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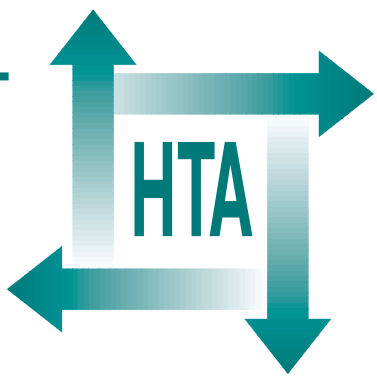

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Contents

List of abbreviations

COI	cost of illness
DSS	Disability Status Scale
EDSS	Expanded Disability Status Scale
ESS	Environmental Status Scale
EQ-5D	EuroQol-5 dimensions
FS	Functional System
GP	general practitioner
GPRD	General Practice Research Database
HRQoL	health-related quality of life
IMS	Intercontinental Medical Statistics
ISS	Incapacity Status Score
MRD	Minimal Record of Disability
MS	multiple sclerosis
ONS	Office of National Statistics
PP	primary progressive
QALY	quality-adjusted life-year
QoL	quality of life
RR	relapsing-remitting
SF-36	Short Form 36-item questionnaire
SP	secondary progressive
VAMP	Value-Added Medical Products

Executive summary

Background

Multiple sclerosis (MS) is a progressive degenerative disease of the CNS with a pattern of symptoms that depends on the type of disease and the site of lesions. As damage accumulates, symptoms become more permanent and progressive disability ensues. MS is a disease characterised by wide variations between patients and for the individual over time, thus making categorisation difficult.

MS has a significant impact on the quality of life (QoL) for most patients over many years, with the disease lasting, on average, 30 years. The disease is twice as common in women than in men, and is at its peak in the most economically productive years of life.

In order to plan for the social and economic impact of MS on patients, their families and society as a whole, a better understanding of the natural history and epidemiology of the disease is needed. In particular there is a need to describe accurately the patterns and impact of disease progression over time.

Aim of the review

There are three main aims to the current report:

- to review existing natural history data
- to review existing epidemiology data
- to review modelling literature and outline the structure of a theoretical model, which could be developed and used in the future to reflect the course of MS in terms of disease progression, health utility and cost at different stages of the disease.

Methods

A literature search was conducted to identify all papers relevant to the natural history and epidemiology of MS and to MS-related models. MEDLINE, EMBASE and the Science Citation Index were used. The following inclusion criteria were applied:

- diagnostic classification system described
- methods of case ascertainment described
- time series conducted in the same place
- geographical studies conducted over a limited period
- case definitions and observers consistent over time and place
- studies with at least 100 cases reported.

Results

Natural history of MS

The most commonly quoted physical and cognitive effects of the disease include: weakness, fatigue, ataxia, bladder complaints, bowel problems, sensory effects and visual impairment.

The most supported tool for the grading of functional effects of MS is the (Expanded) Disability Status Scale ((E)DSS). The scale ranges from 1 (least severe) to 10 (death from MS). However, the scale is not ideal because there is a bias towards the physical effects of the disease (particularly ambulation) rather than the cognitive effects.

Relapse rates in relapsing-remitting MS vary considerably over time for an individual and between individuals, but there is a general pattern of exacerbations of more frequent relapses, followed by long periods of lower rates. This makes assessment of the effects of treatments in an individual extremely problematic. High relapse rates at the onset of the disease give a limited prediction of poor prognosis.

Epidemiology of MS

Epidemiological studies in England and Wales have given a range of prevalence estimates but the average is estimated at about 110 patients per 100,000 population. There is good international evidence of geographical variation in prevalence, best described by increasing prevalence with latitude (both north and south of the equator). This is not seen in the data for England and Wales, but this may be due to other causes of variation masking any trend in the limited data. If such a latitudinal variation did apply to England and Wales, then the prevalence would range from

104 to 156 per 100,000 (south to north), indicating substantial differences in resource consequences. Improved survival has led to increased prevalence.

Modelling

Of 30 papers reviewed on the use of modelling of MS progression, none provide a view of progression from onset to death. A Canadian longitudinal study of over 1000 patients provides the most detailed information available. It is limited by its use of the DSS as a measure of progression and by the level of detail published, but, combined with other work on the utility of DSS states, these Canadian data could be used to prepare a Markov model (a model type well suited to use in a chronic disease).

Cost studies of MS

Cost studies suggest that the general support costs for patients are related to increasing DSS step. The latest and most complete UK study shows that, on average, patients at EDSS 1–3.5 incur costs of around £3350 per annum compared with £9560 per annum at EDSS 6.5–8. Similar published data on health utility show that the health value of time spent in DSS states decreases with increasing DSS step.

Conclusions

MS is a chronic disease of long duration affecting a wide range of human functions. Short research studies of treatment efficacy cannot fully assess meaningful outcomes nor deliver the information needed for health economic analyses. All MS patients should be better monitored throughout the course of the disease both to improve their care and to better understand the natural history of the disease. New methods need to be developed for researching treatments of chronic diseases.

The development of a model of MS progression should incorporate information on costs and QoL at different stages of the disease in order to examine the long-term cost-effectiveness of any changes in progression.

Research recommendations

The following research recommendations have been identified.

- Trials on interventions for MS should be longer in duration to address the range of morbidity characteristic of the disease.
- More information is needed on the effects of MS on QoL and the costs relating to symptoms and disability.
- The (E)DSS requires further development to address its shortcomings in this disease.

Comprehensive data on the progression of MS patients over the long term, including symptoms experienced and rates and length of relapse, are needed for each (E)DSS state to enable accurate modelling of the impact of disease progression.

Chapter 1
Introduction

Aims of the report

This report was commissioned by the Health Technology Assessment (HTA) Programme on behalf of the National Institute for Clinical Excellence. It is intended to provide a source of reference for development of guidance on the management and treatment of patients with multiple sclerosis (MS).

The overall aim of the report is to consolidate and summarise published evidence related to the general natural history and epidemiology of MS. Such information will have direct relevance to the following processes:

- assessment of patient needs
- appraisal of available treatments
- preparation of guidelines for the management of MS
- allocation of resources.

The report is a review of a substantial body of literature for these specific purposes only; it is intended to be neither detailed nor definitive.

Natural history of MS

The natural history of MS, as a description of the patterns of disease progression over time, is crucial to the understanding of the health, social and economic impact of the disease on the individual, their family and carers, and society as a whole. Interventions are intended to change the natural history for the better, and the clinical and economic benefits of those interventions must be judged against the (untreated) natural history.

The natural history will also have a bearing on the conduct of clinical trials of interventions and the interpretation of their results. As MS is a disease characterised by wide variations between patients and for the individual over time, it is particularly important that this variability is taken into account. With trials and treatment being directed at subgroups of patients it is important to understand the natural history of MS in those subgroups, particularly in respect of the continuing validity for an individual patient over time in a chronic disease.

Guidelines based on a clinical assessment of benefit should reflect a clear understanding of treatment benefits to the individual patient compared with changes that might have been seen without treatment. Current guidelines use the classification of MS, based on the course of the disease (relapsing-remitting, secondary progressive, etc.), relapse rates and disability status scales as elements of the treatment criteria; all of these are subject to substantial uncertainties.

Natural history issues to be addressed

The following issues need to be considered in the development of MS-specific management guidelines.

- **MS-related morbidity and mortality**: This needs to include a description of the range of symptoms and associated disabilities endured by MS patients both at an individual and population level.
- **Instruments for measuring disability**: There should be an assessment of the validity of the current instrument for describing disability, the Expanded Disability Status Scale (EDSS).
- **Classification and prognosis of subgroups**: The validity of that classification for the individual patient over time (i.e. any tendency to move between categories) needs to be assessed. Within the relapsing-remitting group, the pattern of relapse rates needs to be described.
- **Models of progression**: Model(s) of the progression of disability, using the EDSS, need to be constructed, if possible, in a way that would permit adjustment of the various coefficients according to the results of clinical trials, and thus permit an estimate of benefit covering a period longer than typical trials.

Epidemiology of MS

Despite intensive epidemiological investigation over many decades in many parts of the world, the geographical distribution and the true prevalence and incidence of MS remain uncertain. In recent years a clearer understanding of the distribution of MS has emerged, though debate continues and uncertainties remain. Variations in prevalence have

long been associated with latitude, which is of key importance if services for MS are to meet the needs in an equitable manner across England and Wales, without causing inequities in other services.

There are three key factors that determine the **true biological prevalence** of a disease.

- **Case definitions**: Studies have used a variety of case definitions. Some are unique to a particular study but others use a small number of accepted 'standards', with later ones typically being enhancements of earlier criteria. The early studies in Scotland used the criteria of Allison and Millar,[1] while more recent studies have used those proposed by Poser and co-workers.[2] (though Allison and Millar may also be reported). Other criteria have been used in this country and other parts of the world.
- **Incidence**: Changes in incidence are likely to occur if there are changes in either the environmental factors that cause MS or in the genetic make-up of the population. Changes in environmental factors can be rapid (e.g. epidemics of infectious diseases or environmental pollution), while population genetics change very slowly.
- **Duration**: The life expectancy of the general population is increasing and it would be surprising if that were not also the case for sufferers of chronic diseases. Survival expectancy for MS patients in 1917 was estimated to be 12 years[3] and was still only 12.6 years in 1957 in Switzerland,[4] but this figure had increased to 30 years by the 1980s.[4,5]

In assessing prevalence and incidence, the degree of case ascertainment is of crucial importance. Repeated surveys are likely to identify increasing numbers as awareness is raised. The place of the survey will have a bearing, with surveys restricted to tertiary centres likely to miss less severe cases. However, surveys from such a centre, serving well-integrated primary and secondary services and running a patient register are likely to generate the most accurate estimates of true prevalence.

Given all these sources of variability, there remain high levels of uncertainty in estimating the current incidence and prevalence of MS across England and Wales, and estimating any likely future changes.

Epidemiology issues to be addressed

The following specific issues need to be considered in the development of MS-specific management guidelines.

- **Changes in prevalence**: Estimates of current prevalence and incidence of MS in England and Wales and their likely changes with time are needed.
- **Geographical variation**: There needs to be an attempt at quantifying any systematic variation in prevalence across England and Wales. The 'latitudinal gradient' long associated with MS prevalence, if it applies to England and Wales, might have considerable implications for differential resource needs (further exacerbating the existing south–north gradient in morbidity for most other diseases). There also appears to be a genetically determined variation in disease prevalence relating to ethnic origins. The reality may be a mixture of these elements with a small general latitudinal gradient superimposed by larger changes at national/ethnic boundaries, though the latter may have little impact in England and Wales.

Modelling the burden of morbidity and disability

MS is a chronic and somewhat unpredictable disease[6] comprising different disease types, ranging from a mild, benign course associated with little disability to a chronic progressive course with rapidly accumulating disability. The evaluation of new interventions for MS is exceptionally difficult due to the considerable uncertainty surrounding the nature and course of the disease. Although a number of valuable studies have examined the epidemiology and natural history of the disease,[1,7–10] there is, as yet, no definitive source of data from which to draw conclusions about the prognosis of patients and expected course of the disease.

Information on the natural history of MS is vital in understanding the potential long-term implications of interventions for the disease, particularly disease-modifying drugs, such as the new immunomodulatory therapies, and in considering the potential impact of introducing drugs at different stages of disease progression. As these long-term implications are rarely examined within trials, it is necessary to model the course of the disease and model long-term effects of interventions in order to gain a realistic understanding of benefits.

Modelling issues to be addressed

The purpose of this section of the report is to first identify and review the existing modelling

literature within this field, and then to discuss and contrast the potential value of various aspects of these models to the production of disease management guidelines. This information is then used to outline the structure of a theoretical model that could reflect the course of the disease, in terms of disease progression and resource use at different stages of the disease. The outline structure of the model is intended to make use of existing sources of information about the natural history of the disease, and incorporate information provided by existing modelling studies.

The proposed natural history model is intended to provide estimates of the expected disease progression for a representative cohort of patients from diagnosis or onset of disease until death, and to provide an indication of the burden of morbidity at different stages of the disease in terms of the number of quality-adjusted life-years (QALYs) lived by the cohort for different progression states.

Ideally such a model, once sufficiently evidence-based, should permit modelling of 'what-if' scenarios in an attempt to take into account the potential progression-altering effects of treatment (as indicated by trial results), and thus provide theoretical estimates of the impact on the QoL of patients with MS.

However, difficulties experienced in obtaining good-quality natural history progression data, at a low enough level of disease classification, make the development of such a model impossible at the time of writing this report.

Chapter 2
Methods

Search strategy for natural history and epidemiology

The initial aim of the search strategy was to search for all papers relating to the natural history and epidemiology and prognosis of MS using established review search standards. An initial scoping search of MEDLINE was carried out for cohort studies and models relating to MS and for reviews relating to the epidemiology of MS. Full searches were then undertaken on MEDLINE, EMBASE and the Science Citation Index. Date and language restrictions were not applied. The search strategies for MEDLINE are shown in appendix 1. Search strategies for other databases are available from the authors.

The literature searches retrieved over 5000 references, including duplicates. It was considered impractical to systematically review all the indicated papers due to the resource constraints of a 'rapid review'. Instead a search technique called 'citation pearl growing', more commonly and recently associated with methodological reviews, was applied. The 80-page bibliography of references listed in *McAlpine's Multiple Sclerosis*,[11] was used to identify relevant references. This book is the definitive British text on the subject, representing the cumulative effort of many experts over many years. The reference lists of these papers were then handsearched for further references and so on.

Inclusion criteria

Quality and content 'standards' criteria were applied in filtering the epidemiology studies identified. The criteria were selected to recognise the underlying complexity of the epidemiology topic and to ensure a tight focus on studies having adequate quality and availability of information pertinent to the purposes of this review (these criteria were interpreted as desirable rather than necessary conditions for inclusion).

- Case definition/diagnostic classification system described (preferably Allison and Millar[1] and/or Poser and co-workers[2]).
- Methods of case ascertainment described (ideally from multiple sources).
- Time series conducted in the same place.
- Geographical studies/series conducted over a limited time span.
- Consistency of observer(s) and of case definitions across time and place.
- Larger studies, ideally with over 100 cases (even with 100 cases the estimate of prevalence/incidence would have 95% confidence intervals of 20%)

The natural history search focussed on longitudinal studies of cohorts of patients.

Search strategy to inform modelling

To review articles relevant to modelling, the original natural history and epidemiology search results (5000+) were searched again for the terms 'cost', 'economic' or 'model', to produce a subset of 499 references. The abstracts of these articles were reviewed to identify any existing models or data sources to inform estimates of the burden of morbidity.

The yield of papers related to the modelling of the natural history in terms of disease progression was very low. A total of 30 papers were considered potentially relevant and these were reviewed.

Chapter 3

Natural history of MS

Total lifetime experience of disease and disability

MS is a progressive degenerative disease of the CNS with a pattern of symptoms that depends on the type of disease and the site of lesions. Relapses are the result of acute demyelination and complete or partial recovery occurs over subsequent weeks or months. As damage accumulates, these symptoms become more permanent and progressive disability ensues. The range of symptoms are similar in relapses and progressive disease, though the severity is greater in relapses, at least until levels of progressive disability become severe. As a potential herald of disease progression, a relapse will be particularly distressing for a patient, over and above the specific symptoms experienced.

Age/sex distribution

Figure 1 shows the age/sex distribution revealed by a survey of MS patients in the south of England.[12]

MS is twice as common in women than men and has a slightly earlier age of onset in women. Prevalence peaks during the most economically productive middle years. Although MS is less common among women of childbearing age, with the social trend towards a delay in childbearing into the fourth decade, MS will have an impact for some women during the most demanding years of motherhood; this may also be a problem for some fathers with MS.

Range of symptoms

Of the 441 patients identified in a survey conducted in south Wales, 301 patients were interviewed and examined.[13] A list of symptoms, with the percentage of the patients affected and the mean duration of symptoms from onset to the time of interview, are summarised in *Table 1*.

The 301 patients interviewed are not representative of the 441 identified. Permission of the general

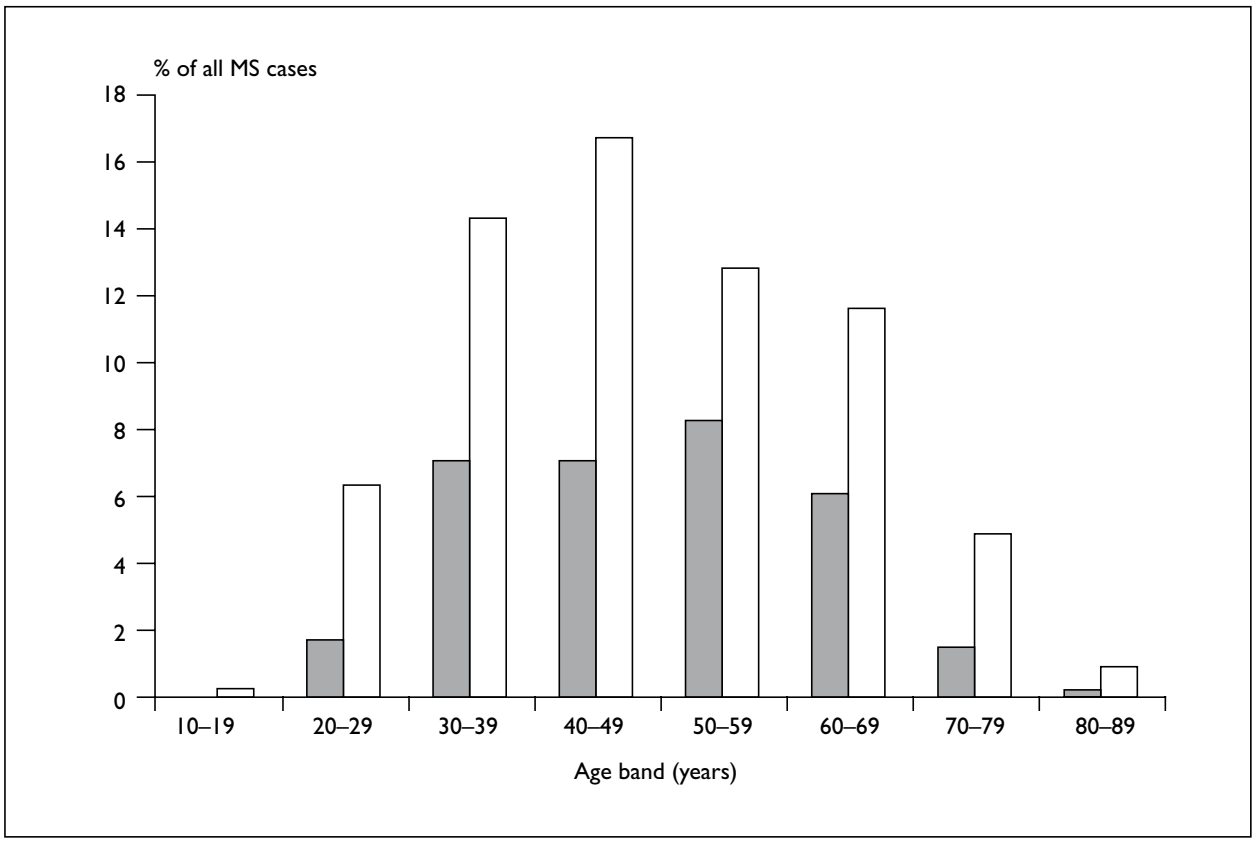

FIGURE 1 *Age/sex distribution of MS (■, male; □, female)*

TABLE I *MS-related symptoms*

Symptom	Symptom at any time (%)	Symptom at onset (%)	Symptom at prevalence (%)	Persistent symptom (%)	Mean time with symptom (years)	Maximum time with symptom (years)
Weakness	89	22	80	62	14.4	52.5
Sensory	87	34	73	52	13.1	44.5
Ataxia	82	11	72	58	12.5	52.5
Bladder	71	1	62	45	8.1	35.5
Fatigue	57	2	48	31	10.9	42.5
Cramps	52	0.6	44	26	8.3	42.5
Diplopia	51	8	26	18	14	44.5
Visual	49	13	33	23	12	40.5
Bowel	42	0	37	19	6	22.5
Dysarthria	37	0.6	25	16	8	38.5
Vertigo	36	4.3	19	13	7.4	28.5
Facial pain	35	2	14	9	8.9	28.5
Poor memory	32	0.3	27	0	6.2	28.5
Headache	30	2	17	7	14	37.5
Neuro-psychiatric	23	0.3	16	7	8.4	26.5
Deafness	17	0.6	13	8	7.6	24.5
Facial weakness	16	1	5	3	11.8	35.5
Dysphagia	13	0.3	10	5	6.4	19.5
Skin sores	12	0	7	4	6.4	40.5
Blackouts	11	0.6	4	2	19.7	35.5
Ageusia	6	0.3	2	0.3	10.1	42.5
Other	10	1	8	5	8.8	38.5

practitioner was needed for the interview and was refused if the patient was unaware of the diagnosis, often when symptoms were mild. On other occasions, the patient declined to be interviewed. It is considered that the 301 patients were probably more severely affected than the average of the 441 patients (Swingler RJ, Dundee Royal Infirmary: personal communication, 1999).

