



UK Multiple Sclerosis Risk-sharing Scheme: developing an improved analysis plan

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5 The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the
6 study being reported; that no important aspects of the study have been omitted; and that any
7 discrepancies from the study as planned (and, if relevant, registered) have been explained.
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**We have read and understood the BMJ Group policy on declaration of interests and declare
the following interests:**

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29
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5
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18

19
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21
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Abstract

Introduction

In 2002, the National Institute for Clinical Excellence concluded that the multiple sclerosis disease modifying therapies; interferon- β and glatiramer acetate, were not cost-effective over the short term but recognised uncertainties over longer term modelling. The UK Risk-sharing Scheme (RSS) was thus set up to ensure cost-effective provision by measuring long-term disability progression in patients prescribed these therapies, and comparing with a modelled natural history cohort. It was agreed that the price of the drugs would be adjusted, if necessary, at each 2 year analysis to achieve the predefined cost per QALY target. The first 2 year analysis identified problems with the model, mainly focussed on unforeseen limitations of the chosen natural history database. This paper outlines the identification of a more suitable untreated cohort and the work undertaken to improve the Markov model.

Methods

All known international databases were screened to identify the most suitable comparator to the UK RSS cohort.

Using transition probabilities from the selected cohort, the original discrete Markov model was compared to a continuous model, with and without the addition of baseline covariates, looking for the best predictive model of the actual progression of the cohort from baseline data alone, assessed by “goodness-of-fit” analysis. .

Analysis

The British Columbia Multiple Sclerosis database was selected as most suitable for the scheme’s purpose.

A continuous Markov model with “age at onset” as a binary covariate was deemed the most suitable model for future RSS analysis, providing the added benefit of allowing the use of data previously excluded due to time-window constraints.

Conclusion

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3 A new statistical analysis plan has been developed for the UK RSS which will be used for price
4 adjustment calculations for future RSS analyses. We believe this will provide a more valid and robust
5 methodology upon which to base future decisions.
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Strengths and limitations of this study

Strengths of this study:

- The validation of an analysis model for observational studies using natural history datasets as a comparator.
- The identification of an MS analysis model which can be applied over a 10 year follow up period.
- The identification of an analysis model which can use data collected at anytime point within the follow up period.
- The identification a model which uses data from a set of MS patients to predict outcomes in a different set of MS patients and in a different MS cohort.

Limitations of this study:

- This model cannot address unseen variations occurring due to the lack of randomisation.
- This model cannot address the bias in outcome due to lost to follow up patients
- Data from the natural history cohort of untreated patients was collected prior to that of the treated cohort and this model cannot adjust for any changes in the background outcome of untreated patients.
- Different techniques to assess long term effects such as propensity modelling cannot be directly compared to this methodology.

Introduction

In January 2002, the UK's National Institute of Clinical Excellence (NICE) opted not to recommend the use of the disease modifying therapies (DMTs) interferon- β and glatiramer acetate for multiple sclerosis (MS) on the basis of cost-effectiveness analyses using data derived from the pivotal 2-3 year randomised controlled trials.¹ However, they recognised that uncertainties over the assumptions made in the modelling could unpredictably influence the long-term estimates of cost effectiveness. Thus in February 2002 the UK's Department of Health launched the 'Risk-sharing Scheme' (RSS)² with a circular entitled the "Cost effective provision of disease modifying therapies for people with multiple sclerosis" in collaboration with the Association of British Neurologists (ABN), the MS Trust, the MS Society and the pharmaceutical companies manufacturing interferon- β and glatiramer acetate. Between 2002 and 2005 the scheme enrolled over 5,000 MS patients initiating a DMT in the UK, with the aim of measuring their disability annually over a ten year period.

The original cost effectiveness model³ produced a target outcome based upon transition probabilities obtained from a pre-existing natural history (DMT naive) cohort of patients from London, Ontario, Canada along with hazard ratios from the pivotal randomised control trials (unpublished data provided to the Department of Health by the manufacturers). Complementary quality of life data collected by the MS Trust⁴ and cost data from Kobelt et al⁵ were used to populate the cost-effectiveness model. The targets ensured that the UK's National Health Service benchmark of £36,000 (46,000 Euro / 56,000 US dollars) per quality adjusted life year (QALY) was reached over a 20 year projection, based on a planned 10 year follow up period within the RSS with 2 yearly interim analyses. At the start of the scheme, the drug costs were reduced where necessary to ensure the predicted targets were on course to reach the 20 year cost effectiveness target.

The two year analysis revealed significant inconsistencies in a number of sensitivity analyses.⁶ Depending on the underlying assumptions, some analyses suggested that observed disability progression in the treated cohort was worse than that predicted from the historical untreated cohort while others demonstrated the contrary effect. A detrimental effect of DMT did not match the described effect on short term, 2-3 year, disability seen in the randomised placebo controlled trials.⁷⁻¹² With the predetermined analytical approach (based on a discrete Markov model) appearing to produce unreliable results with wide variation, a decision was made to postpone any decision on cost

effectiveness to allow for a reappraisal of the process and to reconsider whether the statistical models and control data chosen were “fit for purpose.”

In retrospect, both the control data set and analysis model selected, when setting up the RSS, were found to have intrinsic flaws that made them unsuitable for the task.⁶ The natural history cohort (from London, Ontario, Canada) was unexpectedly found to contain retrospectively smoothed disability data (rather than actual, real-time collected disability scores), censoring any improvement in EDSS. Comparing our uncensored treated cohort to data retrospectively smoothed in this way would have the effect of unpredictably underestimating any treatment effect. In addition, individual-level patient data were not available from the London, Ontario cohort, which prevented precise baseline matching between the two cohorts, limiting our validation of the underlying (Markov) model for disease progression. Furthermore, there were only 342 patients matching the ABN prescribing criteria from which to generate the models.

This paper outlines the development of a more appropriate analysis plan and the choice of a cohort fit for the needs of the scheme. The method described will be applied in the 4 and 6 year cost-effectiveness analyses. The analysis plan was approved by the scheme’s independent Scientific Advisory Group in December 2012 in advance of unlocking the newly collected 4 and 6 year UK Risk-sharing Scheme data planned for autumn 2013.

Methods

Identification of a new multiple sclerosis natural history dataset

An initial screen to identify all published natural history data sets was performed by reviewing the literature and consulting with international experts. Selection criteria included availability of Expanded Disability Status Scale (EDSS) score measurements and access to the unprocessed (actual) scores (i.e. no data smoothing or other data manipulation). Other factors considered were size of the database, prospective data collection and length of follow-up, and the broader setting such as a close match to the UK in terms of the health system and MS prevalence in the underlying population. The British Columbia Multiple Sclerosis (BCMS) database, Canada (est. 1980) was identified as the best natural history comparator cohort for our purposes.^{13,14} In this dataset – as in the RSS – actual EDSS scores were recorded prospectively. It is estimated to capture 80% of the BC MS population^{15,16} and

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3 as such is considered representative of the wider MS population. EDSS scores were recorded by MS
4 specialist neurologists after a face-to-face consultation with the patient; this typically occurred at the
5 annual MS clinic visit. Patient data was not truncated if secondary-progressive MS was reached; i.e.
6 all relapse-onset MS patients and their respective EDSS scores were considered eligible. By 2004,
7 the database had records for over 5900 patients spanning 28 years (>25,000 cumulative years) of
8 prospective follow-up. Until 1996 DMTs were not widely available in British Columbia.
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10 11 12 Patient and data selection from the BCMS database.

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15 In order to generate relevant data for our needs, patients were only selected from the BCMS
16 database if they fulfilled the 2001 Association of British Neurologists (ABN) criteria for interferon- β and
17 glatiramer acetate (IFN- β /GA) use (adapted from Appendix IV Health Service Circular 2002/004),
18 defined as: EDSS \leq 6.5; \geq 18 years old; two relapses in the last 2 calendar years.
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22 Baseline for each patient was the 'first eligibility date,' meaning the first date at which a patient fulfilled
23 the ABN eligibility criteria. Only patients with definite MS (Poser criteria¹⁷) and a minimum of two
24 EDSS scores at least 9 months apart were considered.
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27 In order to be comparable with the RSS data the following adjustments and selection were applied:
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30 1) EDSS scores taken during a relapse or when disability was affected by other factors considered
31 largely unrelated to MS (e.g. hip fracture) were excluded.
32

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34 2) For the original discrete Markov model (see below) as well as visual presentation of the yearly
35 descriptive data (see under results), annual EDSS scores were needed. However, as is typical in
36 clinical practice, not all visits / EDSS assessments occurred at exactly yearly intervals and the
37 exclusion of some EDSS scores (e.g. due to a relapse or hip fracture) also affected the availability of
38 a yearly score. Therefore, data was selected such that only EDSS scores one year apart (+/- three
39 calendar months) were considered. See appendix 1 for further details.
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42 3) For the continuous Markov model, (see below) all eligible EDSS scores were used regardless of
43 their measurement interval i.e. no yearly data selection, as in (2), was needed.
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3 4) All patient data was truncated to the end of 1995 (i.e. the last full year in which the DMTs were not
4 widely available in BC. Although initially it was planned to truncate individual patient profiles only once
5 a DMT was initiated (in order to maximise the number of EDSS assessments), even when this
6 extended past 1995 when treatment would have been available). It became apparent that this
7 introduced a bias into the data, likely related to 'indication bias,' whereby patients 'doing well' would
8 be less likely to start a DMT.
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14 Analysis

