now considered best practice to include EDSS score improvement within any model [43]. In line with the findings of other reviews [7,9], the models from the ScHARR model onward used, at least in part, natural history data from the London Ontario cohort [44], which has been subject to criticism [34]. The recent publication of a nonconfidential natural history data set that allows for improvement will hopefully address this situation in future, both with respect to the problems of confidentiality and by providing an alternative data source for natural history [45].

Use of All-Cause Discontinuation or Discontinuation Due to AEs

There is no agreement between the models from the ScHARR model onward with respect to the type of discontinuation probability applied to the DMTs. The ScHARR model considered the trial evidence not to be robust and made assumptions about discontinuation; the natalizumab, teriflunomide, alemtuzumab, and dimethyl fumarate manufacturers' submissions [24,27,29–31] used all-cause trial withdrawal, whereas the fingolimod manufacturer's submission [28] used trial withdrawal due to AEs. All-cause withdrawal takes into account all possible factors affecting discontinuation, but it also includes withdrawals that are related to the design of the trial. Furthermore, trial designs differ between RCTs and hence a degree of unobserved heterogeneity may be added. It should be noted that discontinuation is an important parameter in these models and that, nonintuitively, a higher discontinuation rate can lead to greater cost-effectiveness, as discussed in the final NICE guidance for dimethyl fumarate and teriflunomide [37,46]. Because the comparability of withdrawal rates between trials is of critical importance, the discontinuation rate modeled is therefore a key decision and a consensus is required as to what is most appropriate.

The Choice of AEs to Include for Each Drug

Another area in which models from the ScHARR model onward differ significantly is the criteria for inclusion of AEs. Some models [23–28] use AEs from external sources or are not clear about the reason for the inclusion of AEs, whereas others [29–31] provide a clear algorithm for the inclusion or exclusion of AEs. This wide range of approaches results in the same DMT being modeled with different AE costs and disutilities in different models, with consequent difficulties for comparison of the results of different models.

Conclusions

Overall, this review has found that UK models for RRMS have converged to a structure of Markov states based on condensed EDSS score categories, but with remaining variation between models. This variation is found in the number of lines of treatment allowed, the long-term assumptions around efficacy waning and withdrawal, the type of withdrawal data used, and the criteria used for selecting AEs to include, all of which preclude meaningful comparison of the different model results. Furthermore, data confidentiality has resulted in problems with some models—even recent ones—failing to allow improvement in the EDSS score in spite of this now being acknowledged as reflective of the true natural history of the condition.

Strengths and Limitations of This Review

This review included manufacturers' submissions to NICE and restricted the inclusion of literature articles to those reporting a UK perspective. This has allowed the review to provide a comprehensive and focused analysis of the economic methodology informing decision makers in the United Kingdom and track the evolution of this over time without the analysis being confounded by the lack of comparability of models between health systems. Such a focus is particularly timely with the prospect of the NICE multiple technology appraisal of DMTs for RRMS expected to initiate towards the end of 2015. In addition, the transparency of the NICE appraisal process has allowed the changes made to initial submissions during the appraisal process to be systematically identified and permitted relevant changes to be included in the results and critique presented in this article.

Limitations of the study include the use of a single reviewer to assess inclusion/exclusion criteria at the abstract review phase; the fact that NICE submissions are not in themselves peer reviewed (however, the NICE review process is in effect an open, rigorous peer review process, the outcomes of which have been captured systematically in this review); the use of confidential data in many reports, which limits our ability to review some aspects of the studies consistently across reports; and the limitation to studies reporting a UK perspective, which, although also a strength, omits any ability to track the evolution of models used to inform decision makers in other health economies.

Implications for Future Modeling

There is now a need to define and model clinically realistic treatment pathways, taking into account the increased number of DMTs, their differing licenses, and the fact that previous treatments potentially restrict the choice of allowable follow-on drugs. As previously discussed, however, this will multiply the

complexity of health economic models considerably. Although Markov cohort models are typically preferred for their relative simplicity and transparency, the required level of model complexity to capture modern RRMS treatment sequences makes this modeling technique infeasible. In addition, Markov models are inherently unable to take into account varying risks by disease history or account for subgroups such as rapidly evolving severe or highly active, other than by modeling them as separate populations. Indeed, if one considers that some recently licensed DMTs and their specific AEs have consequences that last beyond the 1-year cycles used, the Markovian assumption of memoryless homogenous cohorts ceases to hold, again raising the question of whether the choice of model technique itself should now be revisited to better model heterogeneity and treatment complexity.

In considering the best way to address the identified deficiencies and problems in the use of Markov models, it is proposed that DES models have the potential to become the preferred model type to capture the required heterogeneity and complexity. The tracking of individually simulated patients in this type of model allows the events experienced by patients to modify their future trajectory, subject to appropriate data being available to inform the inputs. Markov models cannot capture these effects in a computationally efficient way. Such a change of model type neatly addresses the main methodological points identified in this review, including greatly facilitating analysis of treatment sequences, tracking the long-term sequelae of certain treatments, and changes in efficacy and discontinuation rates with treatment duration. This greater flexibility seems likely to outweigh the potential downsides of DES models in terms of programming transparency and reviewer familiarity with the technique. Although one previous DES model in RRMS has been published [47], that article considered only a simple decision problem comparing two beta interferons, based on extrapolating the results of a single clinical trial over a 4-year period, and did not incorporate many of the features covered in this review. A comprehensive new model structure capable of evaluating the full range of treatment sequences now available therefore remains to be defined.

In conclusion, although the basic structure used to model RRMS in the UK setting has seemingly converged over time, there still remains a great deal of variation between the inputs and assumptions used in the models. With the increasingly complex treatment pathway in RRMS, the Markov model structure designed to assess the first DMTs in 2001 is no longer the most efficient way to model this condition. The time has come for a paradigm shift in UK RRMS models to reflect the clinical advances of the last decade.

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Supplemental Materials

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