A point prevalence study of all MS patients in Olmsted County, Minnesota (December 1991) was conducted specifically to examine impairment, disability and handicap.[14] The researchers chose the Minimal Record of Disability (MRD) for MS, which was developed by the International Federation of MS Societies, as their instrument. It is composed of the EDSS for impairment (see below), the Incapacity Status Score (ISS) for disability, and the Environmental Status Scale (ESS) for handicap. *Table 2* presents the key findings of the study. (NB: EDSS has been excluded due to a data error in the published paper.)

Weakness typically affects the lower limbs more than the upper, and may first present as weakness only after exertion. Exertion may exacerbate weakness, with rest bringing recovery, a potential problem in the assessment of disability levels (see below). Heat from hot weather or a bath also exacerbates weakness. Respiratory weakness can occur acutely in a relapse, but chronic weakness is more common in established disease and particularly in non-ambulatory patients. Severe respiratory weakness may lead to death or susceptibility to chest infections.

Sensory symptoms include disturbances in touch, pin-prick, vibration, position/postural sensations and paraesthesia. Loss of position sense can lead to loss of use of one or both hands in the absence of weakness.

Bladder problems are predominantly those of urgency, frequency and incontinence. Retention is rare but incomplete emptying is common and can lead to infection. Incontinence is compounded

TABLE 2 *Disability and handicap in patients with MS*

ISS **Function**	**Problem**	**%**
Stair climbing	Unable or needing assistance	58.0
Ambulation	Gait aids, orthoses or wheelchair needed	41.4
Bladder	Significant problem	48.1
Bowel	Significant problem	28.4
Bathing	Personal assistance needed	22.8
Dressing	Personal assistance needed	20.3
Grooming	Personal assistance needed	13.6
Feeding	Personal assistance needed	8.7
Vision	Legally blind or needing very large print	11.7
Speech and hearing	Interfering with communication	13.5
Mood and thought	Needing psychotherapy or hospitalisation	4.3
Mentation	Interfering with everyday activities	18.6
Fatigability	Causing impairment of functioning	43.3
ESS **Function**	**Level**	**%**
Work	Unemployed; not able to attend school or do housework	15.4
Financial	In receipt of external financial support	27.7
Home	Institutionalised	8.0
Personal assistance	Needs ≥ 3 hours a day assistance	17.9
Transport	Needs community transport or ambulance	12.4
Community services	Needed on a daily basis	16.1
Social activity	Dependent on initiative of others or inactive	61.75

by loss of perineal sensation so that patients are unaware of their incontinence. Frequency can lead to exhaustion for disabled patients through loss of sleep and the exertion of repeated visits to the toilet. The frequency of bladder problems as a function of age is described in *Table 3*.[15]

Bowel problems include faecal incontinence (uncommon in ambulatory patients), and constipation, particularly in bedridden patients who may require manual evacuation.

Typically occurring with bladder and bowel symptoms is sexual dysfunction. Symptoms most apparent in men are: difficulties with orgasm and ejaculation, and erectile dysfunction. Women complain of loss of libido, lack of lubrication and failure of orgasm. The general psychological impact of MS, loss of genital sensation, fatigue, weakness and spasticity all add to the effects of a damaged autonomic nervous system.

Pain is a common problem: it can be due to MS-related symptoms and disabilities, or directly due to the disease process. Abnormal posture and gait, muscle spasm and spasticity, and the consequences of steroid-induced osteoporosis can all cause pain. The direct results of neural damage (dysaesthetic limb pain, trigeminal neuralgia and headaches) are all difficult to treat.

Spasticity plays a major part in the loss of mobility and can prevent the use of a wheelchair; associated spasms can even eject a patient from a wheelchair. As the disease progresses, the spasticity and spasms increasingly affect the muscles of flexion, causing pain and making nursing more difficult. Bed sores both result from and exacerbate these spasms.

Recently the evidence for changes in cognitive function for some patients, even in early MS, has grown, though there are poor data on the extent of the problem (the psychometric testing necessary to detect changes being impractical for routine use). As the dementia worsens the typical symptoms of dementia become more apparent including problems with memory and reasoning, and linguistic difficulties. This dementia is essentially independent of physical disability, and there is disagreement as to whether the degree of

TABLE 3 *Urinary symptoms and ability to work over course of MS*[15]

Duration of MS (years)	Bladder dysfunction (%)	Incontinence (%)	Unable to work (%)
0–5	27	10	21
6–10	44	27	38
11–15	56	45	60
16–20	73	51	69
21–25	67	50	77
26–30	71	70	93
30+	70	55	92

dementia is a function of disease duration. The point prevalence study of MS patients in Olmsted County, Minnesota found 4% with dementia severe enough to require supervision.[14] A sample of MS patients on a population-based register in the south of England was assessed for cognitive function with a battery of neuropsychological tests chosen for relative independence from physical impairment.[16] While one in three patients were found to have some form of cognitive impairment, there is no indication of what effect these impairments had on functional abilities and QoL for patient and carers.

Depression is more common in MS patients than in the general population.[17] The literature is poor on the topic with disagreement on virtually every element, almost certainly due to the small numbers in each study. Depression is more common during exacerbations and tends to be mild in severity; it is probably a reaction to 'depressing circumstances'.[11]

Optic neuritis is a presenting symptom in 20% of MS patients. Acuity returns to normal for most patients but progressive loss does occur. Deterioration in contrast sensitivity and colour vision is a feature, as are difficulty in judging distance and blind spots, causing considerable concern for drivers. Like weakness, visual problems are accentuated by heat (e.g. from weather, hot baths, exercise).

A survey of an unrepresentative sample of MS patients (attendees at MS Society meetings: 223 members with MS; 80% response rate) indicates symptom prevalence and the perceived importance of various symptoms to MS patients (*Table 4*).[18]

Fatigue was the most commonly reported current symptom and deemed to cause the most difficulty or distress.[18] This fatigue is considered to be a result from a failure of motor cortex drive. While it can follow ordinary exertion, it is also sometimes unrelated to effort.

Disability and its progression

Kurtzke's Disability Status Score (DSS)[19] and EDSS[20] (where half points were added to Kurtzke's original ten point DSS to produce the EDSS)

TABLE 4 *MS Society postal survey of symptoms*

Symptom	Symptom rated as one of worst (% of patients)	Patients currently experiencing symptom (%)
Fatigue	65	86
Bladder or bowel problems	50	66
Balance problems	44	73
Muscle weakness	44	69
Visual problems	20	–
Pain	18	54
Muscle stiffness	17	64
Muscle spasms	14	51
Numbness/tingling	–	64

TABLE 5 *Distribution of (a) DSS and (b) EDSS scores*

(a) Study	DSS state											
	0	1	2	3	4	5	6	7	8	9	10	n/k
London, Ontario, Canada[8*]	–	17	14	11	6	3	19	18	8	2	1	2
Southern Hesse, Germany[15†]	2.5	18.2	17.1	9.9	10.7	6.3	14.9	5.8	6.6	8.0	–	–
British Columbia[21‡]	2.8	15.5	14.4	13.1	6.7	4.9	21.6	12.4	7.0	1.8	–	–
Kurtzke[20](A)[§]	0.3	0.6	6.9	12.6	16	16	13.1	18.3	12.3	4	–	–
Kurtzke[20] (B)[§]	5.4	3.7	8.3	19.8	19.8	15.7	9.1	7.7	4.8	5.6	–	–
South Wales[13¶]	8.6	6.4	8	14.3	10.9	4.7	17.6	6.7	16.9	5.4	–	0.7
Cleveland, Ohio, USA[24**]	7.7	15.1	13.4	16.5	3.1	1.7	21.2	6.6	11.1	3.5	–	–

(b) Study	EDSS state																			
	0	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5	10	n/k
South Wales[13¶]	8.6	4.7	1.7	5.7	2.3	4.3	10.0	10.6	0.3	2.0	2.7	10.3	7.3	4.0	2.7	9.6	7.3	3.7	1.7	–	0.7
Cleveland, Ohio, USA[24**]	7.7	9.9	5.2	8.7	4.7	10.6	5.9	3.1	0	1.2	0.5	11.8	9.4	3.1	3.5	6.8	4.2	3.5	–	–	–

[*] *From a cross section of 1099 MS patients at final review*
[†] *From 363 patients in a prevalence survey*
[‡] *From 780 patients attending University of British Columbia MS Clinic*
[§] *From Veteran's Administration hospital admissions (A) and World War 2 veterans (B) according to Kurtzke*
[¶] *From 301 (of 441) patients in a prevalence survey*
[**] *From 254 patients in a cohort study*
n/k, not known

have become the most widely used tools for measuring disability in MS patients, despite the many flaws (see below).[21–23]

The scales are ordinal; the distribution of scores among a cross section of MS patients is determined by the time spent at that score, and the rates of entry to, and exit from, that score. The distribution is now considered to be, typically, bi-modal, with fewer patients having scores of 4 or 5 and 8 or 9, but Kurtzke's own work, on army veterans, gives a 'Gaussian' distribution (*Table 5* and *Figure 2*; see also appendices 2 and 3 for a description of DSS and EDSS).

Table 6 shows the mean time at each DSS state for patients who progress; as such it underestimates the mean time spent at a DSS for the MS population in the total course of the disease. Of the patients who are shown not to progress, some would have progressed if followed for longer, and others would stick at a DSS state until their deaths. The cohort would have to be followed to the deaths of all the patients to produce the true mean times at each DSS state. The median times to reach selected DSS scores are also presented.

Table 6 also shows the time spent at each disability state and the proportion of patients progressing, indicating the probability of progressing in any one year, depending on the baseline DSS.[25] Patients at DSS 4 and 5 (and to a lesser extent 3) are more likely to progress than others. It has been demonstrated that at a given DSS state, patients with a disease duration of less than 20 years are more likely to progress over the short term.[7,26]

In the London, Ontario cohort many factors were found to predict the time to reach EDSS 6.[27] Not all these predictive factors were confirmed in a second cohort from Ottawa, Ontario,[26] but this smaller and shorter study would not have had the statistical power to do so. Those clinical factors found by most studies to predict more rapid progression are summarised in *Table 7*.

Validity of (E)DSS

Despite its title the (E)DSS is a mixed impairment and disability scale, though it pre-dates the WHO terminology. Scoring on the (E)DSS depends on a combination of scores from a series of Functional System (FS) assessments and degree of mobility.[20] For the first 3.5 points, only the FS assessments

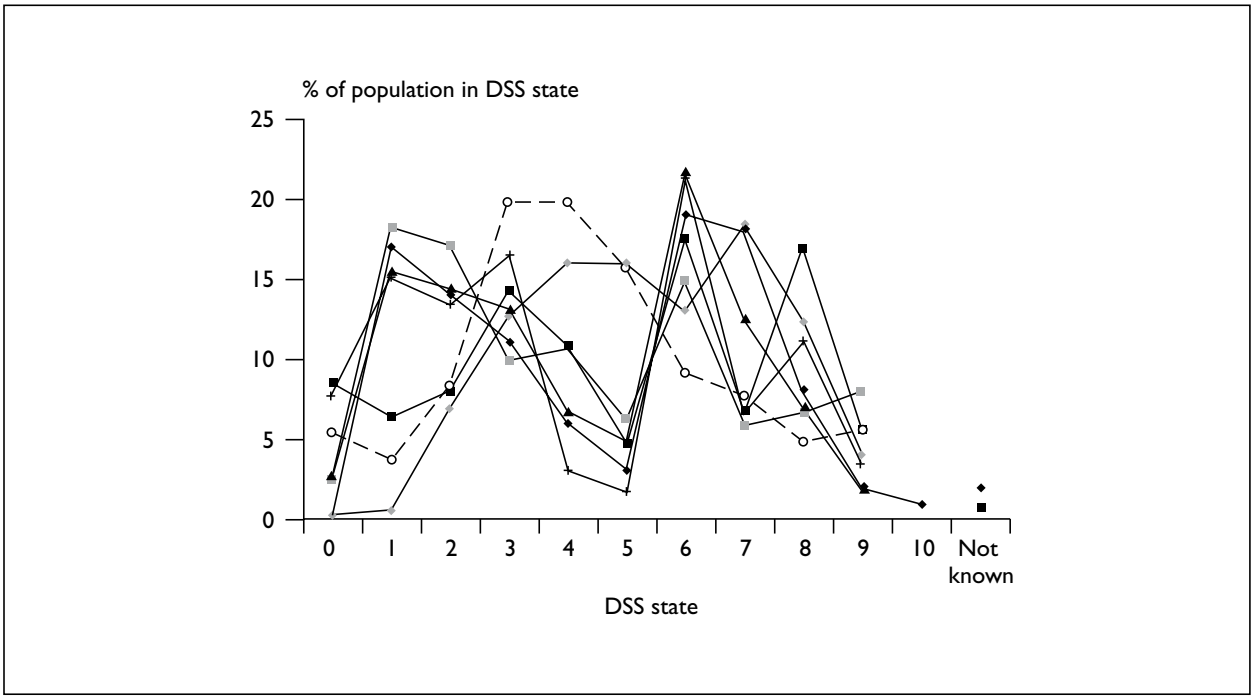

FIGURE 2 *Prevalence of MS by DSS state (–◆–, London, Ontario; –■–, Hesse, Germany; –▲–, British Columbia; –◆–, Kurtzke (A); – –○– –, Kurtzke (B); –■–, South Wales; –+–, Cleveland, Ohio)*

TABLE 6 *Time at each DSS for patients progressing to next state*

Progression measurement	DSS state									
	1	2	3	4	5	6	7	8	9	10
Mean years at DSS[25]	4.09	2.80	1.95	1.22	1.25	3.06	3.77	2.41	2.51	
% Progressing	82	81	82	88	94	60	37	28	41	
Median years to reach DSS[11]			8.13			15.46		26.32		41.18

TABLE 7 *Clinical predictors of disease progression*

Predictors of rapid progression	Predictors of slow progression
Male	Female
Older	Younger
Motor symptoms at onset	Sensory symptoms/optic neuritis at onset
Incomplete recovery	Complete recovery
Short inter-attack interval	Long inter-attack interval
High relapse rate in first years	Low relapse rate in first years
Rapid progression to EDSS 3	Slow progression to EDSS 3

contribute (patient fully ambulatory), and these continue to be the most important factors until score 5. By 6–7, however, the score is essentially concerned with ambulatory status. The FS scores are relatively subjective, using terms such as 'moderate', 'mild' and 'marked'. Assessments of ambulation are of the pass/fail type: 'Able to walk without aid or rest for some 300 metres'.[20] Unfortunately, some of these distances are impractical for assessor rating in the outpatient setting so rely instead on patient reporting.

Assessment of bowel and bladder functions, and of ambulation in the middle scores, depend on symptoms rather than objective neurological examination. Even if walking distances were formally assessed, such abilities are subject to many factors, including diurnal variation in

TABLE 8 *Kappa scores for inter-observer agreement in allocation of EDSS scores*

EDSS/FS	Kappa scores*				
	Noseworthy *et al.*, 1990[22]		Amato *et al.*, 1988[28]		
	Perfect agreement	Agreement to one step	Perfect agreement	Agreement to one step	Agreement to two steps
EDSS	0.62	0.89	0.49	0.94	1.0
Pyramidal	0.47	0.88	0.28	0.95	1.0
Cerebellar	0.32	0.58	0.56	0.87	0.87
Brainstem	0.44	0.90	0.50	0.93	1.0
Sensory	0.31	0.60	0.32	0.93	1.0
Bowel and bladder	0.43	0.82	0.50	1.0	1.0
Visual	0.58	0.81	–	–	–
Cerebral	0.46	0.76	0.32	0.87	0.94

* *0.21–0.40: fair; 0.41–0.60: moderate; 0.61–0.80: substantial; 0.81–1 almost perfect*

abilities, the effects of pre-examination exertion (increasing weakness), and the exertions of the examination itself.

Two studies looking at inter-observer agreement in allocation of EDSS scores (*Table 8*) found the degree of complete agreement to be 'moderate', and agreement to plus or minus one step (i.e. 0.5 score) to be 'almost perfect'. *Table 5* demonstrates the differences in distribution of scores from different observers: that there should be major systematic differences in the populations studied seems unlikely, leaving intra-observer variation the most likely explanation. The relatively good agreement in the 'controlled' conditions of a study may not be applicable to the multiplicity of neurological clinics, except for large changes in EDSS (1–1.5) or 'hard' endpoints such as using walking aid (e.g. stick, crutch or brace), wheelchair-dependent or bed-bound.

EDSS, an ordinal scale, is not a biological variable that follows standard statistical patterns; it is dynamic in the individual, with positive and negative fluctuations set against a temporal trend of a score 'worsening' at variable rates. Among a group heterogenous for EDSS scores, there will be a series of distributions of probabilities of progression, depending on baseline EDSS. In addition, the statistical analysis of data will not be straightforward.

Classification of MS, and its validity

It has been noted that the course of MS follows a number of identifiable clinical patterns, albeit with considerable overlap: these patterns were described by Charcot in 1872[11] and confirmed by McAlpine and co-workers in 1955.[29] The four main categories are:

- relapsing-remitting (RR)
- primary progressive (PP)
- secondary progressive (SP), and
- benign, this latter being essentially retrospective, though many other terms have been used, including chronic progressive and bout/attack onset.

The categories and terms vary over time and with country, due to attempts being made to refine the classification, and thus making the comparison and combining of figures difficult. The category relapsing-progressive, a subcategory of PP with acute worsening, has recently been dropped,[30] and progressive-relapsing, again a subcategory of PP but with superimposed relapses, has also been questioned.[31] To add to this apparent confusion, remissions in RR may be complete or partial, leaving the patient with persistent neurological symptoms. Relapses can continue after the onset of SP, and even in PP, relapses can start 20 or more years after onset.[31] The findings of a number of studies are presented in *Table 9*.