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17 The primary purpose of the analytical work was to find the best statistical model able to predict EDSS
18 progression in a natural history cohort based on entry demographic and clinical data. The following
19 models were applied in the current study and their performances were critically evaluated.
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24 a) The discrete Markov model¹⁸ as in the original 2 year analysis⁶ i.e. disability scores (EDSS) had to
25 be measured at discrete, fixed time points.
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28 b) A continuous Markov model allowing for EDSS scores to be collected at unevenly spaced time
29 intervals, as is typical in clinical practice.¹⁹ Such a model also allowed covariates to be included. This
30 model allows for more complete use of EDSS scores collected at irregular time intervals both in the
31 BCMS and RSS cohorts.
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36 With regard to the "MS course" (i.e. relapsing remitting vs. secondary progressive) as a potential
37 covariate, we did not distinguish between these disease states when developing the Markov models
38 because secondary progressive MS is simply a later stage of the relapsing remitting form of the
39 disease and the transition has considerable overlap.
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44 To keep computations feasible, only integer EDSS values were used and fractional values rounded
45 down (i.e. EDSS 1.5 was scored as 1, 2.5 was scored as 2 etc.). These were referred to as the ten
46 EDSS 'states' (1-10). Transition probability and intensity matrices as the output of these models were
47 then used to predict disease progression in terms of EDSS as follows.
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50 Predicting outcomes in the continuous Markov model (b)

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53 A multi-state model algorithm ('R' library 'msm'¹⁹) allows the EDSS distribution to be predicted at any
54 time t . See appendix 2 for further details).
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Covariates considered in the models

The selection of potential covariates by the scientific advisory group was based upon; (a) those which were reliably and consistently recorded in both the BCMS and the RSS database and (b) *a priori* knowledge of those associated with the outcome of disability progression. As a result, sex, age at MS symptom onset, as well as disease duration and disability (EDSS) - combined into a Multiple Sclerosis Severity Score (MSSS)²⁰ - were tested in the continuous Markov model with up to two covariates. In addition, for the more promising models an alternative model was considered with dichotomous covariates (split at the median) replacing the continuous variables. This has the advantage that the resulting model can be formulated as the aggregate of a small number of discrete Markov models, so computations can be carried out without requiring special software.

Critical evaluation of the models was performed using the following validation techniques, with the goal being to identify the most appropriate model to represent the natural progression of MS. See appendix 3 for further details.

- 1) Transition probabilities derived from the complete eligible, BCMS natural history data were applied to the baseline data to predict outcomes over the subsequent 10 years to assess how well it matched the observed data from which the model was derived.
- 2) The BCMS dataset was repeatedly randomly divided into two subsets of equal size, with one half only being used to derive transition probabilities (as in #1). The probabilities derived from this half were then applied to the baseline characteristics of the second half, generating a model whose goodness of fit could be judged against the actual, observed 10 year disability data of this second half.

Measuring Goodness of Fit

Goodness of fit was assessed via visual inspection of the graphical displays as well as numerically. These included progression over time (mean EDSS profiles) for the cohort as a whole as well as comparisons with the proportions in a particular EDSS state over time.

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3 For the numerical assessment a classical mean square prediction error (weighted root mean square
4 over years of the prediction error in the average quantity shown, weighted by the number of patients
5 contributing data in the given year) and the likelihood, resulting from the maximum likelihood
6 algorithm were calculated for each of the covariate models to allow comparison.
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11 This study was approved by the University of British Columbia's Clinical Research Ethics Board (H08-
12 01544)'
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14 **Results**

15 Data Description

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18 The baseline demographics showed the BCMS and RSS cohorts to be remarkably well matched.
19 Patient characteristics are shown in table 1.
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23 The natural history BCMS comparator dataset comprised of 898 patient profiles with 7335 EDSS
24 scores providing 6357 transitions between consecutive EDSS states, i.e 6357 'events' where EDSS
25 values were recorded at consecutive visits. In any given "transition," a patient's EDSS could increase,
26 decrease or stay the same
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33 Discrete Markov model

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35 When applying the discrete Markov model to the BCMS reference data, the goodness of fit was
36 unsatisfactory, underestimating EDSS in earlier years and overestimating in later years (see figure 1).
37 Consequently, the discrete Markov model was no longer considered appropriate, and development of
38 a continuous Markov model was pursued.
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43 Continuous Markov models

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45 The following continuous 10 state Markov models (EDSS 0 to 9), with and without covariates, were
46 evaluated:
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- 50 1. Model without covariates
- 51 2. One covariate model with age at onset*
- 52 3. One covariate model with MSSS* at baseline
- 53 4. One covariate model with disease duration* at baseline
- 54 5. One covariate model with sex
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6. Two covariate model: sex and age at onset*
 7. Two covariate model: MSSS* at baseline and age at onset*
 8. Two covariate model: disease duration* at baseline and age at onset*
- *two variants were implemented: continuous (original) data and a 'binary' version with the median used for categorisation.

There was a systematic deviation with overestimation when the continuous Markov models without covariates were applied (figure 2). Hence these models were not considered further.

After validation was repeated for all covariate models (table 2), it was noted that inclusion of a second covariate did not reveal any additional benefits. With one covariate, the model with "age at onset" as a binary covariate was selected because it displayed the smallest -2 log likelihood and minimal EDSS prediction error, see table 2. Further, the goodness of fit was acceptable when comparing the predicted and observed EDSS profiles, as shown in Figure 3a. A more detailed comparison of observed and expected proportions 'per EDSS state' is shown in Figure 3b which confirmed that no systematic deviations were present which might otherwise have been overlooked. It was concluded that only random fluctuation remained, and a systematic deviation was no longer visible. When comparing figure 1 with figures 2 or 3 it should be noted that the former is based on the *annual* EDSS data which were obtained as described in Appendix 1 while figures 2 and 3 show the EDSS at any time t , i.e. not necessarily when an observation was recorded (for details on how to define and calculate what is the observed EDSS at a given time see Appendix 2).

Using this 'best' model, transition probabilities were extracted from half of the BCMS cohort and applied to the other half. This gave good predictions, with the mean EDSS profiles (observed versus predicted) being similar to each other and to those of the entire cohort.

Finally, further (external) validation was undertaken using a Welsh dataset of untreated MS patients collated by the Cardiff neurology team. When using the model with "age at onset" as the (only) binary covariate in a continuous Markov model we observed a pattern of congruence similar to that visible in figure 3, but limited to the comparatively shorter observation time in the Welsh cohort (data not shown.) This observation supported our choice of the 'best' model in the sense of finding an appropriate model for EDSS progression in untreated MS patients.

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5 In summary, the continuous Markov model with a single covariate - onset age - was considered the
6 model of choice to be used in future RSS analysis.
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9 10 **Discussion**

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12 This paper outlines the successful identification of a more suitable natural history cohort for the UK
13 MS risk-sharing scheme, with the British Columbia, Canada dataset now replacing the London,
14 Ontario, Canada cohort in the RSS analysis plan. The analytical work is based on a Markov model
15 which has been frequently used for ordinal data from relapsing (remitting) diseases, especially
16 MS.^{21,22,23}
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20 Further, because use of the British Columbian data has now allowed access to a richer dataset,
21 including full access to original, 'real-time' disability (EDSS) assessments, as well as individual
22 patient-level, we have been able to explore and develop more appropriate approaches. Specifically,
23 we were able to employ more advanced statistical models, making use of all the available data and
24 including clinically relevant patient-level characteristics as covariates in order to identify the most
25 accurate predictive model to be applied to the RSS. Finally, we observed that to minimize 'indication
26 bias' in relation to initiation of a DMT in the natural history cohort (British Columbia), censoring (data
27 truncation) was more appropriate at the population (rather than individual) level.
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31 Findings from our validation procedures indicate future feasibility with respect to obtaining reliable
32 cost-effectiveness results in the upcoming 6 year RSS analyses. For instance, visualisation of the
33 predicted and observed outcomes in the final model showed almost perfect overlap, with a one-
34 covariate model, with no additional improvements from introducing further covariates. In addition, the
35 final model was able to predict accurately the MS disease course (disability) in half of the cohort
36 (randomly selected) having obtained the transition probabilities from the other half. We were also able
37 to show that the model showed good fit when using the BCMS dataset to predict outcome of an
38 untreated Welsh cohort. These observations along with the baseline comparability of the BCMS and
39 the RSS cohorts suggest the transition probabilities from the BCMS cohort within this model can be
40 used to predict the untreated progression of patients in the RSS.
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3 An additional strength of this continuous model is the ability to include all valid disability (EDSS)
4 assessments, regardless of their exact timing, maximising data usage. We acknowledge the potential
5 limitations of using of a historical control from a geographically discrete population. It is possible that
6 the natural history of MS has changed over time or that the BCMS population is not representative of
7 a UK one. However, in British Columbia, it has been previously shown that disability progression (as
8 measured by the EDSS) has not substantially changed overtime (1980-2009²⁴). Further, we have
9 previously shown that the use of a 'contemporary' untreated control cohort – i.e. where patients are
10 potentially eligible for a DMT in an era when the DMTs are readily available, but remain untreated - is
11 subject to indication bias and thus a historical control cohort, with data collected pre-DMT use, is likely
12 to be more appropriate.²⁵

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22 Observational studies, such as the RSS, provide a pragmatic approach when assessing drug
23 effectiveness in a disease such as MS. Because MS disability accrues over decades, the cost
24 effectiveness of disease modifying treatments cannot be assessed by short-term randomised
25 controlled trials. However, observational studies are not without their own unique challenges.
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29 Identifying and validating models to predict the untreated outcome of treated cohorts is a crucial step
30 to measuring the long-term benefits of MS treatments. MS is the commonest cause of progressive
31 disability in the western world, thus identification of treatments that might significantly impact long-
32 term disability outcomes in MS could have major cost and quality of life benefits. Additionally, any
33 models developed here would be readily transferable to other chronic diseases.