It is to be expected that most RR patients will eventually develop SP disease (*Table 10*). Thus, the distribution of 'prevalence cases' (i.e. the MS population at any one time) among the categories will be different to that of patients at the onset of the disease because these latter patients will not have SPMS. Treatments directed at RR disease will have greater use among the onset

TABLE 9 *Classification of MS by course of disease*

Disease category	% At onset		% At survey point			
	Sweden[7] *n* = 308	**Canada[8] *n* = 1099**	**South Wales[13] *n* = 301**	**USA[14] *n* = 162**	**Switzerland[4] *n* = 947**	**Germany[15] *n* = 363**
RR	79 ('attack onset')	66 ('RR')	49 ('RR')	58 ('RR')	52 ('remittent')	45 ('intermittent')
PP	14 ('PP')	19 ('chronically progressive')	19 ('progressive from onset')	14 ('PP')	31 ('progressive from the beginning')	18 ('chronic progressive: progressive from onset')
SP			28 ('RR followed by progression')	28 ('SP')		37 ('chronic progressive')
Others	7 (subacute or undefined onset')	14 ('relapsing/ progressive' or not known)	4 ('uncertain')		17 ('remit-progr')	

TABLE 10 *Conversion from RR to SPMS over time[8]*

Duration of MS (years)	% Converted from RR to SP
1–5	12
6–10	41
11–15	58
16–25	66
26+	89

group (i.e. new patients), while treatments directed at SP patients will find more common use in prevalence cases. Thus, service planning and resource allocation would look different for the new patients compared with the 'prevalent group'.

Disability increases relatively slowly for patients with RRMS, but accelerates once they have converted to SPMS.[7] Disability increases from the onset of the disease in PPMS but rates of progression are similar for PPMS and SPMS.[7] PPMS is more common in those with older ages of onset and in men (who develop MS later than women).

There is a tendency for the clinical course of the disease to fluctuate considerably in some patients, thus moving them from one category to another; for example, progressive disease may become stable, or stable disease may progress. *Table 11* illustrates this phenomenon, though using somewhat vague definitions.[24]

Patients preselected for trial entry on the basis of relatively rapid progression will have a tendency

TABLE 11 *Changes in categorisation at 2 years in 163 patients*

Disease type at entry	Disease type at 2 years (%)			
	Stable*	**Progressive**	**RR stable†**	**RR progressing†**
Stable*	59.5	32.4	0	8.1
Progressive	29.5	57.4	1.6	11.5
RR stable†	19.5	26.8	9.8	43.9
RR progressing†	20.8	8.3	16.7	54.2

* *No relapses or progression of disability*
† *RR disease without or with progression of disability unresolved 6 months after a relapse*

to regress to the mean. Proportions of patients subsequently becoming stable (a situation that may then persist for a number of years) may vary between trial arms in such a way as to confound outcomes.

The picture for benign MS is less clear, perhaps because it is a retrospective classification: the proportion of MS patients fortunate enough to escape significant consequences seems to be up to 20%, but this figure may include patients with a diagnosis of 'possible' MS and thus may not actually have had MS.

Relapses and relapse rates

The literature on relapse rates shows wide variations in reported rates and changes in rates with time. Definitions vary (even between recent intervention trials), and some data (retrospective) rely on patient self-reporting. An intercurrent illness may result in symptoms that mimic a relapse.

There is a tendency for RRMS to start with a period of relatively high relapse rates but periods of higher relapse rates can also occur at any time in the course of the disease. This unpredictability is of great importance if clinicians are expected to assess response to treatment in an individual patient. The relationship between the cumulative number of relapses for a patient and the onset of the progressive phase and increasing disability is of importance in assessing the benefits of drugs that reduce the number of relapses.

A purely random rate has implications for studies that select patients with higher than average (pre-trial) relapse rates for trial entry. Such selection from a population with random relapse rates would result in rates in trial years falling due to regression to the mean; this would not be the case if that high relapse rate predicted future high relapse rates. More problematic are the consequences for the ability to assess response to treatment as part of clinical guidelines, particularly when patients are selected for treatment on the basis of high relapse rates.[32] Most of these patients would appear to have a better relapse rate after treatment started due to regression to the mean. In addition, the predictive power of changes in relapse rate as an indicator of treatment response would be confused by the random fluctuations typical to the disease, even among a group expected to suffer high relapse rates. Health economic analyses will need to take account of declining benefits as relapse rates decline naturally and thus marginal benefits of treatments also decline.

It has not proved possible to identify any reports of the changes in relapse rates with time in individuals, though a longitudinal study[33] did show that high relapse rates in the first 2 years did predict a more rapid accumulation of disability; this might indicate that high relapse rates in the first 2 years predict, to some degree, sustained high relapse rates. It has been claimed that relapse rates in the early years of the disease predict rates later in the disease, but no data are provided to support this.[29] Another study claims that: "we could not show… that at a given moment of its course, knowledge of previous events permits anticipation of the occurrence of the next bout", but also provides no data to support the claim.[34] Examples of published relapse rate data are summarised in *Table 12*.

Some of the differences in reported rates have been related to the fact that the first (re)lapse is often the presenting relapse that establishes the diagnosis and defines onset, and thus, the first year has a minimum rate of 1 in this relapse-onset group.

In the London study, more than four relapses over the first 2 years were seen in 4% of the total RR population (3% of entire cohort) and 12% of the seen-from-onset group.[33] However, no information is provided on relapse rates subsequent to those first 2 years. Importantly, the most recent analysis of these data[38] has shown that this high number of relapses (greater than four in the first 2 years) is highly predictive of more rapid progression to disability. Thus the median times to reach DSS 6 and 8 were 7 and 15 years, respectively, compared with at least 14.5 and 24.5 years respectively for those experiencing four or fewer relapses ($p = 0.0001$).

Data in the recent PRISMS study[39] provide some insights into relapse rate patterns over the course of the disease, for patients selected with high relapse rates. The duration of the disease at trial entry varies greatly. The interquartile range of duration of disease for the UK patients was 2.9–11.4 years, indicating that MS patients can suffer high relapse rates many years after onset. There is insufficient detail in these data to identify any relationship between duration of disease and relapse rates, or to show whether patients with high relapse rates late in their disease had suffered high rates throughout their disease history.

TABLE 12 *Relapse rates*[*]

McAlpine & Compston, 1952[35†]		Lhermitte et *al.*, 1973[34†]		Goodkin et *al.*, 1989[24]		Weinshenker et *al.*, 1989[8†]		Patzold & Pocklington, et *al.*, 1982[36]		Gudmundsson, 1971[37†]	
Year(s)	**Relapse rate**	**Year(s)**	**Relapse rate**	**Year(s)**	**Relapse rate**	**Year(s)**	**Relapse rate**	**Year(s)**	**Relapse rate**	**Year(s)**	**Relapse rate**
1	0.23	0–5	0.58	1	0.65	1	1.57	1	1.85	1	0.31
2	0.42	0.1–5	0.30[‡]	2	0.61	2	0.35	2	1.1	2	0.2
3	0.34			3	0.65			3	1	3	0.2
4	0.33							4	0.85	4	0.23
5–9	0.31	6–10	0.33					5	0.65	5	0.18
10–14	0.26	11–15	0.33					7	0.75	6–10	0.17
15–19	0.22							9	0.25	11–15	0.13
20–24	0.22							11	0.6	16–20	0.07
25–30	0.2							13	0.28		
								15	0.3		
								19	0.2		
Mean	**0.39**	**Mean**	**0.48**					**Mean**	**1.1**	**Mean**	**0.14**

[*] *Relapse rate is the annual per person rate*
[†] *For RRMS patients only and including (or not explicitly excluding) onset relapse in year 1*
[‡] *Excludes the first month and therefore the presenting relapse that establishes the diagnosis in some patients*

Discussion and conclusions

Symptoms, impairments, disabilities and handicaps

The selected nature of MS patients who attend secondary care has led to a distorted view of the prognosis of MS, mirrored by patient fears following diagnosis. The information from studies of a whole MS population (as complete as is possible to ascertain), indicated that at least 50% of MS patients remain ambulatory at 15½ years from onset. Nonetheless, the burden of symptoms and impairment is considerable, and significant proportions of patients have major disabilities and handicaps. At any point in time about 30% of MS patients are essentially restricted to a wheelchair or worse, with about half confined to bed; these are levels of disability that may be endured for 10 years or more.

Mean duration of significant symptoms such as weakness can be 14–15 years, while maximum periods with them can be 50 or more years (again for weakness). The benefits of new drugs should therefore be considered in the context of these disease burdens (symptoms, impairments, disabilities and handicaps), and also set against any unmet need to deliver a broad package of services to MS patients.

Thus far, trials have concentrated on demonstrating changes in hard endpoints over short periods of time. These endpoints represent only a fraction of the morbidity burden in a disease with a mean duration of at least 30 years. MS demands longer trials that address the range of morbidity characteristic of this distressing disease. The trials would also provide the data necessary to assess the economic benefits of a range of interventions needed to improve the lives of MS patients.

Assessment of disability and disease progression

The Kurtzke disability scales (DSS and EDSS) are limited in their validity as they cover only part of the spectrum of problems endured by MS patients, and in particular, concentrate on ambulation. There are also considerable technical problems, as indicated by between-study variability. Nonetheless, they are the best available and the most widely used.

There are problems in assessing endpoints in MS studies, be they relapse rates or disability score, both of which have elements of assessor subjectivity. The psychological state of the patient, in a disease associated with reactive depression, may affect endpoints. If unblinding occurs, which is likely to be the case when side-effects are

common, then the knowledge may bias the assessor or affect the clinical status of the patient. With a disease of such large variability and small improvements in outcomes, unblinding could easily favour the treatment arm. Trials should demonstrate the use of fully blinded assessors, but patients cannot be blinded from the side-effects. In the case of trials looking at progression, a study group heterogeneous in terms of baseline EDSS scores may conceal potential confounding due to the differing probabilities of progression that depend on EDSS at entry. Relapse rates in the first 2 years are predictors of rates of disease progression but have not been addressed in trials, though rates of progression prior to trial entry, another predictor, probably have. Reviewers will need to be certain that the statistical methods used to test hypotheses are appropriate for the often complex distributions of patients seen in MS: entry into trials may have been at greatly different times from the onset with no clear indication of the implication this may have for variation in subsequent relapse rates and progression. Even when an attempt is made to address some of these predictive variables through the application of multivariate analysis/covariance techniques, there needs to be a clear understanding as to whether the available data at subgroup level can support those methods and, indeed, that all known confounders have been addressed.

Relapse rates

In recent years, MS categories based on the course of the disease have been used to select patients for clinical trials and subsequently for treatment. Thus, patients with RR and SP have been the subjects of clinical trials that study the effectiveness of immunomodulatory drugs and that result in licence indications and clinical guidelines. In planning services and allocating resources, this categorisation and the estimates of the numbers of patients in each category are of considerable importance. Treatment decisions must be made relatively early on in the disease process, but **accurate** categorisation is essentially a retrospective process. Selection from the prevalence group gives different figures from an incidence group. The inclusion of a patient in a treatment group will very much depend on when the patient is assessed; serial assessments could result in a large proportion of the MS population being identified as eligible for treatment.

While there is some evidence that relapse rates at onset are predictive of outcomes (i.e. the time to the SP phase), there is no indication that this has been the rationale for the selection of patients with higher than average relapse rates in the RRMS studies. While the reason for the selection is not given, it can be presumed that the selection was intended to increase the power of the studies without increasing the numbers of patients; it is easier and quicker to demonstrate a reduction in relapse rate if the starting rates are higher, resulting in a higher aggregate number of relapses over a given period. The adoption of the principles of evidence-based medicine has meant that guidelines typically parallel study entry criteria as this is the only evidence available. The patient group that might be chosen on clinical grounds as the most in need of treatment may differ from the trial group; health economic imperatives may dictate a different group again. Furthermore, cost-effectiveness ratios will vary, often considerably, depending on treatment criteria, particularly when the risk of outcome event varies markedly between groups at the start of treatment (e.g. coronary heart disease risk and the effect of treatment on absolute outcome rates). In the absence of patient stratification in trial data, it is impossible to be sure of the consequences of patient selection criteria differing from trial entry criteria. In addition, where criteria are open to interpretation, observer variation and well-intentioned manipulation, uncertainties increase and treatment effectiveness will decline substantially from trial efficacy.

There are many problems with assessing relapse rates, and these will be even greater outside of trial settings. Selection of patients for treatment in the clinic setting, based on trial entry criteria, may have sensitivities and specificities far short of levels needed to mirror the trials, because of the uncertainties in categorisation (for the observer) and the labile nature of a patient's true clinical status. This variability in disease status in the individual patients over time makes guidelines based on assessment of change in status when on treatment, as a means of deciding on continuation of treatment ('trial of treatment'), highly questionable. Even ('*n*-of-1') placebo-controlled trials on individuals seem unlikely to work as a tool to discriminate responder from non-responder. These issues, particularly the tendency for patients to change categories, require clear guidelines on treatment cessation as well as instigation if there is not to be an unquantifiable demand on resources.

General interpretation and application of trial data and research issues

There are many opportunities for confounding variables to be unequally distributed between

treatment and control arms, and the data provided in trial reports may be insufficient to check for this possibility. Although this can result in either false-negative or false-positive results, submission and publication bias will favour those confounded trials with 'positive' findings.

There are many remaining uncertainties concerning valid scales of disease progression as well as a basic understanding of the overall effect of this disease both at individual and population level. Relapse rates have not been properly studied throughout the course of the disease despite well-organised longitudinal studies.

As yet unpublished data analysis from the London, Ontario cohort does suggest that a small percentage of the MS population suffering high relapse rates in the first 2 years of the disease are at risk of a much more rapid progression to disability, reaching the point of significant ambulatory difficulties (DSS 6) in half the time of other RRMS patients. Although there is no trial evidence relating to this subgroup, if the average benefits of the immunomodulatory trials applied equally to this subgroup, then directing treatment at this subgroup would be more cost-effective, and benefits in terms of delayed progression would show early (by comparison to the London, Ontario cohort by way of historical controls).

Chapter 4
Epidemiology of MS

Although international data are not of direct relevance to the epidemiology of MS in England and Wales, they help with the understanding of the issues of latitudinal gradient and the impact of genetic/ethnic determinants, all of which are of direct relevance.

(NB: all figures quoted for prevalence or incidence are per 100,000 population figures and are not age-standardised.)

Estimates of baseline prevalence in England and Wales

Table 13 summarises the results of prevalence studies in England and Wales (the most recent survey has been quoted where more than one exists). Unfortunately, a complete set of data to one diagnostic standard is not available. As the Poser[2] criteria are the most recent and most rigorous, this set has been chosen (for definite and probable cases) except for Sutton[40] and Suffolk[41] data where cases based on Allison and Millar criteria[1] (probable and early cases) are reported.

These studies have been aggregated to produce an average prevalence for an average year and latitude, weighted by survey size. As the Leeds survey[42] is the largest but gives an unusually low prevalence, its inclusion substantially changes the average estimate (prevalence 100 versus 109, for latitude 52.2 versus 51.7 and year 1991 versus 1989.5).

Also shown in *Table 13*, is an estimate of prevalence using the Value-Added Medicinal Products (VAMP) General Practice Research Database (GPRD), containing clinical information on 3,617,890 patients registered with participating general practitioners (GPs).[43] This gives a prevalence for this population of 102 in 1991. However, information is not available to calculate an average latitude for this group.

It is likely that even the most intensive of surveys using a range of sources will miss cases; most surveys have only included neurology clinic and GP records. In recent years, attempts have been made to adapt the techniques of biologists/ecologists to estimate the numbers of missing cases. This 'capture–recapture' methodology relies on repeatedly resampling a frame and looking at the degree of overlap between samples to calculate missed cases. This is within an essentially **random** process (animal movements in and out of frame and observer error); MS surveys use a variety

TABLE 13 *England and Wales prevalence studies*

Place/study	Year	° Latitude	Prevalence/100,000*	No. of cases*	Population
Leeds[42]	1996	53.8	72 (65–77)	522	732,061
Rochdale[45]	1986	53.6	112 (97–126)	232	207,600
Cambridgeshire S[46]	1993	52.2	131 (119–145)	380	287,700
Cambridgeshire N[47]	1993	52.5	107 (95–116)	401	378,959
Suffolk[41]	1988	52.2	185 (137–232)	58	31,379
SE Wales[48]	1988	51.7	101 (90–111)	379	376,718
Sutton[40]	1985	51.4	104 (88–119)	176	170,000
Southampton[12]	1987	50.9	95 (85–104)	395	417,000
Sussex[49]	1991	50.8	111 (103–120)	665	596,594
Average†/total	1989.5	52.2	100 (97–104)	3208	3,198,011
Average†/total (excl. Leeds)	1991	51.7	109 (105–113)	2686	2,465,950
England (VAMP database)[43]	1991	n/k	102 (98–105)	3677	3,617,890

* *Poser* et al.: *definite + probable cases; or, for Suffolk and Sutton, Allison & Millar: probable + early cases (95% confidence intervals)*
† *All averages weighted for population sizes. Average years expressed using same weighting*
n/k, not known

of data sources that are both **interdependent**, and yet **systematically** different (records from GPs, hospitals and voluntary organisations). Given the remaining uncertainties[44] and novelty of the approach, it does not seem appropriate to attempt to apply the method here. Expert opinion puts the proportion of missed cases at between 10% and 20%, though less severe forms of MS may be over-represented among these missing cases, and thus their unmet needs (and resource requirements) may be marginal.

Some expert opinion suggests that the Leeds[42] estimate remains out of step with most data and is suspect. However, there is nothing unusual in its methods to point to any particular problem, and its size mitigates the possibility of a chance finding. However, as the Leeds study covers the largest population and thus the calculation is sensitive to it (whereas, for example, the Suffolk study with its high rate covers only a small population), analyses both with and without the Leeds data[42] are presented, by way of a sensitivity analysis.

Estimates of latitudinal gradient

Changes in latitude are associated with changes in both environment and the genetic make-up of peoples, the latter being characterised by a slow drift of changes in complex genotypes ('genetic cline'), such as those associated with blood group and the human leukocyte antigen (HLA) system, which may be important in MS. However, there may also be geographic patterns of greater genetic changes relating to ethnic origin and historic ethnic migration, particularly in northern Europe. These patterns may possibly be preserved in the ex-British colonies, with migrants searching for climates similar to those of their geographical origins.[11] Because of the genetic similarities between the USA, Australia and New Zealand, and the UK, data from these countries have been examined. Data from Italy have also been examined to represent a contrast.

Published latitudinal prevalence studies

There is only a change of 5.5° of latitude across England and Wales and only 10.5° across the UK including the Channel Isles. By contrast, mainland USA, excluding Alaska, covers 24° of latitude, Australia 32.5°, and Australia and New Zealand together, 36°. Italy has a 10° change.

Where surveys have been repeated, the most recent data have been used. In each case an exponential curve was found to give the highest r^2:

$$y = bm^x \quad \text{or} \quad y = be^{\ln(m)x}$$

where

y is MS prevalence
x is the latitude
b is a constant (≡ prevalence at equator), and
m is the 'latitudinal gradient' of the curve.

The data are summarised in *Table 14*.

UK prevalence data[11,44,50]

It should be noted that neither data from England and Wales (including Channel Isles) nor Scotland and Northern Ireland, as two separate sets, show a latitudinal gradient, though with so few data points covering little change in latitude, perhaps that is not surprising (*Figure 3*). The data set is not of the best quality as the researchers and methods differ, as do the dates.

UK death data (source: ONS)

Mortality data from England and Wales should represent a reasonably good quality set of data as there is no reason to believe that there is a systematic geographical bias in ascribing cause of death to MS. There is a possibility that local surveys could influence certification through raising awareness, but this is likely to be less of an affect than on prevalence as the giving of a clinical diagnosis at death will be more influenced by past diagnosis. Because of the repeated changes in the administrative boundaries of health services, Office of National Statistics (ONS) Standard Regions have been used to assess geographical trends of crude death rates (*Figure 4*).

The best fit in this case is a linear trend ($y = mx + b$); the slope is negative, that is, rates **decline** with increasing latitude. However it has an r^2 of just 0.03 and very large standard errors for estimates of m (slope) and b (intercept). This finding almost certainly reflects the inadequacies of the underlying data, particularly the small changes in latitude across England and Wales.

Non-UK data[51]

The USA data appear to be of high quality, being from one source and date and collected in a single study. There seems to be little opportunity for systematic bias, though the study is predominantly in men. The geographical patterns of MS in US veterans has been described in the form of case–control ratios for each USA State.[51] A more recent review of USA data by epidemiologists[54] identifies the Mayo Clinic 'centralised diagnostic index' (disease

TABLE 14 *Latitudinal changes: descriptions of the studies and results*

Source/type	Setting	Period	° Latitude	Fit (r^2), gradient (*m*), prevalence at equator (*b*)	Estimated change from latitude 50–55.75 (%)	95% CI (based on range of *m*) (%)
Reviews and primary study[11,44,50]	UK	1974–96	49.2–60 N	r^2 = 0.42 *m* = 1.072 *b* = 2.94	152	120–190
Primary study: case–control study of cohort of US army veterans; predominantly white males; single investigator[51]	USA	1940–69	28–47 N	r^2 = 0.72 *m* = 1.084 *b* = N/A	162	149–175
Review: figures from original studies adjusted for population ethnic mix; collaborative team of investigators[52]	Australia, New Zealand	1981–83	18–46 S	r^2 = 0.90 *m* = 1.074 *b* = 3.02	154	139–170
Primary study of deaths from MS 1970–81[52]	Australia, New Zealand	1970–81	25–41 S	r^2 = 0.86 *m* = 1.072 *b* = N/A	152	140–165
Simple review of primary studies[53]	Italy	1962–81	37–46 N	r^2 = 0.50 *m* = 1.098 *b* = 0.29	175	139–219
Original analysis of MS deaths data (ONS)	England and Wales	1988–98	50–55.75 N	r^2 = 0.03 (linear) *m* = –0.023 *b* = N/A	91	63–205
Best estimate for UK				r^2 = 0.85 *m* = 1.072 *b* = 3.15	149	144–155

CI, confidence interval; N/A, not applicable

register) covering Olmsted County, Minnesota, as the most complete source of data, giving the prevalence as 102 (Poser system, definite plus probable cases). Applying **this** prevalence to the case-control ratios (Minnesota ratio = 1.98), prevalence rates for USA states can be estimated for the year 1985.

The Australia and New Zealand prevalence study also appears to present good quality data. It covers a 3-year period and, although the studies were by three different teams, those teams collaborated in a subsequent review of their research, permitting variance in methods to be addressed. However, the Poser criteria were not used in the study and thus the values tend to be higher than in other studies, but these are the only data currently available for this region.

In contrast, the Italian study is a little more suspect, covering a longer period, and was conducted by many different investigators using different methods.

Combined data

The USA, UK and Australia and New Zealand data have been combined to generate an estimate of average prevalence (*Figure 5*). The curve suggests that a link between latitude and prevalence does exist. However, the exact applicability of this relationship to a UK context remains unclear. In addition, the importance of the ONS published data is doubtful.

Estimates of changes in prevalence with time

Improved awareness of MS by professionals and the public can result in increased case detection causing an apparent increase in both incidence and prevalence; this may be what has happened in the repeated surveys in Scotland and Northern Ireland. Studies of incidence have provided contradictory evidence of increasing, decreasing, constant and fluctuating incidence with time. Changes would

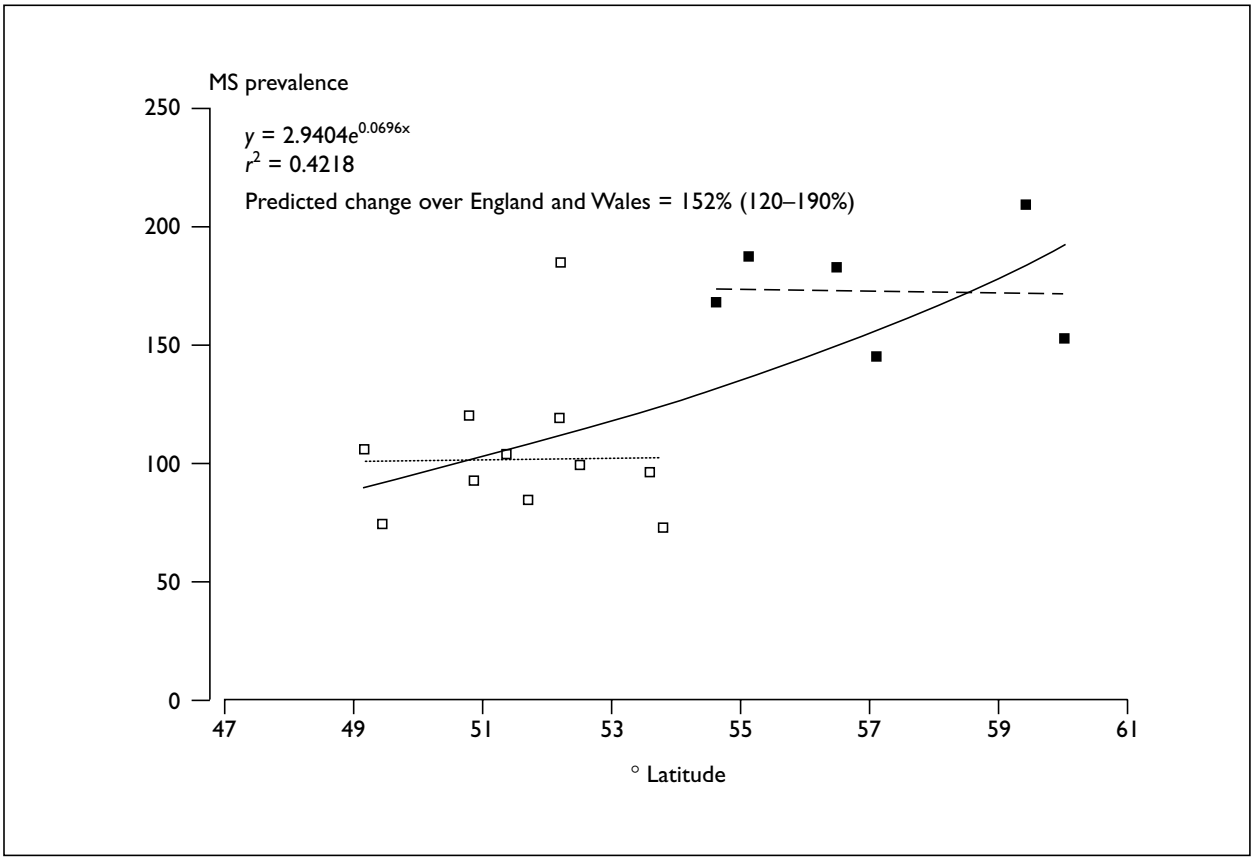

FIGURE 3 *Geographical trends in UK prevalence data[11,44,50] (□, England, Wales and Channel Islands; ■, Scotland and Northern Ireland; ——, UK trend; ·····, England, Wales and Channel Island trend; – – – –, Scotland and Northern Ireland trend)*

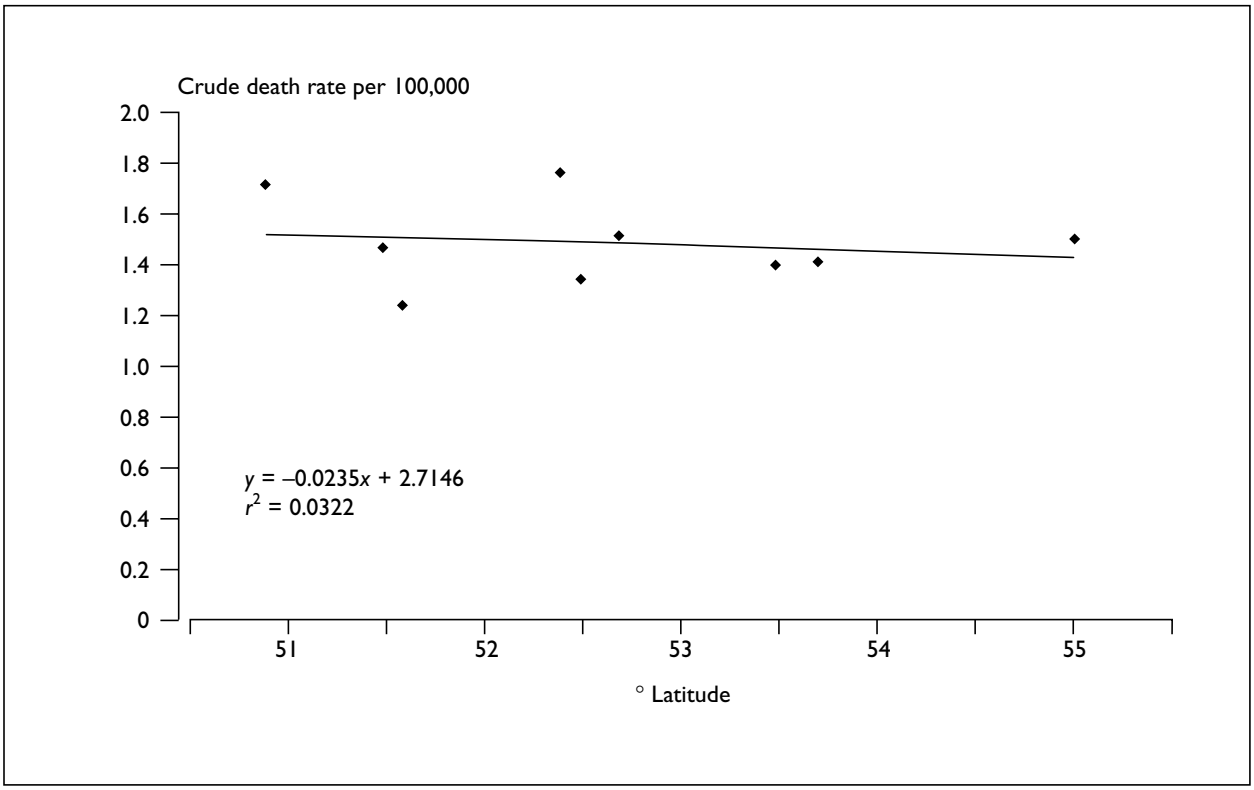

FIGURE 4 *Geographical trend in MS deaths in England and Wales 1988–98 (ONS data)*

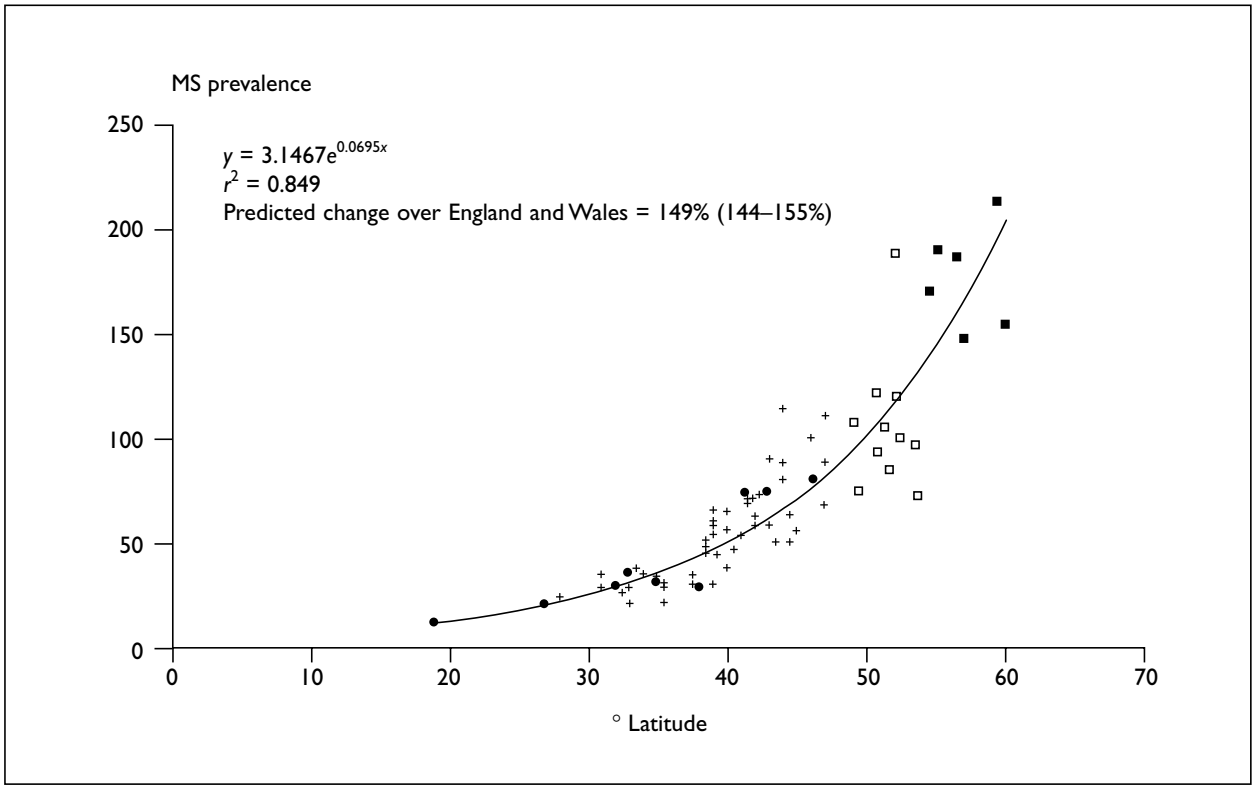

FIGURE 5 *Geographical trend for combined data (USA, UK, Australia and New Zealand) (+, USA; □, England, Wales and Channel Islands; ■, Scotland and Northern Ireland; ●, Australia and New Zealand; ——, combined trend)*

need to be due to changes in the genetic composition of populations or changes in environmental factors that cause MS. Population changes over the periods concerned are improbable. Changes in environmental factors are possible and consistent with, for example, theories of infectious causation. However, data available do not permit a formal testing of such theories or quantitative estimates of their possible effects on incidence and prevalence in England and Wales. **It is therefore assumed in this report that incidence rates are static**.

Prevalence is a function of survival such that, as an approximation:

prevalence = incidence × mean survival

It is assumed here that age of onset of MS has not changed over time and has been estimated at about 30.5 years.[8,15,34] ONS data have been used to estimate the increase in mean age at death from MS since the 1950s. The data are presented in *Figure 6*.

Problems with the accuracy of death certification are well known; however, some aspects of mortality data are much more robust than survey-based prevalence data. While they may not precisely describe the reality at any point in time and place, changes in recorded mortality will reasonably accurately describe the underlying trends in prevalence.

Best fit 'curves' (i.e. those with highest values of r^2) were applied to the data in *Figure 6*: these were straight lines in all cases. For all MS deaths, the average age at death has been rising by about 2 (± 0.2) years a decade since the 1950s. Using the formula

age = 0.2076 × (year) – 353.75

generated from these data (where year = e.g. 1988), the mean age at death for the sample UK population, as described in *Table 13* (including Leeds data, average UK latitude 52.2°) would be 59.5 years, giving a mean survival of 29 years (assuming an age of onset of 30.5 years). With the estimated prevalence at 100 per 100,000 population (see *Table 13*) the annual incidence would be 3.5 per 100,000 population, and thus prevalence would be increasing at about 7 per decade (i.e. 2 years [average survival increase] × 3.5 per 100,000 [incidence rate]).

It is worth noting that the mean age of death from any causes for individuals aged 20+ years (a reasonable comparison as most MS patients

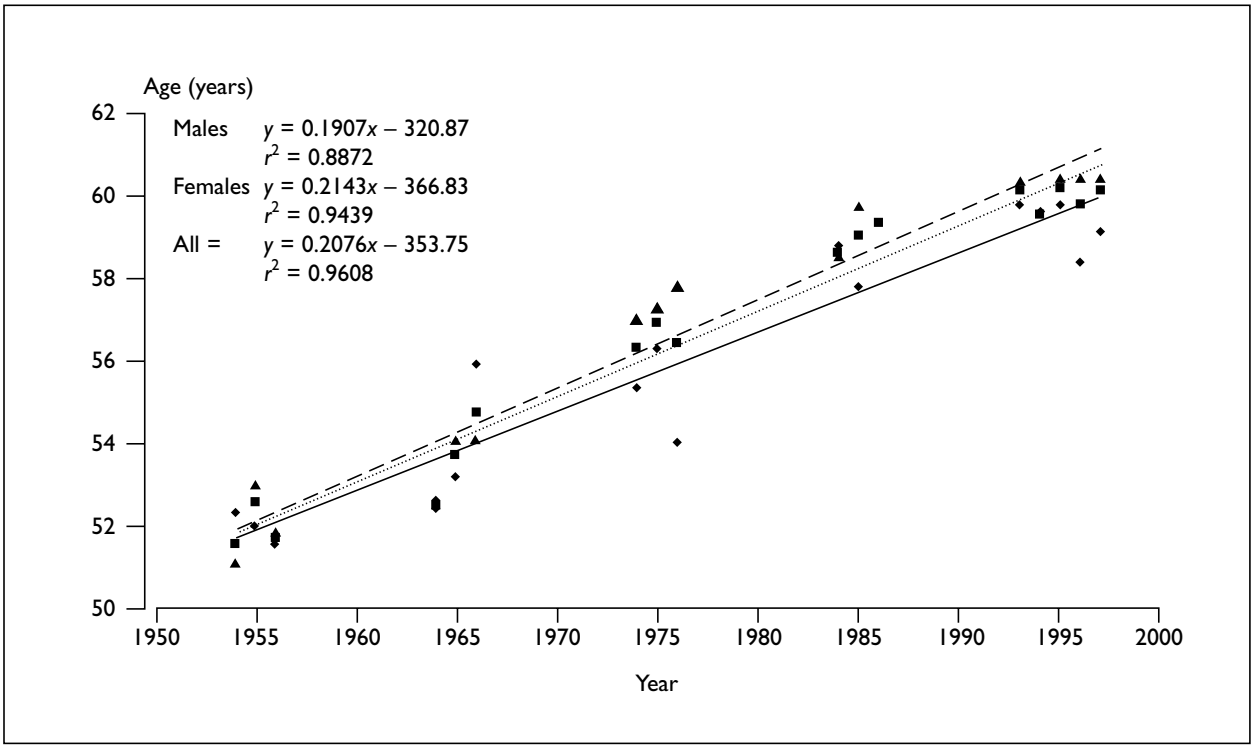

FIGURE 6 *Time trends in average age of death from MS 1954–97 (ONS data) (◆, Males; ▲, females; ■, all; ——, linear (males); – – –, linear (females); ·····, linear (all))*

die over the age of 20 years) has increased by just 1.4 (± 0.1) years per decade.

During the period 1993–97, when there were 3428 deaths due to MS, there were also 3209 death certificates on which MS was mentioned but not the cause of death (source: ONS). Were MS to be mentioned on all death certificates of those who had died with, as well as of MS, then the death rate (cause plus mentioned) would equal the incidence rate. The 6637 deaths above would equate to an incidence of 2.54 per 100,000 population.

Those with a mention of MS survived about 6 years longer on average than those with a cause of death of MS. Mean ages at death for all causes for those who reached 20 or more years were 73.3 years (men) and 79.1 years (women), while for MS deaths they were just 59.1 years (men) and 60.4 years (women).