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40 In summary, the current model described here will form the basis for calculating the drug cost per
41 QALY and for informing decisions on price adjustment in order to deliver the treatments cost
42 effectively to UK MS patients. Further work on repeated measures modelling, testing the models on
43 other untreated appropriate MS datasets and identifying sensitivity analyses (such as the effect of
44 drop outs, switching to a different class of DMT and the effects of treatments on backward transitions,
45 i.e. disability improvements) are also planned.
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3 All authors 1) made substantial contributions to the conception and design, acquisition of data, or
4 analysis and interpretation of data 2) were involved in drafting the article or revising it critically for
5 important intellectual content and 3) were involved in the final approval of the version to be published.
6
7
8 JP is a clinical lead for the UK risk sharing scheme, inputs into the scientific advisory panel, was
9 involved in the identification of the alternative dataset, interpretation of the analysis and was involved
10 in the drafting and revising of the manuscript. TB is the senior statistician in the scheme and the
11 analysis of this work, was involved in the drafting and revision of this manuscript. HT, FZ and JO were
12 responsible for the preparation of the BCMS dataset, analysis of the data, and drafting and revision
13 of the manuscript, MB was a clinical lead for the UK risk sharing scheme, input into the scientific
14 advisory panel, was involved in the identification of the alternative dataset, interpretation of the
15 analysis and was involved in the drafting and revising of the manuscript, MD is a clinical lead for the
16 UK risk sharing scheme, inputs into the scientific advisory panel, was involved in the interpretation of
17 the analysis and was involved in the drafting and revising of the manuscript, CD is a department of
18 health advisor for the scheme, inputs into the scientific advisory panel, and was involved in the
19 analysis of the data, its interpretation and was involved in the drafting and revising of the manuscript.
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At the outset of the Risk-sharing Scheme agreement was reached between the UK Department of Health and the four manufacturers of the DMTs that all costs for this research project would be split 72 centres participated in the collection of data for the Risk-sharing Scheme from across the UK. Data was collected over a 10 year period and thus changes have been seen within the clinical teams. The authors are grateful to all the clinicians for the work undertaken at the centres which made the RSS possible. A list of the centres can be found at <http://www.mstrust.org.uk/research/risksharingscheme/>

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Table 1: Characteristics of patients reaching the Association of British Neurologists criteria in the British Columbia MS database after 1980 (the 'natural history' untreated comparator cohort) and the Risk-sharing Scheme cohort.

| Baseline (eligible for DMT) | BCMS (1980-1995*) | RSS full cohort RSS analysis cohort |
|--|-------------------------|--|
| N | 898 | 5610 4138 |
| Females: n (%) | 666 (74.2%) | 4162 (74.2%) 3125 (75.5%) |
| Age at baseline, years: mean (SD; range) [years] | 37.2 (9.32; 18 - 69) | 39.4 (9.05; 15 - 73) 38.4 (8.58; 18 - 73) |
| Age at onset of MS, years: mean (SD; range) | 29.3 (8.65; 3 - 61) | 30.5 (8.52; 5 - 68) 30.5 (8.38; 5 - 68) |
| Disease duration at baseline, years: mean (SD; range) [years] | 7.9 (6.89; 0.2 to 38.9) | 8.8 (7.47; 0 - 46) 7.7 (6.62; 0 - 41) |
| SPMS documented at baseline# n (%) | 141 (15.7%) | 772 (13.8%) - |
| Relapses in the last two-years prior to eligibility: median (quartiles) | 2 (2 - 3) | 3 (2 - 3) 3 (2 - 3) |
| First eligible EDSS: median (quartiles; range) | 2 (1, 3.5; 0-6.5) | 3.5 (2.0, 5.0; 0 - 8.0) 3.0 (2.0, 4.0; 0 - 6.5) |

Key: 'Eligibility' refers to the first time a patient fulfilled the ABN criteria*data was truncated to 1995 in the final models to minimize DMT exposure in the cohort

#all were still DMT eligible

RSS=Risk-sharing Scheme ; BCMS=British Columbia MS database; SD=standard deviation;

EDSS=Expanded disability status score ; DMT=disease modifying treatment

Table 2: “Goodness of fit” statistics for the ten state* disability (EDSS) Markov models

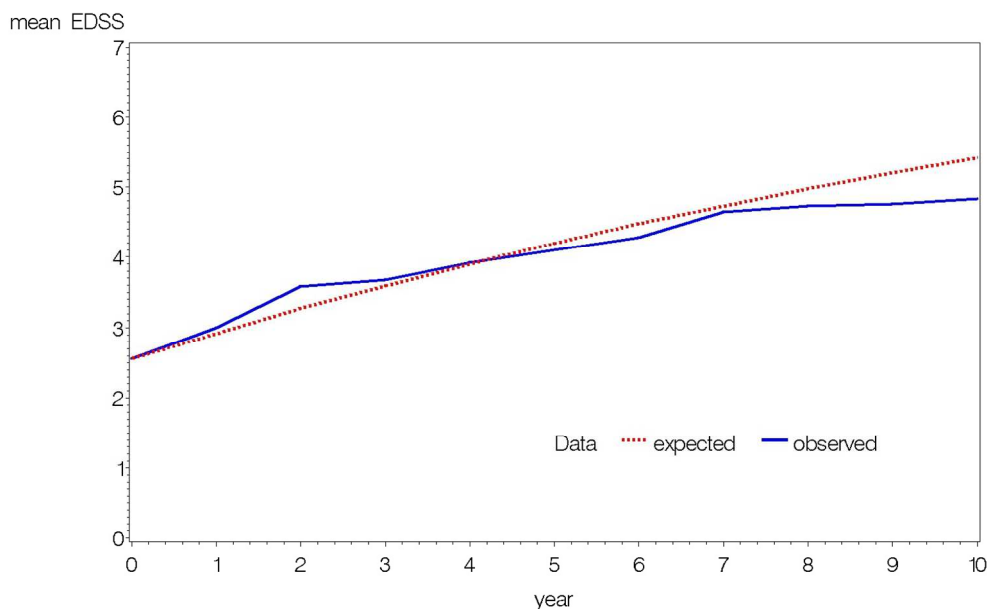
| Description of each ten-state ¹ disability model | Minus 2 log likelihood ² x 1,000 | Prediction errors (years) | | |
|---|---|---------------------------|-------------------------|---------|
| | | Cells | 1-10) ³ EDSS | Utility |
| No covariates | 17.152 | 2.20 | 0.24 | 0.022 |
| One covariate models | | | | |
| Age at onset, binary | 17.458 | 1.39 | 0.09 | 0.009 |
| Age at onset, continuous | 17.599 | 1.58 | 0.13 | 0.007 |
| MSSS at baseline, binary | 17.460 | 1.41 | 0.10 | 0.008 |
| MSSS at baseline, continuous | 17.457 | | | |
| Disease duration, binary | 17.462 | 1.33 | 0.10 | 0.009 |
| Disease duration, continuous | 17.557 | | | |
| Sex | 17.470 | 1.32 | 0.10 | 0.008 |
| Two covariates models | | | | |
| Sex and age at onset, binary | 17.603 | 1.51 | 0.14 | 0.007 |
| Sex and age at onset, continuous | 17.618 | | | |
| Age at onset and MSSS, binary | 17.609 | 1.53 | 0.14 | 0.007 |
| Age at onset and MSSS, continuous | 17.618 | | | |
| Age at onset and disease duration, binary | 17.603 | 1.52 | 0.14 | 0.007 |
| Age at onset and disease duration, continuous | 17.618 | | | |

¹the ten disability states refer to EDSS 0 to 9, i.e. EDSS 0 is “state 1”, EDSS 1 is “state 2” etc.

²log likelihood statistic as calculated by ‘msm’ module, see Jackson¹⁹ for details; lower values implying a better model (to be compared within each class of models, e.g. one-covariate and two-covariate models)

EDSS= Expanded disability status score ; MSSS= Multiple sclerosis status score

³Prediction errors, averaged over years 1-10, for (a) the EDSS distribution in individual cells, (b) average EDSS, (c) average utility (see definitions in the appendix 3, comparing the values predicted by the model with the “observed” values using the method of midpoint interpolation (see appendix 2).



Transition probabilities obtained from the BCC dataset using the discrete Markov model were then applied to the baseline EDSS of the same cohort, projected over 10 years to produce a predicted mean EDSS outcome (red) and compared to the observed mean EDSS course of the cohort (blue).
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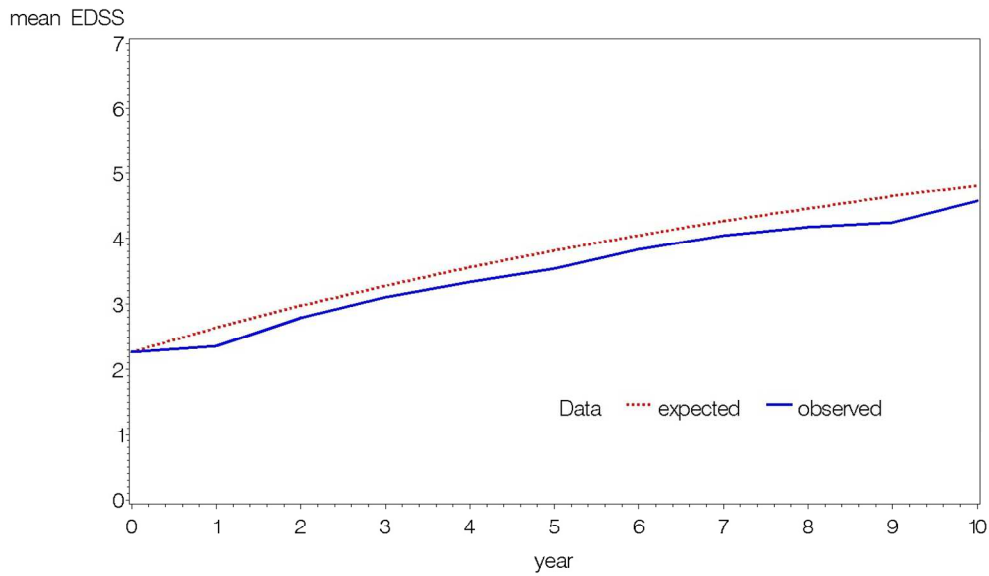