Estimates of prevalence and incidence for the year 2000

The various estimates above can now be combined to derive estimates of prevalence and incidence over England and Wales. They are summarised in *Table 15*.

Implications for service provision in England and Wales

An average district of 500,000 residents would have 522 MS patients at the lower prevalence of 104, but 778 at the higher prevalence of 156, a difference of 256. It has been suggested that as many as 20% of MS patients might be eligible for interferon-beta under Association of British Neurologists guidelines for RRMS and a further 30% if SPMS patients were also treated.[55] Thus a Health Authority on the Scottish Borders could face a bill for interferon-beta (at £10,000 per patient per annum) of £1.3 million more than one on the south coast of England.

Even without the costs of interferon-beta, estimates from Flanders in Belgium[53] of the total (direct medical and social) costs of care for MS patients are as high as £588 per MS patient per year. At £588 per patient, the additional costs to this region would be £150,000. There is no indication as to how comprehensive the services were at the time of this Flanders survey,[53] but it might be reasonable to assume that a service delivered to all who needed it might incur even greater costs, particularly as the survey pre-dates some of the newer drugs used for symptom management.

TABLE 15 *Estimates of MS prevalence and incidence for England and Wales in the Year 2000*

Average prevalence changes	**With Leeds data**	**Without Leeds data**
Mean latitude	52.2	51.7
Estimated prevalence	107 per 100,000	117 per 100,000
Estimated incidence (prevalence/mean survival)	3.5 per 100,000	3.8 per 100,000
Annual rise in life expectancy (from death statistics)	0.2076 years	
Annual rise in prevalence (annual rise in life expectancy x incidence)	0.70	0.76
Geographic variation	**South coast**	**Scottish Borders**
Formula* $y = bm^x$ (m = 1.072)	**° Latitude = 50.00**	**° Latitude = 55.75**
Prevalence incl. Leeds (b = 2.839)	92 per 100,000	137 per 100,000
Prevalence excl. Leeds (b = 3.215)	104 per 100,000	155 per 100,000

* x = *latitude;* y = *prevalence*

NB: Poser et al. *definite + probable case definition*

Discussion and conclusions

Average prevalence in England and Wales

With about 64% of the population of England and Wales living south of the Wash, the prevalence of MS for England and Wales is likely to be in the range of 110–120 or a total of 58,000–63,000 cases. With this estimate based on surveys that pre-date the promise of effective treatments, this estimate may prove to be low.

Geographical variation in prevalence

The weight of international data points strongly to the possibility of a 50% difference in prevalence between the south and north of England and Wales. Either there is evidence in the England and Wales data for an absence of a latitudinal cline in prevalence or there is simply an absence of data of sufficient power. Thus, considerable uncertainties remain concerning estimates of the incidence and prevalence of MS and their relationship with increasing survival, latitude (environment), genetics and ethnicity. Every effort has been made to derive as much information as possible from the often contradictory data; arguably this may be only marginally better than a 'best guess'. Despite some inconsistencies concerning genetics and ethnicity that may confound any environmental factor(s) relating to latitude, the data concerning USA, Australia and New Zealand do appear remarkably consistent. The most appropriate approach to this uncertainty may be a willingness to address the resource consequences of these potential regional differences should they become apparent, otherwise inequalities in provision of care for MS, or other patient groups, will occur.

Chapter 5

Modelling the burden of morbidity and disability

The following section of the report examines the role of modelling in unravelling the underlying natural history of MS and in providing an environment within which to consider the impact of new interventions on the progression of the disease. This review has shown that no such model of MS currently exists in a form that will allow the full progression of patients to be fully considered.

A general overview is provided of existing publications that have used various modelling approaches in evaluating the epidemiology and treatment of MS. The basic principles behind a theoretical modelling structure (modelling approach, measurement of progression, health utility and cost) are also discussed.

It is the authors' opinion that, at the time of writing, raw published epidemiology research data do not exist in sufficient detail and quantity to allow such a definitive model to be constructed. It is therefore important to reiterate that the modelling section provides a description of a potential modelling structure, rather than a finished product itself. Limited published data have enabled some early indicative modelling to take place; this however should be approached with caution given the imprecision and limitations of the input data.

Review of the published modelling literature

The systematic literature search identified published modelling papers that have used some form of modelling/formal analytical approach to investigate the natural history, costs or QoL issues associated with MS. Although UK burden data are the main focus, evidence published from non-UK sources was also reviewed, as many of the natural history parameters considered will be similar.

The research questions addressed by the relevant papers fell into four principal categories.

1. Statistical models using multivariate analyses of a number of prognostic factors to predict the outcomes and course of an individual's disease[7,27,56,57]

These models examine the relationship between the survival experience of patients and a number of explanatory, or prognostic, variables. Such variables are typically based around age, sex, symptoms at onset, disease type and number and rate of relapses. Importantly many of these variables are not independent, such as the obvious link between age at onset and disease type; older people are far more likely to have progressive disease and hence a worse prognosis.

These statistical evaluations of natural history data are essential for understanding the effect of prognostic indicators on the outcome of an individual and, as such, produce vital information when interpreting trial information for patients with different prognostic characteristics. The models provide indications of risk ratios for prognostic factors and other information to help understand disease activity, but generally do not provide information about the likely course and prognosis of a 'typical' cohort of MS patients in terms of disability and functional status. However, these statistical models are based on data sets from which a subset of natural history information can be derived (generally at key summary time points, such as the mean time to EDSS 6). Where such models may fall down is in evaluating the actual experience of the patient across the whole of their lives with the disease, rather than at specific points. Prognostic indicators tend to be more focussed on evaluating the patient at onset and then predicting a single long-term clinical outcome, such as time to a specific EDSS state, change in disease type (i.e. entering progressive disease) or eventual death.

2. State transition or Markov techniques to predict the course of the disease, using derived transition probabilities to examine the likelihood of progression from one disease state to another[58–63]

A small number of papers have used Markov approaches and structures to describe disease progression of patients. The models reported by Confavreux and Wolfson[58–61] are based upon data collected from records of cases in Lyon between 1957 and 1976 (278 'probable' or 'definite' cases of MS) and predict the course of MS in

terms of the defined disease states of pure relapse, relapse with sequelae, progression and death. The probability of transition from one state to another is estimated from the data set, with transition probabilities provided for the whole cohort and for individual prognostic factors including sex, age at onset, initial symptomatology (optic neuritis versus other), mode of onset (mono versus polysymptomatic) and interval between first attacks. The model thus allows the expected survival within each state to be modelled, and models the effect of each prognostic factor on survival expectations.

Albert and co-workers discuss time-series methods of modelling disease activity for RRMS, using stochastic survival models.[62,63] The primary purpose of this approach is to try to predict patterns of relapse (i.e. frequency and duration) from a given set of patient's prognostic indicators. From the point of view of a natural history model of disease progression, this study is limited in its consideration of early disease stages only.

These models allow the stochastic nature of the disease to be understood and provide information on the effect of prognostic factors upon the disease course. However, these studies consider the disease course only in terms of relapse rates and time to progression. These measures are very broad and incorporate many different levels of disability. Similarly, there is no consideration of the progression of the disease once the SP phase has been reached.

3. Burden of disease models examining the medical and social costs associated with the disease, including direct costs, indirect cost and intangible costs[64–76]
A significant volume of the published literature related to the economic issues of MS provides estimates of the overall burden of the disease on society as a whole. As such they generally provide estimates not only of the direct health costs associated with the care of MS patients but also of the wider societal costs of lost productivity, social welfare support and the economic impact of the disease on the lives of carers and family. The general consensus is that the indirect costs far outweigh the direct health costs, and that costs in general increase with disease severity. Where these papers do vary is in the exact definitions of disease staging used and the types of costs included.

Of these studies there are three articles in particular that provide estimates of the cost burden of MS from a UK perspective.[65,71,74] These studies differentiate cost for different levels of disability. These papers are discussed later (see *Estimates of disease management costs*, this chapter).

4. Economic evaluations of treatments for MS using modelling to estimate the cost-effectiveness or cost–utility of the intervention[77–81]
Economic evaluations often use modelling as an approach to estimate the outcomes of the disease, as the extrapolation of trial data is often essential for understanding true cost-effectiveness implications. These models are particularly useful when attempting to reflect on the longer-term burdens of morbidity, as they can synthesise information regarding QoL, costs and benefits, often relating results to disease or disability severity. This is particularly the case in chronic diseases such as MS, as many of the trials cover limited period of follow-up and do not always focus on economic outcomes within their design.

However, the identified published economic evaluations of treatments for MS have only examined a subgroup of patients, typically those with RRMS in relatively early stages of disability (EDSS ≤ 6). Economic evaluations concentrated on the patients for whom the intervention would be considered (i.e. mainly patients who were ambulatory or having a certain number of relapses). Due to the short duration of the trials for MS interventions, the economic analyses do not consider adequately the effects of the interventions upon long-term costs by the delay of disease progression. For example Parkin and co-workers[77] evaluated progression over 5- and 10-year follow-up periods but EDSS state was limited to a maximum of 7.0.

The value of existing modelling literature is limited due to a number of factors. There is no single model reflecting the natural history of MS from onset until death. Articles that do provide estimates of the expected course of the disease do not use consistent outcome measures, examining outcomes in terms of time to progression,[56,59] time to various EDSS states,[25,57,77] and time to death.[82] Similarly, the timescales considered vary greatly, with consideration of between 5- and 25-year periods of the disease.[7,77] Many papers consider only subgroups of patients and do not report upon the different disease types separately.

Overview of a theoretical natural history model

The basic aim of this modelling section is to describe a potential model to represent the natural history and progression for a given cohort of

untreated MS patients from initial diagnosis to death. Importantly, the proposed model structure is not intended for use as a predictor of prognosis for an individual patient; instead it examines the disease from a population perspective. However, it would be intended that any final model of this type would be capable of operating on subsets of input data to represent different disease types and general subgroups of patients (e.g. stratify by number of relapses in first year from onset).

The model structure is intended to provide an environment within which to consider the combined effects of QoL, indicative medical and non-medical patient costs, and rates of disease progression on the burden of disease. As well as helping to clarify the overall burden of 'untreated' MS as it may currently stand (reflecting recently published natural history case-series reports), such a model could also be potentially useful in:

- conveying the true burden of the disease and clarifying the non-linearity of disease progression, as currently evaluated
- identifying specific areas of the natural history of MS that may require further research
- allowing crude 'what-if' scenarios to be examined to begin to explore the potential impacts of new and existing treatments that are focussed on the disease process itself, with possible delays in deterioration.

In selecting a suitable modelling methodological approach there are a number of important factors to consider.

- Exactly how should the stages of disease progression be defined?
- What form of modelling approach is most appropriate to the task?
- What patient groups could be considered?
- Over what period, or disease stages, should the model consider the progression of disease?
- Should the model focus more on the underlying progressive nature of the disease or should it reflect the cyclical nature of the relapse/remission process in the early stages of disease?
- How can the rates of progression between disability states be computed from the available published epidemiological data?
- How can QoL be explicitly recognised within the modelling structure?

Choice of disease status outcome measure

The standard measure of disease progression reported within epidemiological, economic and trial data is the EDSS.[20] Criticisms of the scale are:

- the inability to measure many of the MS symptoms that are important to people with the disease (e.g. fatigue)
- the measurement of impairment rather than disability
- the heavy reliance on patient ambulation.[79,80]

Also, the EDSS measure is a non-linear scale. Each step change of the EDSS does not necessarily correspond to the same degree of increased disability.[78,83] This is a particular issue when published studies report the proportion of patients achieving at least a single step change in EDSS without providing details on initial EDSS levels.

However, the EDSS has been recommended as the most useful scale for rating impairment by the International Federation of MS Societies in its MRD for MS,[84] and is the only standardised testing element common to both clinical trials and natural history studies.

Therefore, it seems most appropriate for the proposed model to examine the progression of the disease in terms of the DSS scale (graded on a 1 to 10 scale with increments of 1.0). The DSS is preferable to the smaller half point steps of the EDSS, as the level of uncertainty surrounding estimates of costs and QALYs is such that the use of EDSS points would provide little additional accurate information (*Table 5*).

The use of DSS states to reflect progression rather than other outcomes, such as time to progression, allows for more realistic consideration of resource use and QoL indicators. Both resource use and QoL (utility) have been demonstrated to be related to DSS state.[65,66,68,85] Importantly, published cost and QoL utility data are available only for DSS states, and are even restricted to groupings of DSS states in many cases.

Although the use of DSS states alone does not explicitly account for any change in QoL or resource use during periods of remission or relapse, the resource consequences related to relapses are short-lived. Also, resource usage and QoL data at early DSS levels will include implicitly average periods of relapse.

The use of DSS states as a principal outcome measure inherently assumes any effects of disease-modifying drugs will be reflected in the progression of the disease in terms of delayed

movement to the next DSS step. Thus, any effect a drug (e.g. interferon-beta) may have on reductions in numbers of relapses will not be considered unless there is some impact on the DSS level itself. As such the proposed model structure, built on progression through DSS steps, focusses on a longer-term view of disease progression, rather than the shorter-term consideration of the impact of relapses.

Consideration of patient subgroups

The variation in outcomes for patients with MS is considerable,[86] and it is important to consider the different subgroups of patients separately when modelling the survival expectations of MS patients. Many existing models consider only specific patient subgroups, for example examining implications of interferon for patients with RRMS. In order to produce a more realistic model that would provide baseline estimates of progression and morbidity for all patients, the ideal model would need to consider the different disease types separately due to the considerably different levels of progression between the disease classifications. The consideration of subgroups separately would reflect the different resource needs for the patient groups of RRMS, SPMS, PPMS and benign MS.

Modelling methodology

A number of different modelling approaches to estimate the burden of disease for different EDSS states have been reported within the literature.[77,78] The potential approaches for modelling the disease course and associated burden of morbidity are briefly discussed below.

Parkin and co-workers[77] produced a model to estimate the cost–utility of interferon-beta in RRMS. This model estimates the proportion of a cohort of patients within each disability state at specific time intervals, based upon trial data. The costs and QoL associated with each EDSS state, and those associated with relapse, are estimated from a patient study. The cost–utility estimate is based upon estimates of time spent within each EDSS state for 5- and 10-year scenarios. This approach uses the area under the curve/Kaplan–Meier survival curve approach to estimate the time spent on average within each disease state, and provides estimates for QALYs gained based upon the different shape of the curve for different arms of the trial.

This approach has the advantage of being calculable directly from survival estimates derived from trial data or natural history studies. However, the use of static survival curves to estimate the burden of morbidity is inflexible and does not easily allow for consideration of long-term outcomes resulting from disease modifying interventions. For example, if trial data indicated a difference in progression from EDSS 3 to 4 between the trial and placebo arms, the effect on QALYs for the difference would be modelled for these disease states, but the impact upon higher disease states would not be considered.

The use of a state transition model, such as a Markov model, examines the disease progression for a cohort using a series of transition probabilities based upon the likelihood of moving from one disease state to another for a specified time period (e.g. annual). This form of model was used by Wolfson and Confavreux,[59–61,87] and examined the likelihood of transition between the states relapsing, relapsing with sequelae, progression and death. A more appropriate form of this model for our purposes would examine the likelihood of transition between each DSS state. For example, the model would calculate the proportion of people expected to be within each DSS state for each year based upon the proportion of people within that state on the previous year and the likelihood of moving to another state in that year. Thus, given assumptions as to the consistency of transition probabilities, the model can be used to examine the potential long-term effects of a shift in probability of moving from, for example, DSS 3 to 4.

The use of a state transition model is considerably more flexible than that of a static decision model. However, the model itself is considerably more complex and the form of state transition model to use depends upon the nature of the data. For a simple Markov model, the model assumes each curve follows an exponential distribution and that transition probabilities are independent (e.g. the probability of moving from DSS 1 to DSS 2, given that they are in DSS 1 at the beginning of the time period, is the same in year 1 as in, for example, year 10). Such models are often described as having no memory of past events. A semi-Markov model would utilise different transition probabilities for different durations (e.g. the probability of moving from DSS 1 to DSS 2, having been in state 1 for 10 years, will be different from the probability of moving from DSS 1 to DSS 2 having been in that state for 1 year).

In selecting an appropriate modelling approach it seems logical that, given the chronic nature of the disease and the gradual movement through recognised disease stages, the proposed

model should follow a Markov approach and, as discussed, use DSS disability or disease states to define the health states between which the patients would move.

The rationale for using DSS state rather than broader disease types (e.g. RRMS, SPMS and PPMS) used in other Markov models, is that DSS is far more consistent in definition across the research evidence, and more importantly, the DSS stages are far more closely linked to the actual changes in function status and resource usage of patients. As one of the key uses of a model would be to evaluate the economic impacts of treatments in delaying progression, the ability to track closely functional changes is critical.

The time spent by patients in different DSS stages should, in principle, be derived from published natural history cohort data that can be used to estimate the survival curves for subgroups of patients for each level of disability. The survival curves provide estimates of the number of life-years lived by an average patient within each DSS state. A QoL utility value, associated with each DSS state, could also be applied to each DSS state in order to estimate the number of QALYs lived. The cost per QALY for different levels of disability could then theoretically be estimated by applying the average annual cost of care for patients with different DSS scores.

This model should allow, for example, the effect of slowing progression from DSS 3 to 4 by 10% upon the total QALYs lived by the cohort to be modelled, and allow assumptions of the effects upon long-term survival to be tested. For example, is the delay in progression maintained over the long term or is there a rebound progression after treatment?

The remainder of this chapter considers the key elements of such a theoretical Markov model, and discusses the most appropriate sources of data to populate the model, as well as indicating the likely baseline results.

Model structure

As discussed the purpose of a proposed MS natural history model would be to simulate the full progression of a cohort of MS patients through the individual DSS states associated with the disease. This is best done using a Markov cohort modelling approach, whereby at the end of each cycle patients are filtered through the model, either remaining in their current state of disease or progressing to the next DSS state(s). This is shown in the model structure (*Figure 7*).

The overall timescale selected for the model to run need not be fixed because the model is effectively run repeatedly (it would be best considered on an annual or half-yearly basis, given the chronic nature of the disease). However, given the typical age at onset and the chronic nature of disease, running the model for 50 years would seem appropriate. To some extent, the exact cycle time used by the proposed model would depend on the periods used in the available published epidemiology data. In the example calculations of transition probabilities covered later in this chapter, a 6-month model cycle was used.

As empirical evidence regarding the natural progression of the disease is limited, the model structure, as detailed, attempts to provide reasonable data on transition probabilities upon which patients either remain in their present state, or progress to the next alternative DSS state. In general, it has been assumed that within a single cycle (6 months), patients may only move in a progressive direction (i.e. move to higher DSS states) and may only move to the next DSS state. They cannot for example, move from DSS 2 to DSS 5 in one movement (*Figure 7*). The model presented here uses a 6-month cycle. However, this definition of progression is quite restrictive, in that patients would only be capable with the model structure of moving two DSS steps in a year. Therefore, a fast-track progression route has also been included within the model allowing patients to rapidly move to DSS 6 in a single 6-monthly cycle (after which the restriction of no more than two additional DSS levels in a single year holds). This is shown in *Figure 7*.

An assumption within the model is that all patients enter the simulation at DSS 1 whereby they have a normal neurological exam. At the end of the first cycle, patients may then either remain in DSS 1 until the end of the next cycle, or they may progress to the next state, DSS 2. Patients may then either remain in DSS 2 for that particular period, or progress to DSS 3. This process continues until the patient reaches DSS 9, whereby the patient may either remain in DSS 9 or transit to DSS 10, which represents death from MS. The patient may die of other causes during any cycle; this is represented by the transition from any DSS state to the 'other cause mortality' health state. The probability of dying from other causes may be calculated using standard life tables based on the age of the cohort.

Figure 7 also shows the possibility that patients may rapidly progress in a single model cycle up to DSS 6 from any of the previous DSS states.

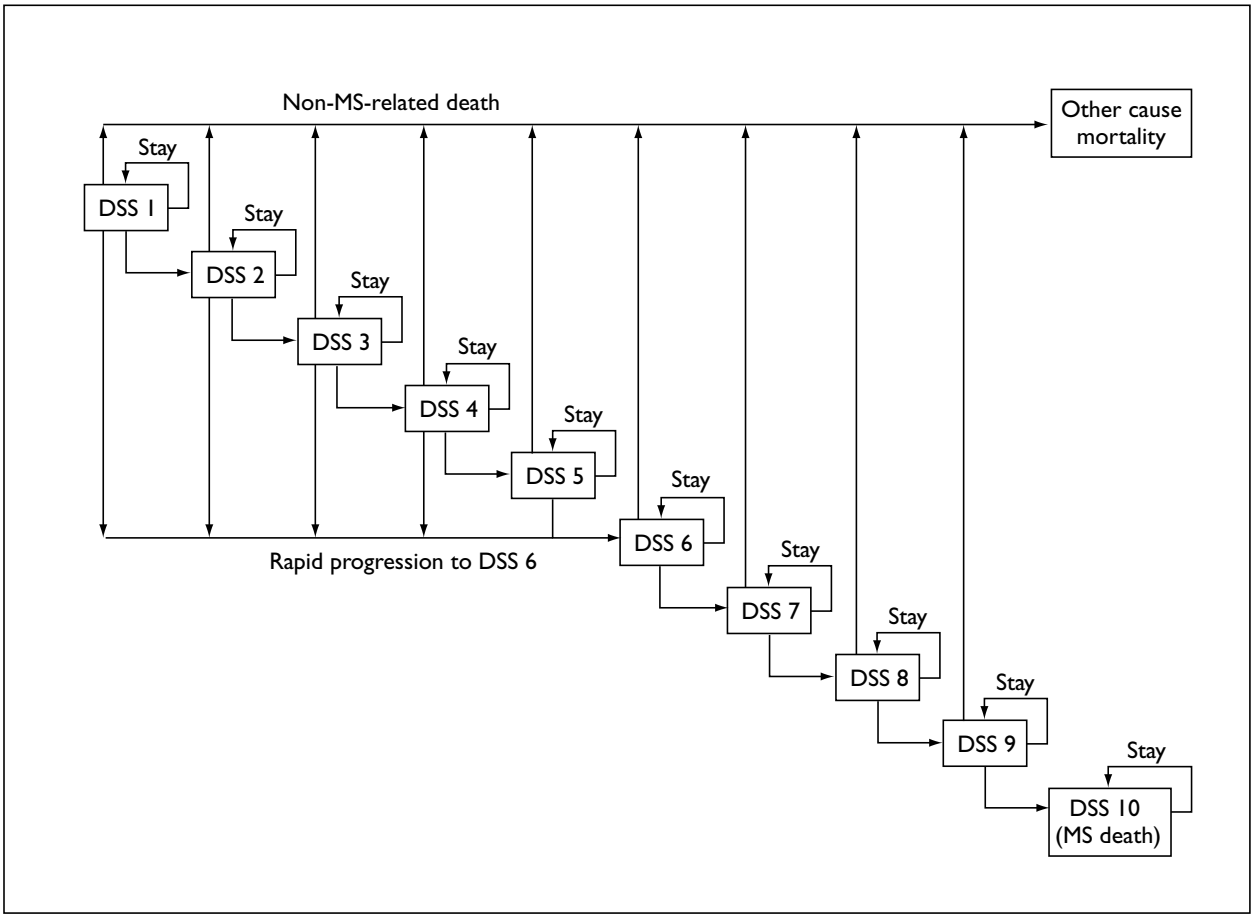

FIGURE 7 *Representation of proposed model structure (6-monthly cycle)*

This element was included in the model structure as it enabled a better fit to the published data on the proportions of patients below DSS states when estimating transition probabilities. In reality, enabling this rapid transition represents a significant simplification, as patients may be subject to rapid advancements to other DSS states, when the true nature of the disease is not as prescriptive.

However, the real constraint here is a lack of sufficient data on progression to and from each DSS state, over short periods of time. Without this information the model must limit the number of potential progression moves (as has been done here) for a feasible solution to be found for the transition probabilities. If movement between all DSS states was allowed for each period (i.e. the ideal with the most fluid model structure), then inevitably there would be too many unknown variables for the mathematical data-fitting procedures to handle, given the paucity of available detailed progression data.

Sources of natural history data

Ideally, the proposed model would use transition probabilities calculated from the best available data on the progression of patients with MS, recorded from initial onset up to final death. Such data were identified from the literature and by contacting experts (Professor Ebers, Radcliffe Infirmary, Oxford). These data were available on an annual basis from onset up to death for over 1000 patients. Importantly the data were differentiated by disease type (i.e. RR, PP and SP), considered separately those patients with less than five relapses within the first 2 years from onset (anecdotal evidence suggests this to be an important prognosis group), and was available annually for periods in excess of 40 years. However, these data were not available for the current review and remain unpublished at the time of writing.

Therefore, only data from published sources are used in the analysis, though it is possible that the same model structure may be useful in analysing future data as they becomes available. There are a number of studies on the natural history of MS reported within the literature that provide data sources used for modelling the disease.[7,9,25,59] The published data come from a subgroup of a population of MS patients from the MS Clinic, London, Ontario.[8,25,27,33,88,89] The data set includes

1099 patients with a median age of 29 years and a median disease duration of 10 years. This is recognised as one of the most valuable datasets for MS reported within the literature and contains relevant information about disease type, DSS classification, age and other prognostic characteristics (*Figure 8*).[90] Unfortunately, the method by which these data were collated was ultimately less accurate than the proposed unpublished data, and assumptions have therefore been made.

The actual observed data were available for the following combined DSS step groupings:

- up to and including DSS 2
- up to and including DSS 5
- up to and including DSS 7
- up to and including DSS 9
- DSS 10 (death).

The epidemiology of the disease itself suggests that not only is the disease progression typically slow, but also that MS patients may live a natural duration of life with the disease. It should also be noted that progression is not equivalent between all stages; the transition from DSS 1 to DSS 2 is unlikely to be as significant as the transition from DSS 8 to DSS 9, where the progression may have a more severe impact on the patient. The limited evidence available suggests that disease progression is typically bimodal, peaking in states before and after DSS 6. This reflects the conversion from RRMS to progressive disease, and should be recognised as a significant step for patients. It is therefore assumed that an adequate model should correctly reflect this type of distribution in both its fitted data and its longer-term predictions of progression.

Estimation of indicative transition probabilities

The model structure, as described above, was calibrated to data extracted from the published graphs covering the first 25 years from onset (*Figure 8*). Data over 25 years from onset were used to validate the fitted model predictions. The variance between the fitted and the actual observed values were calculated using data points taken directly from the published graphs at 5-year intervals. The sum of differences between these data pairs was minimised by the model using a least squared approach, as the transition probabilities were iterated through a range of feasible solutions by the Microsoft Excel™ solver routines.

It is crucial to acknowledge clearly that given the limited detail in the published data on MS progression, a perfect reflection of disease progression through the DSS states cannot be obtained at this present time (i.e. various solutions to the transition probabilities using the model may be found). It would require data that are detailed down to individual movements between each possible DSS step for a more accurate reflection of progression to be modelled. However, using the actual

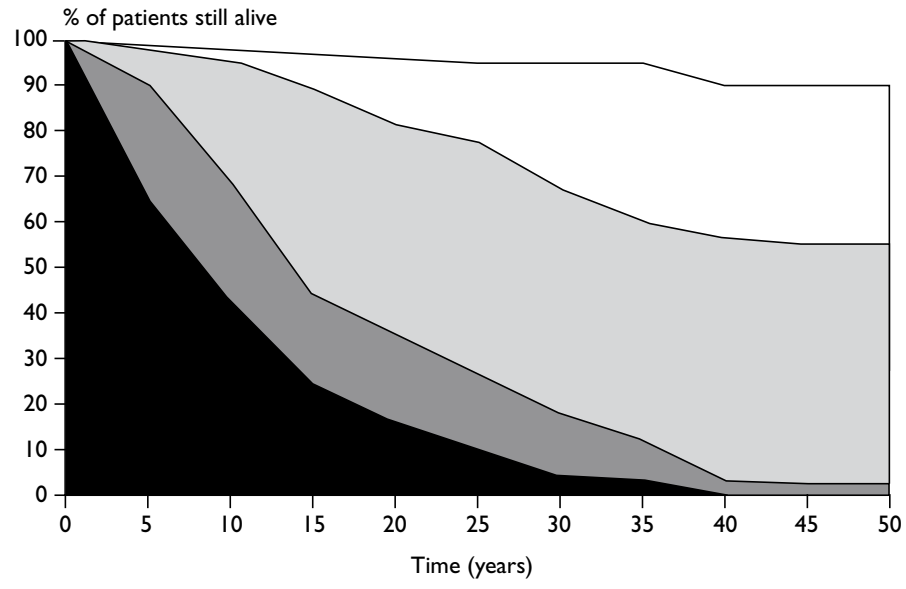

FIGURE 8 *Published data on progression through DSS steps*[90] (□, ≤ DSS 9; □, ≤ DSS 7; ■, ≤ DSS 5; ■, ≤ DSS 2)

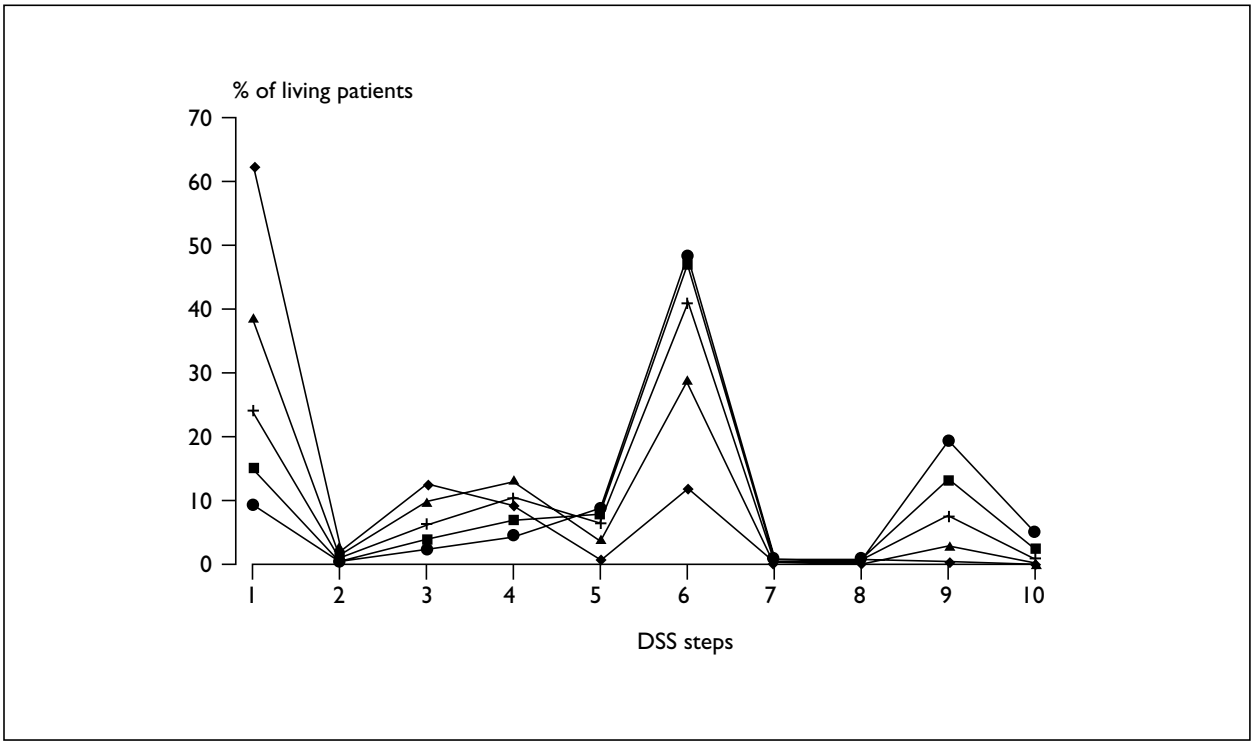

FIGURE 9 *Predicted patient distribution across DSS steps – model fitted to first 25 years after onset (from published DSS data) (–◆–, 5-year data; –▲–, 10-year data; –+–, 15-year data; –■–, 20-year data; –●–, 25-year data)*

observed data for groups of DSS steps, it was possible to find an adequate match against the distribution of the actual data. The model predicted values as shown in *Figure 9*.

The exact proportions of living patients in each of the individual DSS steps, rather than at specific combined points on the DSS scale remains uncertain with the model as it currently stands. Provided the overall proportion of patients in the combined DSS steps are similar in the model to that of the observed data, then the transition probabilities will look 'acceptable' to the fitting procedures, even if they look slightly odd to the experienced eye. To counter this problem of data flexibility in transition probabilities within the DSS groups, further boundaries or constraints could be imposed based on some level of prior knowledge. For example, it may be logical to assume that the probability of remaining at DSS 2 for a single cycle should remain within 5% of that for either DSS 1 or DSS 2. Such additional constraints could be used to further tighten the model's 'best fit' set of transition probabilities.

By fitting the data up to the first 25 years (*Figure 9*), transition probabilities were obtained (*Table 16*).

The model seems to suggest that patients progress slowly through DSS 1 followed by a rapid progression from DSS 2 to DSS 3. Progression from DSS 3 to DSS 6 is then slow. According to these probabilities, patients then experience rapid progression while in DSS 7 and 8. Patients then transit to DSS 9, where they have a low risk of death – approximately a 2% chance of death due to MS in each 6-month period. This modelled pattern of disease progression looks intuitive given the published epidemiological data; however, the exact values remain uncertain.

TABLE 16 *Indicative transition probabilities – fitted to 25-year data points*

Health state	Probability of remaining in DSS state	Probability of moving to DSS 6 in a single model cycle
DSS 1	0.95	0.01
DSS 2	0.01	0.01
DSS 3	0.84	0.01
DSS 4	0.84	0.13
DSS 5	0.99	
DSS 6	0.98	
DSS 7	0.01	
DSS 8	0.01	
DSS 9	0.98	
DSS 10	1.00	

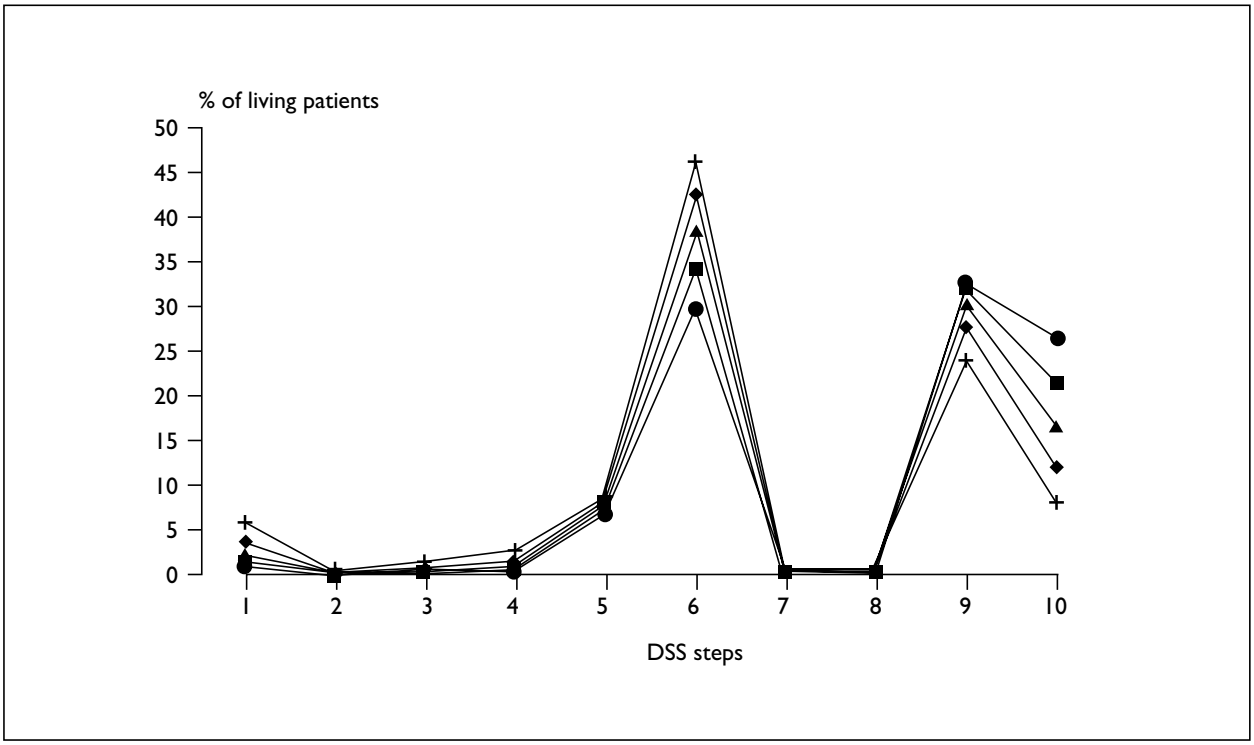

FIGURE 10 *Predicted patient distribution across DSS steps – model fitted to the first 25 years from onset (from published DSS data) (–+–, 30-year data; –◆–, 35-year data; –▲–, 40-year data; –■–, 45-year data; –●–, 50-year data)*

Given the set of feasible transition probabilities as described, the fitted model predicts the distribution of patients across DSS steps for time greater than 25 years (*Figure 10*).

It is vital to note that the transition probabilities shown in *Table 16* represent just one possible combination that was found to fit the observed data well. Again, with data only available for specific groups of DSS steps, the model can, and does, find a number of acceptable solutions to the fitting of the data points. This can also be influenced by the initial parameters assigned to the transition probabilities, which if wildly out at the beginning of the model calibration process, will lead away rather than towards the optimal solution.

In line with the disease itself, there is also a small chance that a patient may enter the model at DSS 6, which is generally seen as a turning point whereby the symptoms of the disease become progressively worse. This reflects the known natural history of the disease and makes the indicative transition probabilities appear reasonable.

Graphs showing the closeness of fit to the observed data are shown in *Figure 11*. Each graph corresponds to an exact year since onset, and shows the actual data for the five DSS groups compared with the fitted model values. The first 25 years were used to calibrate the model, and as such should be expected to fit reasonably well. However, the last 25 years data provide a visual validation of the model's predictive power.

Estimating disease management costs

As MS is a chronic condition, the economic impacts of the disease are widespread and evolve over a relatively long period of time. Both primary and secondary symptoms of disease can have significant associated economic costs. Importantly, the balance of costs is spread across both direct and indirect costs, and a significant burden falls directly on the patients and their families/carers.