Figure 2: Transition probabilities obtained from the BCC dataset using the continuous Markov model were then applied to the baseline EDSS of the same cohort, projected over 10 years to produce a predicted mean EDSS outcome (red) and compared to the observed mean EDSS course of the cohort (blue).
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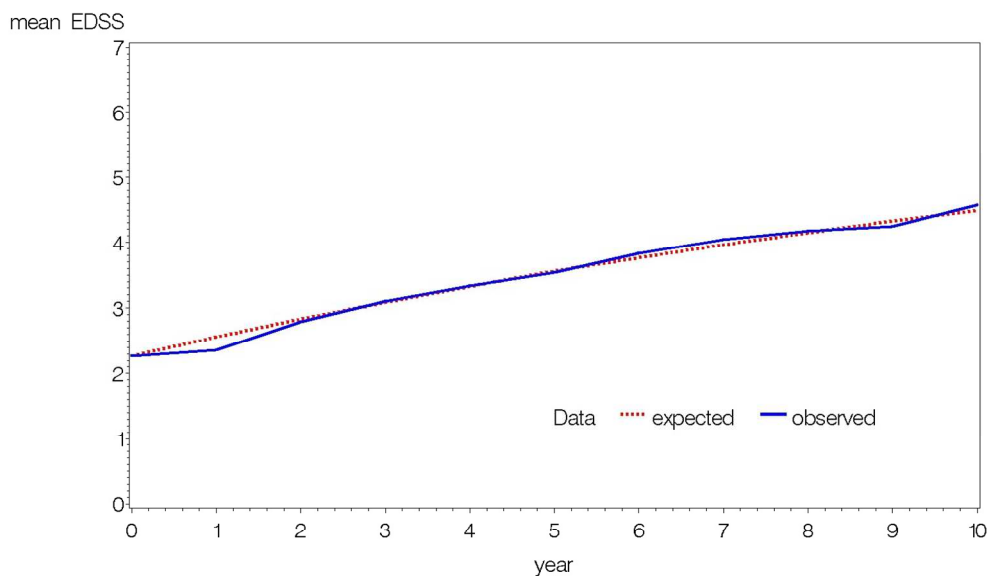


Figure 3: Transition probabilities obtained from the BCC dataset using the continuous Markov model with one covariate “age at onset” (binary version) were then applied to the baseline EDSS of the same cohort, projected over 10 years to produce a predicted outcome (red) compared to the observed course of the cohort (blue):

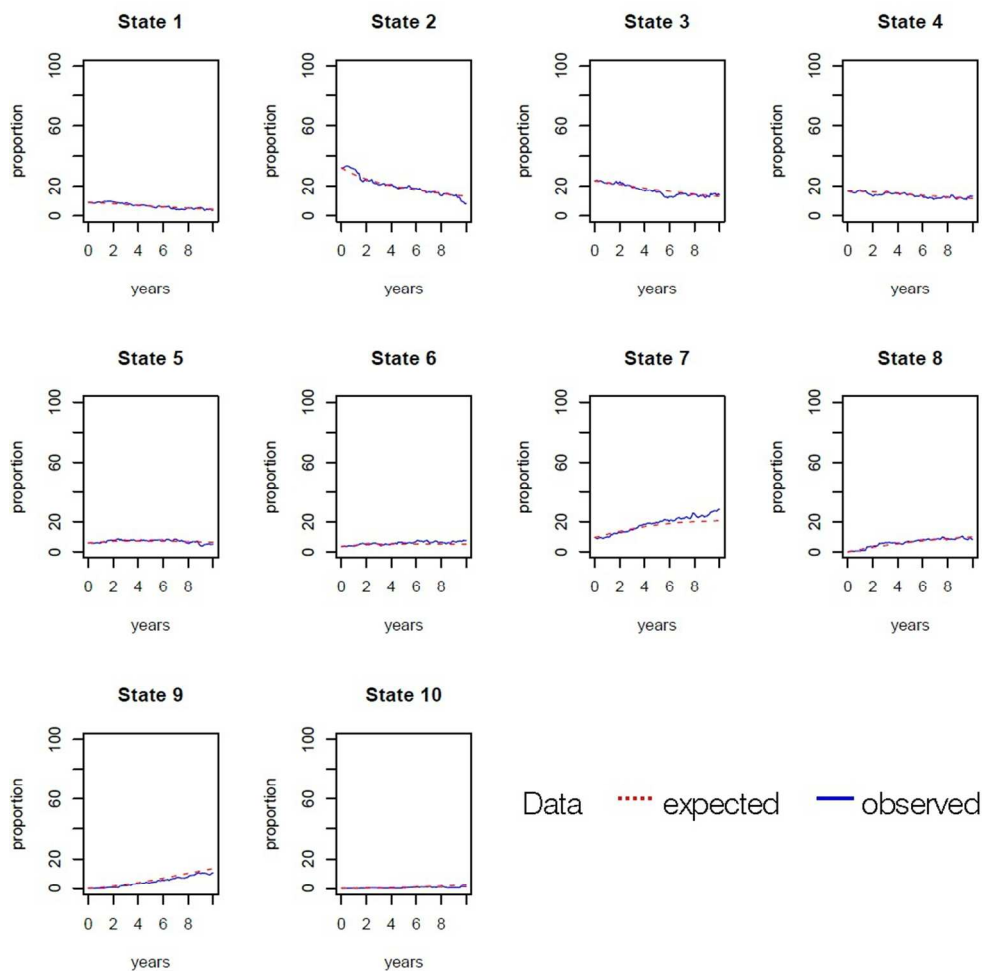
- a) Mean EDSS shown in the predicted and actual cohorts
- b) The proportion of patients predicted to be in each of the 10 EDSS states over time (state 1; EDSS 0, state 2; EDSS 1 and 1.5, state 3; EDSS 2.0 and 2.5, state 4; EDSS 3.0 and 3.5, state 5; EDSS 4.0 and 4.5, state 6; EDSS 5.0 and 5.5, state 7; EDSS 6.0 and 6.5, state 8; EDSS 7.0 and 7.5, state 9; EDSS 8.0 and 8.5, state 10; EDSS 9.0 and 9.5).

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Appendix 1 EDSS data extraction from the BCMS database

For the discrete Markov model and for tabular display of annual data the EDSS data were extracted and processed as follows. If the baseline EDSS fell when it was not the 'usual' yearly visit period, then subsequent EDSS scores could be lost. To maximize the number of EDSS transitions per patient, but keeping the yearly (+/- three calendar months) interval, EDSS scores were also 'individualized' as follows: the baseline EDSS became the baseline year, within that year, we searched to find the optimal new, individualized baseline for which the patient would, over the coming years have the most number of yearly EDSS scores. For some patients, this new individualized baseline date would not coincide with a clinic visit and would therefore not have an EDSS score present. When a baseline EDSS was required (e.g. for the discrete Markov model), data was also 'shifted' such that each patient would have a baseline EDSS. This lag between baseline ('eligibility') and EDSS was considered consistent with clinical practice in that it is not unusual to have a lag time between a patient becoming eligible for treatment and actual treatment initiation.

Appendix 2 Algorithms to forecast EDSS distributions at any given time

The 'msm' algorithm allows the EDSS distribution to be forecasted at any time t .¹⁹ To define what is the actual EDSS at a given time t (i.e. not necessarily when an observation was recorded) 'msm' offered two variants: (i) the last observation carried forward (LOCF) for each individual patient, and (ii) a 'midpoint interpolation' algorithm in which the EDSS state for a given patient at time t was taken as the score closest in time to the actually observed EDSS. Suppose an individual was observed in EDSS states S_{r-1} and S_r at two consecutive times t_{r-1} and t_r , and we wanted to estimate "observed" proportions at a time t between t_{r-1} and t_r . LOCF then meant that individuals were assumed to be in state S_{r-1} at time t , the same state as they were at t_{r-1} . Midpoint interpolation meant if $t \leq (t_{r-1} + t_r) / 2$, the midpoint of t_{r-1} and t_r , the state at t was assumed to be S_{r-1} , otherwise S_r . Option (i) would be more appropriate if EDSS values were always measured immediately after each transition. Option (ii) would be more appropriate if EDSS values were measured at mixed time intervals ('fixed or random'). Option (ii) was considered to mimic the clinical setting more closely and is also appears more applicable in progressive diseases.¹⁹ Therefore all results presented in this paper were based on this 'midpoint interpolation' approach.

For the continuous Markov model we limited the range of transitions which can be regarded as 'instantaneous' to +/- 3, which meant that at any time t an instantaneous progression (or improvement) into another EDSS state was only possible when not exceeding three consecutive states (an instantaneous transition from 1 to 2, 3, or 4 was possible, for example, whereas 1 to 5 was not). This restriction was recommended to avoid computationally inefficient modelling of hazard rates which were virtually 0.

Appendix 3 Validation of the models

The following validation techniques were applied when evaluating the different Markov models.