There are a number of published studies that have reported estimates of the cost burden of MS from USA, Canada and Europe. The studies utilise different methodologies and include various combinations of cost elements relevant to the country of study (see appendices 4 and 5). Cost of illness (COI) studies can be conducted from either a prevalence perspective (i.e. reviewing a cross-section of the affected population) or a lifetime approach (where an incidence cohort is tracked from onset until death). A recent

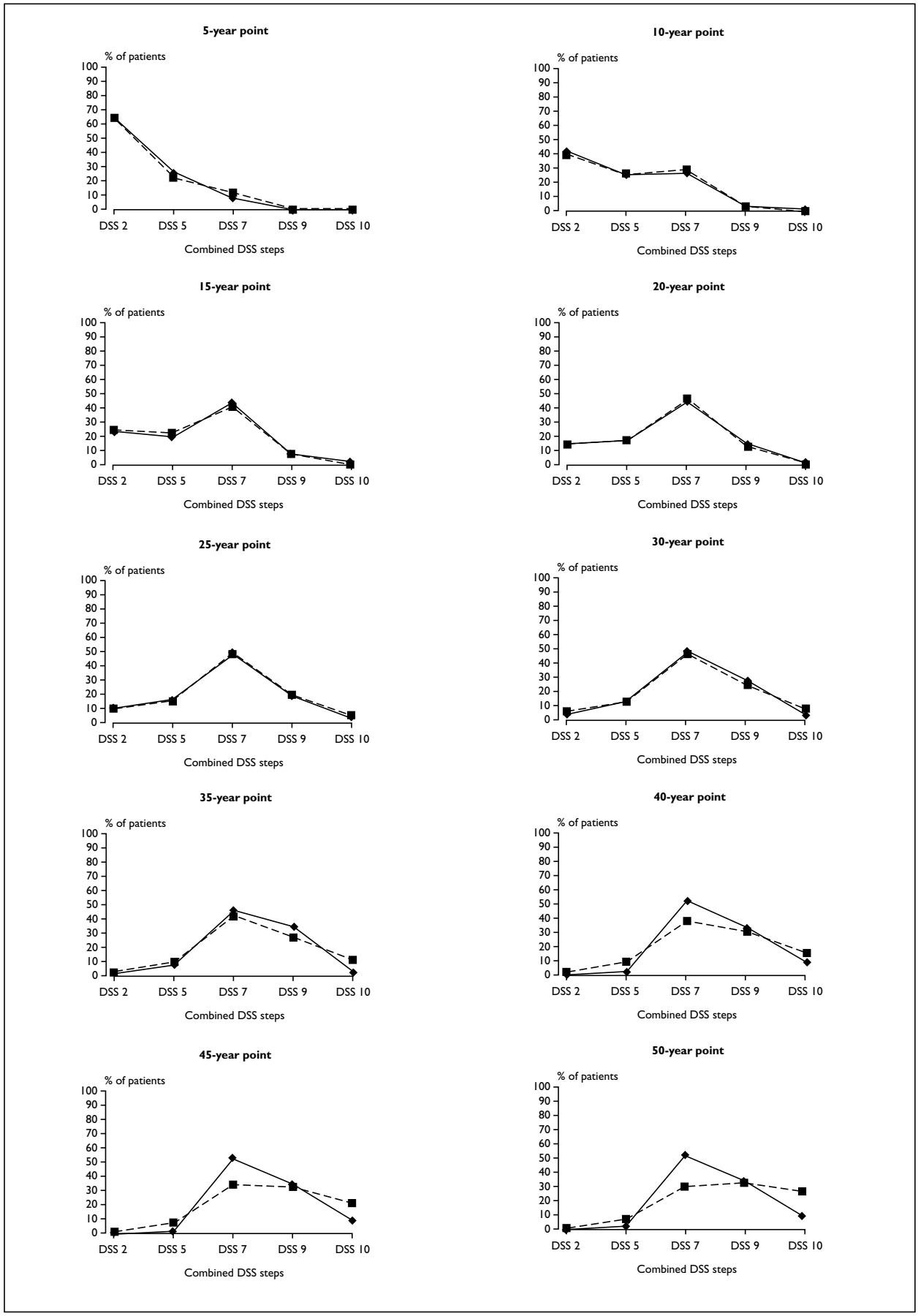

FIGURE 11 *Graphs of model-fitted data points (—◆—, Actual; - -■- -, fitted)*

published review of COI studies of MS by Grudzinski and co-workers in 1999 provides a good overview of the role of such work and also considers the difficulties of conducting cost-effectiveness work in treatments for MS.[69]

Three of the studies identified examined the cost of MS for England and Wales (Blumhardt and Wood[71]) and the UK (Holmes *et al.*[74] and Murphy *et al.*[65]). The total cost of MS in 1994/95 was estimated at between £553 million for England and Wales (Blumhardt *et al.*[71]) and £1.2 billion for the UK (Holmes *et al.*[74]).

A later study by Murphy and co-workers did not report an overall cost but examined the costs of MS in France, Germany and the UK, categorising patients into severity groups according to EDSS status.[65] Patients were matched to a control group on the basis of age and gender. The total cost of MS for 3 months in the UK was US$5125, US$6751 and US$14,622 for patients with mild (EDSS 1–3.5), moderate (EDSS 4–6) and severe (EDSS 6.5–8) MS, respectively. Translating back into UK sterling using Purchasing Power Parities (2000), this equates to £3352, £4415 and £9563 per annum for each of the three groups.

While Holmes and co-workers grouped patients by disease severity, this was done using a general health state description that is not directly related to the EDSS scale. Although Murphy and co-workers did not attempt to place a national estimate of cost on their work, if the same population prevalence data and disease severity proportions as used by Holmes are assumed, a figure of about £1.5 billion can be derived from the Murphy data.

Due to the considerable variation within the cost methodologies used, it remains difficult to derive accurate cost estimates for the UK. However, there are a number of general conclusions regarding the costs that are manifest throughout the literature.

The cost of MS to society and to the individual is significant, with the total annual cost of MS to the UK previously estimated at around £1.2 billion in 1994.[74] In addition to the direct medical costs incurred from GP visits, physiotherapy, inpatient and outpatient hospital visits, pharmaceutical and other rehabilitation costs, there are considerable indirect costs. Due to the onset of disease in early adult life, lost productivity is significant and has been reported to account for 18–26% of total costs.[68,74] Studies have demonstrated that between 50% and 80% of adults with MS are unemployed within 10 years of diagnosis.[91,92] Other important indirect costs are attributable to social security payments (residential care, community care, social care costs and disability benefits). Indirect costs are estimated to be higher than direct costs, accounting for about 60% of the total costs.[64,71,74]

The costs associated with MS have been shown to increase with disease severity.[65,66,68,72,74,76] In a study of US veterans with MS, direct and indirect costs were found to correlate significantly with the EDSS and ISS.[66] Other studies examining costs for subgroups of patients also noted an increase in cost associated with increased disability.[53,65,68,72,74]

There are inherent difficulties in interpreting COI studies. First, any comparison across studies needs to fully acknowledge any differences in patient groups. This is a particular issue in MS where case definitions are notoriously difficult to standardise. Second, while COI studies can certainly help in pitching the overall economic impacts of a disease in very general terms, they frequently fail to provide much more beyond this, unless they begin to consider subgroups of the patient population. Only when a clear picture of cost (both fixed and variable) linked to specific disease stage and patient group is available can the potential impact of new interventions be considered. Perhaps the optimal use of COI studies is in directing more detailed treatment-related economic research.

In selecting an appropriate source of cost data for inclusion into a UK model of the natural history of MS there are two primary requirements.

First, the data must be representative of the UK healthcare market. The cost studies confirm that the level of resource spending on MS patients varies considerably across different countries. The Murphy study clearly shows this when comparing the UK experience of MS treatments with both Germany and France. The UK has much lower rates of hospitalisation and shorter lengths of stay. Importantly the UK has much higher rates of carer provision, which carries a significant indirect cost burden.

Second, the data need to allow costs to be attributed to specific patient groups as described by severity of disease. The currently adopted tools for grading disease severity are the EDSS and DSS grading structures, which provide at least some measure of general disability and yardstick for rates of progression.

From the published data identified, the cross-sectional study by Murphy and co-workers provides the most suitable data in that it fulfils these two important criteria. It also includes a comprehensive range of costs (including those related to carers), and was conducted relatively recently (September 1995–July 1996).[65]

Estimating QoL for DSS steps

Impact of MS on QoL

A number of recent studies have examined QoL for people with MS in order to understand the effect the disease has upon different aspects of life. People with MS have been shown to have a lower QoL compared with the able-bodied general population,[85,93–95] due to interference with social activities, unemployment, fatigue, mobility limitations and other MS symptoms.

A recent Canadian study of over 200 patients with MS revealed that there were significant reductions in QoL compared with a matched cohort of the general population, when assessed using the standard Short Form 36-item (SF-36) questionnaire.[93] Even at relatively mild disability levels of EDSS ≤ 2.5, reductions were clear across all eight key domain areas, with an average drop of 30% from those of control patients of similar age. The study noted that the key SF-36 areas of physical functioning and social functioning decreased significantly with increasing disability of MS patients. The correlation was more significant for the components of physical function, role-physical and social function than for the emotional and mental health states. This may be explained to some extent by the bias of the EDSS towards physical disability. The mental score did not decrease significantly with disease progression, partly due to the low baseline score, but could also be due to the fact that many people may have adapted to the disease.[93]

Murphy and co-workers performed a study of QoL of patients with MS in France, Germany and the UK, using the Functional Status Questionnaire.[85] It focusses in particular on work-related issues, and cognitive impairment, as seen in MS, can impact heavily on this area of life quality. Murphy used grades of EDSS scores to categorise patients (1.0–3.5, 4.0–6.0 and 6.5–8.0), as well as assessing QoL in a control group of patients who consulted their GP during the same period. This study paralleled an evaluation of direct and indirect costs of MS in what appears to be the same patients.

Physical function scores and general well-being were found to be 40–50% lower than those of the control group and, although physical function decreased significantly with disease severity, general well-being diminished less with the later stage of disease severity, again suggesting patients may come to terms with the disease. Social role function was about 20% lower than for the control group but did not decrease significantly with increasing severity for UK MS patients.

Both these studies may underestimate the impact of MS on QoL for the most severely affected patients, as patients who were institutionalised were not included within the studies. Murphy also excluded any patients with an EDSS greater then 8, or those with serious comorbidity.

Aronson performed another study of Canadian MS patients and their carers in 1993–94.[94] Using a questionnaire-based approach and similar modified questions to those used in the Canadian General Social Survey (5-point satisfaction scale on areas of health, job, housing, family and friendship), the results were compared with a matched sample of the general population. Health had a very low rating with less than 15% satisfied compared with 25% in the general population.

Brunet and co-workers considered health-related QoL (HRQoL) in 97 Canadian MS patients and found that patients scored poorly in HRQoL domains of physical and role functions, energy and vitality according to the RAND 36-item Health Survey. The RAND survey covers eight domains similar to the SF-36. However, the correlation between decreased QoL and increased disability (EDSS scale) was most evident in the physical functioning domain. In particular the EDSS level appeared to miss the significant impact of MS on the pain and emotional aspects of the condition. The authors suggest again that the focus on ambulation of the EDSS makes it somewhat insensitive to the overall HRQoL impact of MS, and that it is most useful for monitoring general disease progression in the narrower physical sense.

The use of generic QoL scores to estimate the effect of MS upon QoL therefore may provide misleading information if concentrating upon the physical dimensions of the scale. It seems more likely that a generic QoL tool as a core with additional dimensions, encapsulating the specific effects of the disease itself, proves the most sensitive approach to measuring HRQoL in MS patients. The recently developed MSQoL-54,

based on the SF-36 general QoL questionnaire and an additional 18 disease-specific questions covering sexual and cognitive dysfunction, is such a hybrid of generic and specific QoL measurement.[95]

Valuing the utility of MS health status

It is of primary importance that specific HRQoL tools are used within the context of trials and epidemiological studies in order to recognise and assess the impact of both disease progression and treatments on the daily life of patients. Such tools allow researchers to describe the QoL profile of a patient and, on a cohort level, assess movements between levels over a given period of time.

However, within the context of a health economic analysis there is a clear incentive to attempt to place an actual valuation, or relative utility weighting, of time spent in particular health states. For example, if a patient can avoid spending the coming year bed-ridden what is this actually worth relative to a year spent in perfect health? There are two commonly used approaches to valuing health status: patients are asked either to compare the value of different times spent in a range of defined health states (time trade-off approach), or to accept a new fully curative intervention given associated probabilities of failure leading to death (standard gamble). Each of these approaches has its merits and both are used with equal frequency in the published literature. This kind of utility approach, summing the valuation to a single figure, is often referred to as index measurement of QoL. An alternative approach is to use the results of a generic QoL measurement tool, such as the EuroQol-5 dimensions (EQ-5D), and translate the individual numerical results into a single index measure of utility, using previously calculated weightings applied to each of the dimensions.

The recent introduction of expensive immunomodulatory therapies for MS (including glatiramer acetate (Copaxone®), interferon beta-1b (Betaseron®), and interferon beta-1a (Avonex ® and Rebif®)) has resulted in a number of economic studies being conducted that formally attempt to place index valuations of QoL for patients with MS, in order to estimate the overall cost–utility of the new drugs. However, many of these studies focus almost exclusively on the benefits of reduced relapse rate rather than delayed progression. Many of the original trials cover too short a period to judge adequately the impact on progression, and placebo levels are also commonly noted as being small. More recent work in SPMS allows the utility of MS disease stages to be considered further.

For this report, and the proposed modelled analysis, the estimates of QoL utility associated with MS are derived from population-based economic and natural history studies reported within the literature.[77,81] However, due to variations in treatment focus none of these studies provides estimates across the full range of MS-related disability, measured using the formal DSS (or EDSS) stages. Therefore the results have had to be combined in places and at the extremes of the DSS levels, some assumption of likely health status have necessarily been made, according to a similar methodology used in previous QoL studies.

In an attempt to assess the overall cost–utility value of interferon beta, Parkin and co-workers examined patients with RRMS who would be considered for treatment, thus examining only patients of DSS status between 3 and 7.[96] Parkin specifically considered the utility of recorded health states from a 6-month retrospective patient-recorded diary. The health states were scored on five health dimensions using the EQ-5D (based on the EuroQol). Tariffs, or weightings, for each of the dimension scores were used to calculate a single summed utility for each overall health state, as recorded by patients. Importantly, these data were available from individual DSS scores (calculated separately) to suggest an average valuation for each level. Although not available by DSS grade, a separate analysis of QoL utility using time trade-off approaches showed that for severe health states, patients graded their utility higher than that of the general public. Therefore, utilities for the higher DSS grades may be over-pessimistic when judged by healthy respondents.

Table 17 shows the profile of individual QoL scores by DSS level. The five scores correspond to the dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The grades are scored either 1, 2 or 3 reflecting no problems, some problems or extreme problems, respectively. Each patient response is included before a final average utility is calculated.

It is important to reiterate the fact that this study was focussed in particular on RRMS and, as such, included a mix of patients (i.e. those that had relapses and those that did not). It is not clear if the patient group over-represented relapsing patients, although the patient selection criteria appears to be representative of the typical MS cohort.

TABLE 17 *QoL utility scores by DSS level (Parkin* et al.[77])

Disease disability status	DSS 3	DSS 4	DSS 5	DSS 6	DSS 7
Mean tariff value (utility score)	0.71	0.66	0.52	0.49	0.35
Individual EQ-5D scores	12111	21111	11211	22211	22221
	11211	21121	21111	22211	22222
	21111	21221	22221	21212	22321
	11122	21221	22221	21221	22323
	21121	21221	21222	21222	
	21221	21212	22222	21311	
	21212	21222	22222	22221	
	21222	22222	22222	22312	
	22222	22222	21322	22222	
	22222	22222	33322	22222	
				22222	
				22322	
				22333	

TABLE 18 *Health utility scores (Forbes* et al.[81])

Postal ambulation score	Ambulation level	Assumed equivalent EDSS	Utility
1	Unrestricted	0–3.5	1.00
2	Walk unaided up to 500 metres	4–5.5	0.62
3	Walk up to 250 metres with aid	6	0.64
4	Walk indoors with help	6.5	0.39
5	Wheelchair	7	0.02
6	Bed	8–9	–0.26

Similarly, Forbes and co-workers considered only SPMS patients for whom interferon beta may be considered as a treatment, thus examining very few patients within the low and high DSS disability levels.[81] Forbes used six grades of ambulation, which map reasonably well onto EDSS grading between 0 and 9, with 10 representing death and a nominal utility of 0. *Table 18* presents the utilities suggested by Forbes with the equivalent EDSS steps estimated by matching the ambulation descriptors to EDSS descriptions.

It is noticeable that in the later stages of disability (EDSS > 7), the utility is actually negative, implying that the QoL is extremely poor and is, in theory, valued at worse than death by the average patient. The scores correlate reasonably well with those of Parkin and co-workers, although direct comparison is difficult because Forbes used EDSS grading rather than DSS, and combined data into ranges of EDSS score. However, Forbes scored DSS 7 much lower than Parkin (0.02 versus 0.35).

As an alternative to using the difference in quality-adjusted time spent in health states in calculating cost–utility ratios, some researchers have relied on the simpler currency of avoided disability to calculate cost-effectiveness ratios. That is, they calculate the shift in raw EDSS scores over a given period of time. For example, delaying the move from EDSS 5 to EDSS 6 for a 6-month period is equivalent to an avoided 0.5 year of disability (1 EDSS point × 0.5 years).

Brown and co-workers used this approach to consider the impact of interferon beta in Canadian patients.[78] However, they also suggested that further research should be done to allow the EDSS states to be mapped directly onto generic HRQoL indices (e.g. EQ-5D) to allow a utility value to be calculated. As an interim measure, the authors roughly estimated that an avoided EDSS disability year needed converting to QALYs using a factor of about 1.25 for RRMS patients (1.71 for chronic progressive). Using the full range of EQ-5D dimensions, this rose to 1.9 and 2.62, respectively. This implies that using simple avoided disability years underestimates the health benefits of avoided progression, which fits well with the ambulatory focus of the EDSS scale.

It is important in using such conversion factors to acknowledge that there will be variation in the

TABLE 19 *Assumed utility scores for high and low DSS levels*

Assumptions	Description	EQ-5D profile	Utility
DSS 1	No problems	11111	1.00
DSS 2	Moderately anxious or depressed	11112	0.85
EDSS 8		22223	0.08
EDSS 8.5		32223	–0.16
DSS 8	(EDSS 8 and 8.5)		–0.04
DSS 9	Bedridden patients – can communicate and eat	33333	–0.56

TABLE 20 *Utility data used in natural history model*

DSS state	Source	Utility value	Marginal step utility differences
1	Derived from EQ-5D*	1.00	–
2	Derived from EQ-5D*	0.85	0.15
3	Parkin *et al.*[77]	0.71	0.14
4	Parkin *et al.*[77]	0.66	0.05
5	Parkin *et al.*[77]	0.52	0.14
6	Parkin *et al.*[77]	0.49	0.03
7	Parkin *et al.*[77]	0.35	0.06
8	Derived from EQ-5D*	–0.04	0.39
9	Derived from EQ-5D*	–0.56	0.52

* See Table 19

utility of disability years at different points on the EDSS scale. The mid-range EDSS stratified utility data of Parkin and co-workers suggest that the utility of avoided disability years in this point of the EDSS range is much lower. That is, to move up a single EDSS step is more influential on health utility at the earlier and later stages of disease, than in the middle range EDSS steps 4–6.

In the theoretical natural history model presented here, utility data that ideally hold for each DSS level were required. Parkin and co-workers provided a good source of data in the mid-range of DSS levels. Likewise, the Forbes and co-workers data provided some indication of data at the extremities of DSS levels. However, the data were not sufficiently broken down for the needs of this report. Therefore, for those states at greater than DSS 7 and less than DSS 3, where no other data were available, estimates were derived directly from the EQ-5D and assumed states for each level of disability (*Table 19*). This approach, although not ideal, has been used previously in mapping DSS scores into generic HRQoL index scores in order to provide an indicative level of utility.[78,79]

Combining these estimates for EDSS 8 and 8.5 provides an estimate of utility for DSS 8 at –0.04 (which simply combines patients at both grades). Also if the DSS 9 and DSS 8 utility scores are combined as suggested by the approximations to EQ-5D grades, an average utility figure of –0.3 is obtained, which is very similar to the –0.26 utility suggested for the same patients by Forbes and co-workers.