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3 The most straightforward method for the discrete Markov model consisted of applying the transition
4 matrix (and the 2nd, 3rd etc. power) to the vector of the baseline EDSS distribution in the BCMS
5 reference database, calculating the forecasted EDSS distribution for t=1, 2, 3... years and comparing
6 against the actual EDSS. A similar validation was performed in the continuous Markov model, as
7 described by Jackson.¹
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10 As a second validation we divided the BCMS dataset randomly into two subsets of equal size, using
11 one half to derive the model separately for the two subgroups, and then assessing the goodness of
12 fit in the other half of the dataset. Although Jackson¹⁹ emphasises that “Assessing the goodness of
13 fit of this class of models [...] is worth further research” we decided to use a classical mean square
14 prediction error (weighted root mean square over years of the prediction error in the average
15 quantity shown, weighted by the number of patients contributing data in the given year) to compare
16 competing models. Moreover, the computed likelihood itself as a result of the maximum likelihood
17 algorithm was used to rank the different one and two covariate models.
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UK Multiple Sclerosis Risk-sharing Scheme: a new natural history dataset and an improved Markov model

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UK Multiple Sclerosis Risk-sharing Scheme: a new natural history dataset and an improved**Markov model**

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3 The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the
4 study being reported; that no important aspects of the study have been omitted; and that any
5 discrepancies from the study as planned (and, if relevant, registered) have been explained.
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Abstract

Objectives: In 2002, the UK's National Institute for Health and Care Excellence concluded that the multiple sclerosis (MS) disease modifying therapies; interferon- β and glatiramer acetate, were not cost-effective over the short term but recognised that reducing disability over the longer-term might dramatically improve the cost-effectiveness. The UK Risk-sharing Scheme (RSS) was established to ensure cost-effective provision by prospectively collecting disability-related data from UK treated MS patients and comparing findings to a natural history (untreated) cohort. However, deficiencies were found in the originally selected untreated cohort and the resulting analytical approach. This study aims to identify a more suitable natural history comparator cohort and to develop a robust analytical approach using the new cohort

Design: The Scientific Advisory Group review, recommended the British Columbia Multiple Sclerosis (BCMS) database, Canada, as providing a more suitable natural history comparator cohort.

Transition probabilities were derived and different Markov models (discrete and continuous) with and without baseline covariates were applied.

Setting: MS clinics and analysis groups in Canada and the UK.

Participants: From the BCMS database, 898 'untreated' MS patients considered eligible for drug treatment based on the UK's Association of British Neurologists criteria.

Outcome measure: The predicted disability, as measured by the Expanded Disability Status Scale (EDSS) score was collected and assessed for goodness of fit when compared to actual outcome.

Results: The BCMS untreated cohort contributed 7335 EDSS scores over a median 6.4 years (6357 "transitions" where EDSS values were recorded at consecutive visits) during the study period (1980-1995). A continuous Markov model with "age at onset" as a binary covariate was deemed the most suitable model for future RSS analysis.

Conclusion: A new untreated MS cohort from British Columbia, Canada has been selected and will be modelled using a continuous Markov model with age as a baseline covariate. This approach will now be applied to the treated UK RSS MS cohort for future price adjustment calculations.

Strengths and limitations of this study

Strengths of this study:

- Identification of a new natural history cohort for the UKRSS, consisting of untreated MS patients in an era when disease-modifying drugs for MS were not available, minimizing potential selection bias
- Identification and validation of a Markov model for disease progression in MS which can be applied to data collected in clinical practice over multiple years of follow up.
- The identification of an analytical model which can use data collected at any time point within the follow up period.

Limitations of this study:

- The study related to observational data collected in clinical practice; unseen or unmeasured confounding cannot be adjusted for.
- Different techniques to assess effectiveness of drugs in observational studies such as matching on propensity scores cannot be directly compared to this methodology.

Introduction

In January 2002, the UK's National Institute of Health and Care Excellence (NICE) opted not to recommend the use of the disease modifying therapies (DMTs) interferon- β and glatiramer acetate for multiple sclerosis (MS) on the basis of cost-effectiveness analyses using data derived from the pivotal 2-3 year randomised controlled trials.¹ However, they recognised that uncertainties over the assumptions made in the modelling could unpredictably influence the long-term estimates of cost effectiveness. Thus in February 2002 the UK's Department of Health launched the 'Risk-sharing Scheme' (RSS)² with a circular entitled the "Cost effective provision of disease modifying therapies for people with multiple sclerosis" in collaboration with the Association of British Neurologists (ABN), the MS Trust, the MS Society and the pharmaceutical companies manufacturing interferon- β and glatiramer acetate. Between 2002 and 2005 the scheme enrolled over 5,000 MS patients initiating a DMT in the UK, with the aim of measuring their disability annually over a ten year period.

The principle In the RSS is to use a Markov model to predict, for each DMT separately, the expected movement of patients between the EDSS states both "on" and "off" treatment. For patients "off" treatment, the model uses a matrix of transition probabilities derived from the actual progressions seen in the 'natural history' comparator cohort. These transition matrices are modified for patients "on" treatment by multiplying by the hazard ratio (relative rate of disease progression) derived separately for each DMT from the pivotal randomized controlled clinical trials. The model then predicts how the distribution of patients will evolve over a 20-year horizon, starting with the actual distribution at baseline for the primary analysis RSS cohort. Comparing the average observed loss of utility (average utility-weighted disease progression) for patients in the RSS to the expected loss calculated by the Markov model for patients "on" treatment; it is calculated as follows. The *expected* 'benefit' of treatment (with a specific DMT) is the "hypothetical" difference between the expected outcome without treatment and with treatment, as calculated in each case from the Markov model. The *actual* 'benefit' of treatment is the "observed" difference between the expected outcome without treatment and the actual outcome with treatment. The 'deviation' of the actual benefit from the expected is the primary outcome measure and calculated as a percentage of the expected benefit. This measure can have negative or positive values so that a negative deviation implies that the observed benefit was greater than predicted, a positive deviation suggesting that it was worse than

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3 predicted and a value of 0 indicating that it was exactly as predicted. A positive deviation beyond the
4 level agreed (confidential and individual between each pharmaceutical company and the Department
5 of Health) would lead to a price adjustment down to achieve the target cost effectiveness. Details can
6 be found in the Health Service Circular².
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11 The original cost effectiveness model³ produced a target outcome based upon transition probabilities
12 obtained from a pre-existing natural history (DMT naive) cohort of patients from London, Ontario,
13 Canada along with hazard ratios from the pivotal randomised control trials (unpublished data provided
14 to the Department of Health by the manufacturers). Complementary quality of life data collected by
15 the MS Trust⁴ and cost data from Kobelt et al⁵ were used to populate the cost-effectiveness model.
16
17 The targets ensured that the UK's National Health Service benchmark of £36,000 (46,000 Euro /
18 56,000 US dollars) per quality adjusted life year (QALY) was reached over a 20 year projection,
19 based on a planned 10 year follow up period within the RSS with 2 yearly interim analyses. Before
20 being allowed to enter the scheme, the costs of each drug was assessed against the NICE bench
21 mark over a 20 year time horizon. Price reductions were implemented to ensure each product
22 reached the target cost per QALY using the original NICE calculations³, an average 13.7% price
23 reduction was achieved for the NHS at the outset of the Scheme.
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34 The two year analysis revealed significant inconsistencies in a number of sensitivity analyses.⁶
35 Depending on the underlying assumptions, some analyses suggested that observed disability
36 progression in the treated cohort was worse than that predicted from the historical untreated cohort
37 while others demonstrated the contrary effect. A detrimental effect of DMT did not match the
38 described effect on short term, 2-3 year, disability seen in the randomised placebo controlled trials.⁷⁻¹²
39
40 With the predetermined analytical approach (based on a discrete Markov model) appearing to
41 produce unreliable results with wide variation, a decision was made to postpone any decision on cost
42 effectiveness to allow for a reappraisal of the process and to reconsider whether the statistical models
43 and control data chosen were "fit for purpose."
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51 In retrospect, both the control data set and analysis model selected, when setting up the RSS, were
52 found to have intrinsic flaws that made them unsuitable for the task.⁶ The natural history cohort (from
53 London, Ontario, Canada) was unexpectedly found to contain retrospectively smoothed disability data
54 (rather than actual, real-time collected disability scores), censoring any improvement in EDSS.
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3 Comparing our uncensored treated cohort to data retrospectively smoothed in this way would have
4 the effect of unpredictably underestimating any treatment effect. In addition, individual-level patient
5 data were not available from the London, Ontario cohort, which prevented precise baseline matching
6 between the two cohorts, limiting our validation of the underlying (Markov) model for disease
7 progression. Furthermore, there were only 342 patients matching the ABN prescribing criteria from
8 which to generate the models.
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15 This paper outlines the development of a more appropriate analysis plan and the choice of a cohort fit
16 for the needs of the scheme. The method described will be applied in the 4 and 6 year cost-
17 effectiveness analyses. The analysis plan was approved by the scheme's independent Scientific
18 Advisory Group in December 2012 in advance of unlocking the newly collected 4 and 6 year UK Risk-
19 sharing Scheme data planned for autumn 2013.
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24 **Methods**

25 Identification of a new multiple sclerosis natural history dataset

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31 The Scientific Advisory Group undertook a detailed examination of all the available dataset through
32 literature reviews, expert opinion, discussion with the clinical leads for the RSS and discussion with
33 the Sylvia Lawry Centre for Multiple Sclerosis Research, Germany (<http://www.slcmr.net>). Selection
34 criteria included availability of Expanded Disability Status Scale (EDSS) score measurements and
35 access to the unprocessed (actual) scores (i.e. no data smoothing or other data manipulation). Other
36 factors considered were size of the database, prospective data collection and length of follow-up, and
37 the broader setting such as a close match to the UK in terms of the health system and MS prevalence
38 in the underlying population. Whilst no single perfect dataset existed the British Columbia Multiple
39 Sclerosis (BCMS) database, Canada (est. 1980) was identified as the best natural history comparator
40 cohort for our purposes.^{13,14} In this dataset – as in the RSS – actual EDSS scores were recorded
41 prospectively. It is estimated to capture 80% of the BC MS population^{15,16} and as such is considered
42 representative of the wider MS population. EDSS scores were recorded by MS specialist neurologists
43 after a face-to-face consultation with the patient; this typically occurred at the annual MS clinic visit.
44 Patient data was not truncated if secondary-progressive MS was reached; i.e. all relapse-onset MS
45 patients and their respective EDSS scores were considered eligible. By 2004, the database had
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3 records for over 5900 patients spanning 28 years (>25,000 cumulative years) of prospective follow-
4
5 up. Until 1996 DMTs were not widely available in British Columbia.
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7

8 Patient and data selection from the BCMS database. 9

10
11 In order to generate relevant data for our needs, patients were only selected from the BCMS
12
13 database if they fulfilled the 2001 Association of British Neurologists (ABN) criteria for interferon- β and
14
15 glatiramer acetate (IFN- β /GA) use (adapted from Appendix IV Health Service Circular 2002/004),
16
17 defined as: EDSS \leq 6.5; \geq 18 years old; two relapses in the last 2 calendar years.
18

19
20 Baseline for each patient was the 'first eligibility date,' meaning the first date at which a patient fulfilled
21
22 the ABN eligibility criteria. Only patients with definite MS (Poser criteria¹⁷) and a minimum of two
23
24 EDSS scores at least 9 months apart were considered.