Details of the source for each utility value is shown in *Table 20.*

Model summary

The proposed structure and data combine to provide an indicative model regarding the progression of MS patients through the DSS states. The current transition probabilities are only estimates, which appear to be a good fit according to observed data. However, these published data are often representative of combined DSS steps, and therefore further epidemiology data would be required to arrive at a more evidence-based model of progression for MS.

However, given such data the structure described, the cost and utility data, together with revised transition probabilities could easily be combined

into a Markov model structure. Such a model would be easy to construct within a general software package, such as Microsoft Excel™, or in more bespoke decision analysis software geared towards Markov modelling. An important element to consider would be the potential effects of discounting of costs.

Supplementary data regarding different parameters may be added to the existing model in order to run scenarios. Based upon the assumption that time spent in each state requires different degrees of healthcare and resource usage, and also that different DSS states have different QoL values, the model could be used to look at, for example, the effects of a new treatment. The user could not only look at the progression of the disease and how this is affected by the new treatment, but also consider cost implications, whether the treatment can be seen to slow down disease progression, and also whether the new treatment offers any utilities to the patient.

Discussion and conclusions

The use of modelling is important and necessary in assessing the potential long-term impacts of treatments in chronic diseases such as MS, and in understanding the true life-time burden that such a disease places on both the individual and society, through demand for health (and social) services. The cost-effectiveness of interventions could be modelled if a model existed that estimated the progression of disease for a cohort of patients and considered costs and QoL for different disease states.

A Markov state transition approach would provide a useful structure for considering the movement of MS patients through MS-related health states over time. However, the usefulness of such a model depends upon the existence of reliable outcome measures for measuring disease progression. The (E)DSS, which is currently the main outcome measure used in trials and health economic evaluation, has been shown to relate to disease-related costs and QoL and, although imperfect, is therefore the best available outcome measure to use. While the (E)DSS may be considered to measure progression of physical disability, particularly in terms of ambulation, it may not be such an accurate measure of disease progression for measuring other important symptoms. Similarly, the full effect of relapses on costs and QoL will not be fully considered in a model that considers progression in terms of (E)DSS alone. It may be useful to combine levels of relapse rate into the model in order to consider the effect of reducing relapse rates on the overall lifetime burden. However, although relapse may have a considerable effect upon QoL and cost, it is unlikely to have a significant effect upon the long-term costs and QoL when looked at over a lifetime.

In creating a Markov model it is necessary to estimate transition probabilities (i.e. the likelihood of moving from one (E)DSS level to another over a given period). Ideally, these data should be derived from natural history data sets of patients with MS, showing movements between all combined pairs of (E)DSS level. In considering a possible modelling framework, this report used published 'survival-curve' data of aggregated DSS levels, which required a number of assumptions to be made.

The model requires good-quality data on costs and QoL for each level of disability, in this case DSS level. Existing data are inadequate for this purpose. The published health economic evidence shows that there is a relationship between level of DSS and costs and QoL, but accurate figures are not yet available for all states.

The country-specific context has a significant impact on the health cost implications of patients in different DSS steps. In the UK, the evidence shows that NHS resource usage is significantly lower than in other western European countries, with more reliance on social, care and family networks. Non-medical costs clearly have a greater significance in MS than direct medical care costs.

Previous studies have attempted to assign utility weights to the DSS scale. However, it is currently necessary to make some assumptions towards the extremities of the scale as empirical health utility data are not available. There is a need for further research regarding QoL of patients with MS, preferably using MS-specific QoL measures combined with index measures that will allow utility values to be derived.

Previous modelling studies have been conducted to attempt to address some of the above issues, but as yet no single model has attempted to encompass the full lifetime progression patterns of MS for different patient groupings. In evaluating the published epidemiological data, it seems that the level of necessary detail is currently unavailable to achieve this aim with confidence.

Chapter 6

Research recommendations

MS is a chronic disease of long duration affecting a wide range of human functions. Short research studies of treatment efficacy, albeit randomised controlled trials, cannot fully assess meaningful outcomes. All MS patients should be better monitored throughout the course of the disease both to improve their care and to enable the natural history of MS to be better understood. New methodologies need to be developed for researching treatments of chronic diseases.

There is a need for longer trials on interventions for MS that address the range of morbidity that characterises this distressing disease. More accurate information on QoL for patients with MS and costs relating to symptoms and levels of disability are needed. Outcome measures used within trials should include economic and QoL measures in order to allow the cost-effectiveness of interventions to be examined.

Local research ethical committees should not sanction research that is designed solely to deliver results as quickly as possible (to meet the requirements of medicines licensing as cheaply as possible), performed on discrete subsets of patients unlikely to reflect clinical practice and with endpoints that do not properly reflect the impact of the disease on patients.

The widely used measure of disease progression, the (E)DSS developed by Kurtzke, is flawed and either this needs further development to address its shortcomings or a new instrument is needed.

Access to a comprehensive data set recording progression of MS patients over the long term (i.e. more than 20 years) is a key requirement to enable modelling in this disease area. These data should include information on symptoms experienced, and rates and length of relapse. Providing this information for individual (E)DSS states (or any other measure of disease progression) would allow more accurate modelling of the impact of disease progression.

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The views expressed in this report are those of the authors, who are also responsible for any errors.

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Appendix 1

Search strategies

A detailed summary of the search terms used is shown below. The aim of the search was to identify a body of literature related to the epidemiology and natural history of MS.

MEDLINE search (1966–October 1999)

Initial scoping search – (reviews of epidemiology or cohort studies or models)

1 Multiple sclerosis/ep [Epidemiology]
2 review.pt.
3 1 and 2
4 limit 3 to yr=1990-1999
5 exp Cohort studies/
6 1 and 5
7 Multiple sclerosis/
8 exp Models, theoretical/
9 7 and 8
10 exp decision support techniques/
11 7 and 10
12 9 or 11
13 4 or 6 or 12
14 ontario.af.
15 7 and 14
16 13 or 15

Epidemiology search

Multiple sclerosis/
exp Epidemiology
exp Morbidity
ep.xs.
2 or 3 or 4
1 and 6

Prognosis search

1 Multiple sclerosis/
2 Disease progression/
3 Prognosis/
4 exp survival analysis/
5 Survival rate/
6 course.tw.
7 natural history.tw.
8 6 or 7
9 multiple sclerosis.tw.
10 ((course or natural history) adj6 multiple sclerosis).tw.
11 or/2-5
12 1 and 11
10 or 12

Appendix 2

Disability Status Scale[19]

Status	Description
1	No disability and minimal neurologic sign
2	Minimal disability – slight weakness or stiffness, mild disturbance of gait or mild visual disturbance
3	Moderate disability – monoparesis (partial or incomplete paralysis affecting one or part of one extremity), mild hemiparesis (slight paresis affecting one side of body), moderate ataxia, disturbing sensory loss, prominent urinary or eye symptom, or a combination of lesser dysfunction
4	Relatively severe disability, but fully ambulatory without aid; self-sufficient and able to be up and about 12 hours a day; does not prevent the ability to work or carry on normal living activities, excluding sexual dysfunction
5	Disability is severe enough to preclude working; maximal motor function involves walking unaided up to 500 metres
6	Needs assistance walking, for example a cane, crutches, or braces
7	Essentially restricted to a wheelchair but able to wheel oneself and enter and leave the chair without assistance
8	Essentially restricted to bed or a chair; retains many self-care functions and has effective use of arms
9	Helpless and bedridden
10	Death due to MS – results from respiratory paralysis, coma of uncertain origin, or following repeated or prolonged epileptic seizures

Appendix 3

Expanded Disability Status Scale[20]

Status	Description
0.0	Normal neurologic exam
1.0	No disability, minimal symptoms
1.5	No disability, minimal signs in more than one functional system
2.0	Slightly more disability in one functional system
2.5	Slightly greater disability in two functioning systems
3.0	Moderate disability in one functional system; fully ambulatory
3.5	Fully ambulatory but with moderate disability in one functional system and more than minimal disability in several others
4.0	Fully ambulatory without aid; self-sufficient; up and about some 12 hours a day despite relatively severe disability; able to walk without aid or rest some 500 metres
4.5	Fully ambulatory without aid; up and about much of the day; able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterised by relatively severe disability; able to walk without aid or rest some 300 metres
5.0	Ambulatory without aid or rest for about 200 metres; disability severe enough to impair full daily activities (work a full day without special provisions)
5.5	Ambulatory without aid or rest for about 100 metres; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 metres with or without resting
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 metres without resting
7.0	Unable to walk beyond approximately 5 metres even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorised wheelchair
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of day; has some effective use of arms retains some self care-functions
9.0	Helpless bed patient; can communicate and eat
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

Appendix 4

Cost of illness studies (UK)

Study	Differentiation of disability	Methodology	Costing elements	Results	Key messages
Murphy *et al.*, 1998[65] UK (London/ Liverpool)	1 = Mild: EDSS 1–3.5 2 = Mod: EDSS 4.0–6.0 3 = Severe: EDSS 6.5–8.0 NB: EDSS > 8.0 excluded (two patients)	***Methods***: Cross-sectional study – clinical centre recruitment 3-month time period Costs at 1995/96 prices UK-based study of 88 patients (also considered Germany and France) Patients matched to non-MS control subjects by age/sex who had recently consulted GP (30 patients) Based on patient interview, clinical records review and clinical assessment Extra Contractual Referral tariffs used to cost of hospitalisation Friction based approach to lost productivity (80% reduction) Personal time costs at 40% productive time ***Patient profile***: Average age = 45.2 years 67% female Average time since onset = 14.6 years Excluded: institutionalised patients, patients < 18 years, recent trial involvement, major co-morbidity and other non-MS CNS diseases	• NHS costs (hospital visits and consultations, paramedical services, lab/ diagnostic tests, medication, specific equipment and medical supplies) • Individual burden (lost workdays, lost personal time, transport, community assistance, care-giving and home medication) • Health insurance (tests, equipment, hospitalisations, consultations, paramedical services, workdays lost, transport and community assistance)	***Average 3-month patient costs by type***: (Converted at £0.654 = US$1 from 2000 OECD Purchasing Power Parities) *Societal perspective*: UK: 1 = $5125, 2 = $6751, 3 = $14,622 France: 1 = $1928, 2 = $3941, 3 = $5678 Germany: 1 = $2772, 2 = $2056, 3 = $5701 *Health insurance perspective*: UK: 1 = $783, 2 = $901, 3 = $2956 France: 1 = $1217, 2 = $2324, 3 = $1750 Germany: 1 = $1090, 2 = $1027, 3 = $1788 ***Converted annual UK total patient cost by type***: 1 = £9453, 2 = £12,243, 3 = £28,125 **Total annual cost burden = £1.5 billion** (assuming prevalence as of Holmes *et al.*[74]) ***Resource usage per patient (3-month mean)***: No. hospitalisations: 1 = 0.1, 2 = 0.1, 3 = 0.2 % consulted: 1 = 96.7, 2 = 93.1, 3 = 89.7 No. consultations: 1 = 3.8, 2 = 2.3, 3 = 3.0 33% had lab/diagnostic tests Caregiver used: 1 = 66.7%, 2 = 82.8%, 3 = 93.1% Caregiver daily hours: 1 = 2.5, 2 = 3.5, 3 = 7.4	Used lost productivity as opposed to state benefits Hospitalisation rates and length of stay lower for UK than either Germany or France (even for control patients) Care-giving much more common in UK and the most significant element on non-medical costs (64–70%) UK has much greater non-medical costs than either Germany of France Societal costs for stage group 3 patients is approximately twice that in either Germany or France

continued

Study	Differentiation of disability	Methodology	Costing elements	Results	Key messages
Blumhardt & Wood, 1996[71] England and Wales	None given	Top-down population estimate of cost burden based on 1993 resource usage Uses national health activity databases and published literature ***Assumptions***: Used population estimates of unemployment linked to MS • 50% of MS men unable to work • 20% of MS women unable to work Used IMS data to explore GP activity and prescription activity • 335,000 prescriptions (in 56.2% of all MS patients) • 594,000 GP consultations Assumed two outpatient visits per annum per patient Assumed 10,000 inpatient admissions at £2000 per admission ***Patient profile***: England and Wales represented approximately 88% of the UK population Prevalence estimated at 60,000 Assumed 66% were female Assumed 20% had severe disease	• NHS costs (inpatient care, outpatient visits, GP consultations, prescription costs) • Individual burden (lost earnings, higher cost of living) • DSS benefits (social security payments and benefits) • Community-based care (community care workers, district nursing)	***Health service related costs***: GP consultation: £10.54 million (assumes 12 minutes per consultation at £1.68 per minute) Prescriptions: £2.07 million Outpatient care: £15.48 million Inpatient care: £20.0 million ***Non-medical costs***: Lost earnings: £250.12 million Social security: £117.81 million Social services: £124.8 million Private care costs: £12.48 million (*increased cost of living of £50 per week*) Total medical costs: £48.09 million Total non-medical costs: £457.12 million **Annual total costs of MS are estimated at £505.21 million**	Overall MS non-medical costs are over five times greater than NHS costs Calculations of social security benefits are based on theoretical entitlement not uptake Lost earning are a significant part of non-medical costs but still excluded costs related to carers No individual costs data provided on disease severity but a higher cost is implied in the paper

continued

Study	Differentiation of disability	Methodology	Costing elements	Results	Key messages
Holmes *et al.*, 1995[74] UK	A = "I can walk unaided for an unlimited distance" B = "I can walk unaided but only over a limited distance or with the aid of a walking stick" C = "I need to use a wheelchair on most days/every day."	Cross-sectional sample of patients in the MS Society register UK-based study of 672 responding patients 66% female Average age = 55 years Mean time since diagnosis = 14 years 11.8% type A 48.5% type B 39.7% type C 6-month resource usage recorded 9.4% in full-time employment Estimated UK MS population at 87,873 based on market research	• NHS costs, including hospital visits, GP consultation, GP practice nursing, district nursing, physiotherapy, other treatment services, drugs, transport, nursing homes/hospices. • Individual burden	***Average annual costs***: Total state burden per patient, including NHS costs, state benefits and lost tax revenue: A = £2106, B = £6056, C = £11,901 Total individual burden per patient, including lost earnings (net) and private expenses: A = £2643, B = £7792, C = £10,756 Total annual (state and individual) cost: £1.2 billion–£1.4 billion	Lost earnings represents the largest single contributor to overall cost burden at 33% NHS costs contribute around 13% to the overall cost burden

Appendix 5

Cost of illness studies (non-UK)

Study	Disease differentiation	Cost elements considered	Results	Comments
Inman, 1984[72] USA	1 = No limitation 2 = Mild limitation "difficulty with some daily tasks" 3 = Moderate limitation "difficulty in mobility and some tasks or difficulty in all tasks" 4 = Severe limitation "complete mobility restrictions"	• Medical (hospitalisation, nursing, physiotherapy, counselling) • Non-medical (equipment, household relocations, lost earnings)	***Average annual medical cost (US$)***: 1 = $692, 2 = $743, 3 = $1368, 4 = $2246 ***Annual lost earnings***: Male (group 4) = $4247–$13,113 Female (group 4) = $2409–$5594	Little information provided as to how costs calculated. More discussion of methodology used to consider economic loss Resource use captured by a 90-day expenditure diary and a retrospective patient interview
Whetten-Goldstein *et al.*, 1998[67] USA	None given	• Medical (hospital, nursing home, physician, other health professional, drugs) • Non-medical (paid care, unpaid care, domestic help, retraining, equipment, housing adaptations, lost earnings, health insurance, income subsidies)	***Annual cost (US$)***: Per person = $34,103 Per person (no informal care) = $27,651 Average annual earnings loss = $17,900 (*inc. in above figures*) Lifetime cost per case = $6.8 million	Postal survey of 659 patients of whom 70% were women Assumed that 20% had chronic MS (compared with 50% in the survey)
Carton *et al.*, 1998[53] Belgium	1 = EDSS 0–2 2 = EDSS 3–5 3 = EDSS 6–7 4 = EDSS 8–9	• Medical (hospitalisation, drugs, nursing aids, GP, specialist, rehabilitation nurses, physiotherapist, occupational therapist, speech therapist, psychologist, prosthetics and adaptive devices) • Non-medical (social worker, home carer, Actvities of Daily Living, helper, nursing home stay, house and auto-mobile adaptations, mobility aids) • Costs based on a prospective 4-week diary of resource use and invoices for 199 patients in 1995–96	***Annual cost***: 1 (home) = ECU 1383 2 (home) = ECU 5107 3 (home) = ECU 13,133 4 (sheltered housing) = ECU 20,748 4 (home) = ECU 21,468 4 (sheltered housing) = ECU 42,776 4 (nursing Home) = ECU 25,760	Bottom-up costing methodology of direct costs only Patients residing in an institution at time of interview were not considered Over-representation of more severely disabled patients is adjusted using disability proportions from prevalence studies (1 = 35%, 2 = 24%, 3 = 23%, 4 = 18%)

continued

Study	Disease differentiation	Cost elements considered	Results	Comments
Asche *et al.*, 1997[64] Canada	None given	• Direct costs (hospitals and other institutions, medical services, other health professionals, drugs, professional fees, and other) • Indirect costs (lost productivity from disability and premature mortality)	***Total population cost (Can$)***: Direct costs = $181.6 million Indirect costs = $ 313.7 million ***Annual cost***: Per patient = $18,673	Top-down approach Year of cost study = 1994 63% of costs were indirect Lost income from premature mortality was discounted at 6%
Henriksson & Jonsson, 1998[73] Sweden	None given	• Direct costs (inpatient care, ambulatory care and drugs) • Indirect costs (short-term absences from work, early retirement pensions, lost production as a result of mortality)	***Annual cost [1991 figures]***: Total expenditure SEK 1735 million [1513 million] Direct = SEK 370 million [428 million] Indirect = SEK 1366 million [1085 million]	Top-down methodology Year of cost study = 1994 Direct costs account for 20% of total costs Used national survey of lost productivity and national health resource databases
Midgard *et al.*, 1996[75] Norway	None given	• Direct (hospitalisation, nursing homes and outpatient care, long-term care in nursing homes, ambulatory care) • Indirect costs (loss of production due to short-term illness, rehabilitation, disability pensions, premature mortality)	***Annual cost***: Direct costs = NOK 5.7 million (approx. US$891 million) Indirect costs = NOK 42.4 million (approx. $6625 million) Indirect costs = 88% of total Lost productivity = 56% of indirect costs	124 patients Year of cost study = 1991 Costs only small subset of paper – the aim is mainly to examine the degree of handicap and disability Little detail as to costing methodology provided
Auty *et al.* (Canadian Study Group), 1998[68] Canada	1 = EDSS 1.0 – 2.5 2 = EDSS 3.0 – 6.0 3 = EDSS 6.5 – 10	• Medical direct (hospitalisations, physician consultations, other healthcare worker consultations, laboratory tests, procedures, drugs, medical expenses) • Non-medical direct (non-medical expenses, person expenses, transportation) • Indirect (days missed form work, foregone work income, time lost)	***Direct medical resources (Can$)***: 1 = $2250, 2 = $1969, 3 = $7233 ***Direct non-medical resources***: 1 = $912, 2 = $1663, 3 = $7787 ***Indirect costs***: 1 = $11,360, 2 = $18,068, 3 = $22,002 Overall cost = $1.0 billion	Bottom-up costing Year of study = 1995 198 patients 3-month follow-up period

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