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26 In order to be comparable with the RSS data the following adjustments and selection were applied:
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29 1) EDSS scores taken during a relapse or when disability was affected by other factors considered
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31 largely unrelated to MS (e.g. hip fracture) were excluded.
32

33
34 2) For the original discrete Markov model (see below) as well as visual presentation of the yearly
35
36 descriptive data (see under results), annual EDSS scores were needed. However, as is typical in
37
38 clinical practice, not all visits / EDSS assessments occurred at exactly yearly intervals and the
39
40 exclusion of some EDSS scores (e.g. due to a relapse or hip fracture) also affected the availability of
41
42 a yearly score. Therefore, data was selected such that only EDSS scores one year apart (+/- three
43
44 calendar months) were considered. See appendix 1 for further details.
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47 3) For the continuous Markov model, (see below) all eligible EDSS scores were used regardless of
48
49 their measurement interval i.e. no yearly data selection, as in (2), was needed.
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52 4) All patient data was truncated to the end of 1995 (i.e. the last full year in which the DMTs were not
53
54 widely available in BC Although initially it was planned to truncate individual patient profiles only once
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56 a DMT was initiated (in order to maximise the number of EDSS assessments), even when this
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58 extended past 1995 when treatment would have been available). It became apparent that this
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introduced a bias into the data, likely related to 'indication bias,' whereby patients 'doing well' would be less likely to start a DMT.

Analysis

The primary purpose of the analytical work was to find the best statistical model able to predict EDSS progression in a natural history cohort based on entry demographic and clinical data. The following models were applied in the current study and their performances were critically evaluated.

a) The discrete Markov model¹⁸ as in the original 2 year analysis⁶ i.e. disability scores (EDSS) had to be measured at discrete, fixed time points.

b) A continuous Markov model allowing for EDSS scores to be collected at any time, i.e. at any unevenly spaced time intervals, as is typical in clinical practice.¹⁹ Such a model also allowed covariates to be included. This model allows for more complete use of EDSS scores collected at irregular time intervals both in the BCMS and RSS cohorts.

With regard to the "MS course" (i.e. relapsing remitting vs. secondary progressive) as a potential covariate, we did not distinguish between these disease states when developing the Markov models because secondary progressive MS is simply a later stage of the relapsing remitting form of the disease and the transition has considerable overlap.

Predicting outcomes in the continuous Markov model (b)

A multi-state model algorithm ('R' library 'msm'¹⁹) allows the EDSS distribution to be predicted at any time t . See appendix 2 for further details).

To keep computations feasible, only integer EDSS values were used and fractional values rounded down (i.e. EDSS 1.5 was scored as 1, 2.5 was scored as 2 etc.). Moreover, 'msm' as a tool for *multi-state modelling* requires a consecutive numbering of (disease) states, starting with "1". Therefore the (rounded down) EDSS 0 became 'state 1', EDSS 1 'state 2' etc., leading to the ten EDSS 'states' (1–10) representing EDSS 0–9. Transition probability and intensity matrices as the output of these models were then used to predict disease progression in terms of EDSS as follows.

Covariates considered in the models

The selection of potential covariates by the scientific advisory group was based upon; (a) those which were reliably and consistently recorded in both the BCMS and the RSS database and (b) *a priori* knowledge of those associated with the outcome of disability progression. As a result, sex, age at MS symptom onset, as well as disease duration and disability (EDSS) – combined into a Multiple Sclerosis Severity Score (MSSS)²⁰ were tested in the continuous Markov model with up to two covariates. In addition, for the more promising models an alternative model was considered with dichotomous covariates (split at the median) replacing the continuous variables. This has the advantage that the resulting model can be formulated as the aggregate of a small number of discrete Markov models, so computations can be carried out without requiring special software, especially since the EDSS values in the RSS have been collected at strict yearly intervals, as opposed to the BCMS data which was based on routine clinical practice, and therefore do not necessitate a continuous model.

Critical evaluation of the models was performed using the following validation techniques, with the goal being to identify the most appropriate model to represent the natural progression of MS. See appendix 3 for further details.

- 1) Transition probabilities derived from the complete eligible, BCMS natural history data were applied to the baseline data to predict outcomes over the subsequent 10 years to assess how well it matched the observed data from which the model was derived.
- 2) The BCMS dataset was repeatedly randomly divided into two subsets of equal size, with one half only being used to derive transition probabilities (as in #1). The probabilities derived from this half were then applied to the baseline characteristics of the second half, generating a model whose goodness of fit could be judged against the actual, observed 10 year disability data of this second half.

Measuring Goodness of Fit

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3 Goodness of fit was assessed via visual inspection of the graphical displays as well as numerically.
4 These included progression over time (mean EDSS profiles) for the cohort as a whole as well as
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6 comparisons with the proportions in a particular EDSS state over time.
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9 For the numerical assessment a classical mean square prediction error (weighted root mean square
10 over years of the prediction error in the average quantity shown, weighted by the number of patients
11 contributing data in the given year) and the likelihood, resulting from the maximum likelihood
12 algorithm were calculated for each of the covariate models to allow comparison.
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17 This study was approved by the University of British Columbia's Clinical Research Ethics Board (H08-
18 01544)'
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20 21 22 **Results**

23 24 Data Description

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27 The baseline demographics showed the BCMS and RSS cohorts to be remarkably well matched.
28 Patient characteristics are shown in table 1.
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32 The natural history BCMS comparator dataset comprised of 898 patient profiles with 7335 EDSS
33 scores providing 6357 transitions between consecutive EDSS states, i.e 6357 'events' where EDSS
34 values were recorded at consecutive visits. In any given "transition," a patient's EDSS could increase,
35 decrease or stay the same
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38 39 40 Discrete Markov model

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43 When applying the discrete Markov model to the BCMS reference data, the goodness of fit was
44 unsatisfactory, underestimating EDSS in earlier years and overestimating in later years (see figure 1).
45 Consequently, the discrete Markov model was no longer considered appropriate, and development of
46 a continuous Markov model was pursued.
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49 50 51 Continuous Markov models

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54 The following continuous 10 state Markov models (EDSS 0 to 9), with and without covariates, were
55 evaluated:
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58 1. Model without covariates
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- 3 2. One covariate model with age at onset*
- 4 3. One covariate model with MSSS* at baseline
- 5 4. One covariate model with disease duration* at baseline
- 6 5. One covariate model with sex
- 7 6. Two covariate model: sex and age at onset*
- 8 7. Two covariate model: MSSS* at baseline and age at onset*
- 9 8. Two covariate model: disease duration* at baseline and age at onset*
- 10 - *two variants were implemented: continuous (original) data and a 'binary' version with the
- 11 median used for categorisation.
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17 There was a systematic deviation with a slight overestimation when the continuous Markov model
18 without covariates was applied (figure 2). Hence this model was not considered further.

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21 After validation was repeated for all covariate models (table 2), it was noted that inclusion of a second
22 covariate did not reveal any additional benefits. With one covariate, the model with "age at onset" as a
23 binary covariate (median: 28 years) was selected because it displayed the smallest -2 log likelihood
24 and minimal EDSS prediction error, see table 2. Further, the goodness of fit was acceptable when
25 comparing the predicted and observed EDSS profiles, as shown in Figure 3a. A more detailed
26 comparison of observed and expected proportions 'per EDSS state' is shown in Figure 3b which
27 confirmed that no systematic deviations were present which might otherwise have been cancelled out
28 when only looking at an average EDSS profile. It was concluded that only random fluctuation
29 remained, and a systematic deviation was no longer visible. When comparing figure 1 with figures 2
30 or 3 it should be noted that the former is based on the *annual* EDSS data which were obtained as
31 described in Appendix 1 while figures 2 and 3 show the EDSS at any time t , i.e. not necessarily when
32 an observation was recorded (while the continuous Markov model takes into account all observations
33 at any time t it is not straightforward to define what the 'observed EDSS' at any time t is in a graphic
34 representation; for details on how to define and calculate what is the observed EDSS at a given time
35 see Appendix 2).

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38 Using this 'best' model, transition probabilities were extracted from half of the BCMS cohort and
39 applied to the other half. This gave good predictions, with the mean EDSS profiles (observed versus
40 predicted) being similar to each other and to those of the entire cohort.
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3 In summary, the continuous Markov model with a single covariate - onset age - was considered the
4 model of choice to be used in future RSS analysis. The respective transition matrices are presented in
5
6 Table 3.
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9 **Discussion**

10 This paper outlines the successful identification of a more suitable natural history cohort for the UK
11 MS risk-sharing scheme, with the British Columbia, Canada dataset now replacing the London,
12 Ontario, Canada cohort in the RSS analysis plan. The analytical work is based on a Markov model
13 which has been frequently used for ordinal data from relapsing (remitting) diseases, especially
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15 MS.^{21,22,23}
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21 Further, because use of the British Columbian data has now allowed access to a richer dataset,
22 including full access to original, 'real-time' disability (EDSS) assessments, as well as individual
23 patient-level, we have been able to explore and develop more appropriate approaches. Specifically,
24 we were able to employ more advanced statistical models, making use of all the available data and
25 including clinically relevant patient-level characteristics as covariates in order to identify the most
26 accurate predictive model to be applied to the RSS. Finally, we observed that to minimize 'indication
27 bias' in relation to initiation of a DMT in the natural history cohort (British Columbia), censoring (data
28 truncation) was more appropriate at the population (rather than individual) level.
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33 Findings from our validation procedures indicate future feasibility with respect to obtaining reliable
34 cost-effectiveness results in the upcoming 6 year RSS analyses. For instance, visualisation of the
35 predicted and observed outcomes in the final model showed almost perfect overlap, with a one-
36 covariate model, with no additional improvements from introducing further covariates. In addition, the
37 final model was able to predict accurately the MS disease course (disability) in half of the cohort
38 (randomly selected) having obtained the transition probabilities from the other half. These
39 observations along with the baseline comparability of the BCMS and the RSS cohorts suggest the
40 transition probabilities from the BCMS cohort within this model can be used to predict the untreated
41 progression of patients in the RSS.
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46 An additional strength of this continuous model is the ability to include all valid disability (EDSS)
47 assessments, regardless of their exact timing, maximising data usage. We acknowledge the potential
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3 limitations of using of a historical control from a geographically discrete population. It is possible that
4 the natural history of MS has changed over time or that the BCMS population is not representative of
5 a UK one. However, in British Columbia, it has been previously shown that disability progression (as
6 measured by the EDSS) has not substantially changed overtime (1980-2009²⁴). Further, we have
7 previously shown that the use of a 'contemporary' untreated control cohort – i.e. where patients are
8 potentially eligible for a DMT in an era when the DMTs are readily available, but remain untreated - is
9 subject to indication bias and thus a historical control cohort, with data collected pre-DMT use, is likely
10 to be more appropriate.²⁵ Although we are proposing using a dataset from Canada (as was the
11 original RSS natural history dataset) and cannot rule out differences between the BCMS patients and
12 the UK RSS cohort, we are reassured that the baseline features are comparable except baseline
13 EDSS, but in the underlying Markov model we calculate the transition probabilities between EDSS
14 'states', and different baseline EDSS distributions would only matter if baseline EDSS as such had a
15 prognostic value, which doesn't seem to be the case when we were looking at the rates of EDSS
16 progression stratified by EDSS at baseline. In addition, the underlying ethnicity of the two jurisdictions
17 was similar; around the time of the cohort selection in British Columbia, 30.2% of the population self-
18 identified as British and within the wider BCMS database, >90% were Caucasian,^{26,27} which is
19 comparable to the UK cohort. Both cohorts may have enrolled a small number of patients with
20 neuromyelitis optica (we estimate this to be less than 0.5% of the total²⁸) because the availability of
21 the antibody assay occurred after 2007 (and after enrolment to the RSS scheme). An additional
22 limitation is the potential for different ways of measuring the EDSS scores between the BCMS and the
23 UK RSS cohorts because of changes in how the EDSS is interpreted over time and also because of
24 differences in the physicians performing the assessments.

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Observational studies, such as the RSS, provide a pragmatic approach when assessing drug effectiveness in a disease such as MS. Because MS disability accrues over decades, the cost effectiveness of disease modifying treatments cannot be assessed by short-term randomised controlled trials. However, observational studies are not without their own unique challenges.

Identifying and validating models to predict the untreated outcome of treated cohorts is a crucial step to measuring the long-term benefits of MS treatments. MS is the commonest cause of progressive disability in the western world, thus identification of treatments that might significantly impact long-

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3 term disability outcomes in MS could have major cost and quality of life benefits. Additionally, any
4 models developed here would be readily transferable to other chronic diseases.
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8 The current model described here will form the basis for calculating the drug cost per QALY and for
9 informing decisions on price adjustment in order to deliver the treatments cost effectively to UK MS
10 patients in an ongoing manner. The model will be used to calculate the Hazard Ratio at which each
11 product delivers efficacy against the NICE agreed cost per QALY and should any product fall short
12 price reductions will be implemented by the DH.
13
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16
17 Further work on repeated measures modelling, testing the models on other untreated appropriate MS
18 datasets and identifying sensitivity analyses (such as the effect of drop outs, switching to a different
19 class of DMT and the effects of treatments on backward transitions, i.e. disability improvements) are
20 also planned.
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4 All authors 1) made substantial contributions to the conception and design, acquisition of data, or
5 analysis and interpretation of data 2) were involved in drafting the article or revising it critically for
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7
8 JP is a clinical lead for the UK risk sharing scheme, inputs into the scientific advisory panel, was
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17 the analysis and was involved in the drafting and revising of the manuscript, CD is a department of
18 health advisor for the scheme, inputs into the scientific advisory panel, and was involved in the
19 analysis of the data, its interpretation and was involved in the drafting and revising of the manuscript.
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23 **We have read and understood the BMJ Group policy on declaration of interests and declare**
24 **the following interests:**
25

26
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43
44

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JP is a clinical lead for the UK risk sharing scheme, inputs into the scientific advisory panel, was involved in the identification of the alternative dataset, interpretation of the analysis and was involved in the drafting and revising of the manuscript. TB is the senior statistician in the scheme and the analysis of this work, was involved in the drafting and revision of this manuscript. HT, FZ and JO

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2
3 were responsible for the preparation of the BCMS dataset, analysis of the data, and drafting and
4
5 revision of the manuscript, MB was a clinical lead for the UK risk sharing scheme, input into the
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7 scientific advisory panel, was involved in the identification of the alternative dataset, interpretation
8
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12
13 interpretation of the analysis and was involved in the drafting and revising of the manuscript, CD is a
14
15 department of health advisor for the scheme, inputs into the scientific advisory panel, and was
16
17 involved in the analysis of the data, its interpretation and was involved in the drafting and revising of
18
19 the manuscript.
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22 23 **Data Sharing Statement**

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26 The British Columbia MS database is held at the host institution and analysis and access to the data
27
28 is limited to on site access. More detailed analysis results are available on request to the
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30 corresponding author.
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Table 1: Characteristics of patients reaching the Association of British Neurologists criteria in the British Columbia MS database after 1980 (the ‘natural history’ untreated comparator cohort) and the Risk-sharing Scheme cohort.

| Baseline (eligible for DMT) | BCMS (1980-1995*) | RSS full cohort RSS analysis cohort** |
|--|-------------------------|--|
| N | 898 | 5610 4138 |
| Females: n (%) | 666 (74.2%) | 4162 (74.2%) 3125 (75.5%) |
| Age at baseline, years: mean (SD; range) [years] | 37.2 (9.32; 18 - 69) | 39.4 (9.05; 15 - 73) 38.4 (8.58; 18 - 73) |
| Age at onset of MS, years: mean (SD; range) | 29.3 (8.65; 3 - 61) | 30.5 (8.52; 5 - 68) 30.5 (8.38; 5 - 68) |
| Disease duration at baseline, years: mean (SD; range) [years] | 7.9 (6.89; 0.2 to 38.9) | 8.8 (7.47; 0 - 46) 7.7 (6.62; 0 - 41) |
| SPMS documented at baseline# n (%) | 141 (15.7%) | 772 (13.8%) - |
| Relapses in the last two-years prior to eligibility: median (quartiles) | 2 (2 - 3) | 3 (2 - 3) 3 (2 - 3) |
| First eligible EDSS: median (quartiles; range) | 2 (1, 3.5; 0-6.5) | 3.5 (2.0, 5.0; 0 - 8.0) 3.0 (2.0, 4.0; 0 - 6.5) |

‘Eligibility’ refers to the first time a patient fulfilled the ABN criteria

**data was truncated to 1995 in the final models to minimize DMT exposure in the cohort*

*** “analysis cohort” is the subset of patients eligible for the analysis (e.g., treated patients, at least one post-baseline EDSS available etc.)*

#all were still DMT eligible

RSS=Risk-sharing Scheme ; BCMS=British Columbia MS database; SD=standard deviation;
EDSS=Expanded disability status score ; DMT=disease modifying treatment

Table 2: “Goodness of fit” statistics for the ten state* disability (EDSS) Markov models

| Description of each ten-state ¹ disability model | Minus 2 log likelihood ² x 1,000 | Prediction errors | | (years Utility) |
|---|---|-------------------|-------------------------|-----------------|
| | | Cells | 1-10) ³ EDSS | |
| No covariates | 17.152 | 2.20 | 0.24 | 0.022 |
| One covariate models | | | | |
| Age at onset, binary | 17.458 | 1.39 | 0.09 | 0.009 |
| Age at onset, continuous | 17.599 | 1.58 | 0.13 | 0.007 |
| MSSS at baseline, binary | 17.460 | 1.41 | 0.10 | 0.008 |
| MSSS at baseline, continuous | 17.457 | | | |
| Disease duration, binary | 17.462 | 1.33 | 0.10 | 0.009 |
| Disease duration, continuous | 17.557 | | | |
| Sex | 17.470 | 1.32 | 0.10 | 0.008 |
| Two covariates models | | | | |
| Sex and age at onset, binary | 17.603 | 1.51 | 0.14 | 0.007 |
| Sex and age at onset, continuous | 17.618 | | | |
| Age at onset and MSSS, binary | 17.609 | 1.53 | 0.14 | 0.007 |
| Age at onset and MSSS, continuous | 17.618 | | | |
| Age at onset and disease duration, binary | 17.603 | 1.52 | 0.14 | 0.007 |
| Age at onset and disease duration, continuous | 17.618 | | | |

¹the ten disability states refer to EDSS 0 to 9, i.e. EDSS 0 is “state 1”, EDSS 1 is “state 2” etc.

²log likelihood statistic as calculated by ‘msm’ module, see Jackson¹⁹ for details; lower values implying a better model (to be compared within each class of models, e.g. one-covariate and two-covariate models)

EDSS= Expanded disability status score ; MSSS= Multiple sclerosis status score

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3³Prediction errors, averaged over years 1-10, for (a) the EDSS distribution in individual cells, (b)
4 average EDSS, (c) average utility (see definitions in the appendix 3, comparing the values predicted
5 by the model with the “observed” values using the method of midpoint interpolation (see appendix 2).
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9 Primary goodness of fit statistic is -2 log likelihood; prediction errors have only been calculated for the
10 binary versions of the individual models except for the “final” model with age at onset as covariate
11 where prediction errors have been calculated for both versions.
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Table 3: Transition matrices for the ten state disability (EDSS) Markov model with “age at onset” as binary covariate and annual transition probabilities

| age at onset < 28 yrs | | | | | | | | | | | |
|-----------------------|---|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| to EDSS | | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| from EDSS | 0 | 0.68704 | 0.21102 | 0.07195 | 0.02236 | 0.00434 | 0.00136 | 0.00176 | 0.00012 | 0.00003 | 0.00000 |
| | 1 | 0.06122 | 0.67867 | 0.16643 | 0.06462 | 0.01698 | 0.00474 | 0.00667 | 0.00052 | 0.00014 | 0.00001 |
| | 2 | 0.01692 | 0.12656 | 0.59550 | 0.17291 | 0.04537 | 0.01842 | 0.02190 | 0.00182 | 0.00054 | 0.00005 |
| | 3 | 0.00620 | 0.05215 | 0.11647 | 0.54386 | 0.09452 | 0.05730 | 0.11480 | 0.01070 | 0.00366 | 0.00035 |
| | 4 | 0.00176 | 0.02251 | 0.06617 | 0.12107 | 0.48737 | 0.10090 | 0.16644 | 0.02621 | 0.00690 | 0.00067 |
| | 5 | 0.00055 | 0.00562 | 0.02915 | 0.05936 | 0.09153 | 0.47268 | 0.28098 | 0.03961 | 0.01910 | 0.00143 |
| | 6 | 0.00012 | 0.00141 | 0.00447 | 0.02516 | 0.03208 | 0.04241 | 0.72834 | 0.11509 | 0.04566 | 0.00525 |
| | 7 | 0.00001 | 0.00016 | 0.00052 | 0.00260 | 0.00730 | 0.00419 | 0.12197 | 0.68145 | 0.16286 | 0.01895 |
| | 8 | 0.00000 | 0.00001 | 0.00004 | 0.00030 | 0.00057 | 0.00053 | 0.01884 | 0.05747 | 0.86099 | 0.06124 |
| | 9 | 0.00000 | 0.00000 | 0.00000 | 0.00002 | 0.00004 | 0.00004 | 0.00178 | 0.00596 | 0.17090 | 0.82125 |
| age at onset ≥ 28 yrs | | | | | | | | | | | |
| to EDSS | | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| from EDSS | 0 | 0.69537 | 0.20294 | 0.07251 | 0.02170 | 0.00422 | 0.00137 | 0.00175 | 0.00011 | 0.00003 | 0.00000 |
| | 1 | 0.05826 | 0.69501 | 0.15783 | 0.06088 | 0.01638 | 0.00458 | 0.00643 | 0.00048 | 0.00013 | 0.00001 |
| | 2 | 0.01586 | 0.12133 | 0.60789 | 0.16796 | 0.04458 | 0.01849 | 0.02159 | 0.00174 | 0.00052 | 0.00004 |
| | 3 | 0.00594 | 0.04960 | 0.12006 | 0.54422 | 0.09109 | 0.05845 | 0.11649 | 0.01030 | 0.00355 | 0.00030 |
| | 4 | 0.00165 | 0.02214 | 0.06660 | 0.11519 | 0.48935 | 0.10388 | 0.16811 | 0.02580 | 0.00671 | 0.00056 |
| | 5 | 0.00052 | 0.00533 | 0.02942 | 0.05866 | 0.08736 | 0.48695 | 0.27310 | 0.03880 | 0.01883 | 0.00102 |
| | 6 | 0.00012 | 0.00133 | 0.00444 | 0.02497 | 0.03069 | 0.04080 | 0.74069 | 0.10897 | 0.04377 | 0.00423 |
| | 7 | 0.00001 | 0.00015 | 0.00052 | 0.00247 | 0.00727 | 0.00385 | 0.11684 | 0.69269 | 0.16061 | 0.01559 |
| | 8 | 0.00000 | 0.00001 | 0.00004 | 0.00029 | 0.00055 | 0.00050 | 0.01881 | 0.05574 | 0.90340 | 0.02066 |
| | 9 | 0.00000 | 0.00000 | 0.00000 | 0.00002 | 0.00004 | 0.00003 | 0.00176 | 0.00568 | 0.17414 | 0.81832 |

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8 **UK Multiple Sclerosis Risk-sharing Scheme: a new natural history dataset and an improved**

9 **Markov model**

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The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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**We have read and understood the BMJ Group policy on declaration of interests and declare
the following interests:**

30 Jacqueline Palace serves on the scientific advisory board for Charcot Foundation, and has performed
31 advisory work for Biogen Idec, Merck Serono Ltd, Bayer Schering Pharma, Novartis Pharmaceuticals
32 UK Ltd, Teva Pharmaceutical Industries Ltd, Gilenya, Ono Pharmaceutical Co Ltd, Primary i-research,
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34 QIDIS, Merck Serono Ltd, Novartis Pharmaceuticals and Bayer Schering Pharma, plus conference
35 expenses from Novartis and Merck Serono Ltd.
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42 Thomas Bregenzer –as an employee of PAREXEL International (Department of Biostatistics) has
43 been working for numerous pharmaceutical companies, including those which are participating in the
44 UK MS Risk Sharing Scheme. no financial interests to declare.
45
46
47

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53 British Columbia Multiple Sclerosis Research Program, Bayer Pharmaceutical (speaker, 2010,
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3 honoraria declined), Teva Pharmaceuticals (speaker 2011),ECTRIMS (2011, 2012), UK MS Trust
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5 declined), Novartis Canada (2012) and the US National MS Society (2012, honorarium declined).
6
7

8 Unless otherwise stated, all speaker honoraria are either donated to an MS charity or to an
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11

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21 Feng Zhu – no financial interests to declare
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23
24 Mike Boggild sits on advisory boards for Bio CSL, genzyme & Biogen Idec. Recieved sponsorship to
25 attend international meetings from Novartis & BioCSL. Department has received funding to develop
26 services from Biogen Idec, Genzyme and Novartis.
27
28

29
30 Martin Duddy over the past 5 years MD has received speaker honoraria, consulting fees and travel
31 grants from, Bayer, BiogenIdec, Novartis, Merck-Serono and Teva
32
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35 Charles Dobson – no financial interests to declare
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Abstract

Objectives: In 2002, the UK's National Institute for Health and Care Excellence concluded that the multiple sclerosis (MS) disease modifying therapies; interferon- β and glatiramer acetate, were not cost-effective over the short term but recognised that reducing disability over the longer-term might dramatically improve the cost-effectiveness. The UK Risk-sharing Scheme (RSS) was established to ensure cost-effective provision by prospectively collecting disability-related data from UK treated MS patients and comparing findings to a natural history (untreated) cohort. However, deficiencies were found in the originally selected untreated cohort and the resulting analytical approach. This study aims to identify a more suitable natural history comparator cohort and to develop a robust analytical approach using the new cohort

Design: The Scientific Advisory Group review, recommended the British Columbia Multiple Sclerosis (BCMS) database, Canada, as providing a more suitable natural history comparator cohort. Transition probabilities were derived and different Markov models (discrete and continuous) with and without baseline covariates were applied.

Setting: MS clinics and analysis groups in Canada and the UK.

Participants: From the BCMS database, 898 'untreated' MS patients considered eligible for drug treatment based on the UK's Association of British Neurologists criteria.

Outcome measure: The predicted disability, as measured by the Expanded Disability Status Scale (EDSS) score was collected and assessed for goodness of fit when compared to actual outcome.

Results: The BCMS untreated cohort contributed 7335 EDSS scores over a median 6.4 years (6357 "transitions" where EDSS values were recorded at consecutive visits) during the study period (1980-1995). A continuous Markov model with "age at onset" as a binary covariate was deemed the most suitable model for future RSS analysis.

Conclusion: A new untreated MS cohort from British Columbia, Canada has been selected and will be modelled using a continuous Markov model with age as a baseline covariate. This approach will now be applied to the treated UK RSS MS cohort for future price adjustment calculations.

Strengths and limitations of this study

Strengths of this study:

- Identification of a new natural history cohort for the UKRSS, consisting of untreated MS patients in an era when disease-modifying drugs for MS were not available, minimizing potential selection bias
- Identification and validation of a Markov model for disease progression in MS which can be applied to data collected in clinical practice over multiple years of follow up.
- The identification of an analytical model which can use data collected at any time point within the follow up period.

Limitations of this study:

- The study related to observational data collected in clinical practice; unseen or unmeasured confounding cannot be adjusted for.
- Different techniques to assess effectiveness of drugs in observational studies such as matching on propensity scores cannot be directly compared to this methodology.

Introduction

In January 2002, the UK's National Institute of Health and Care Excellence (NICE) opted not to recommend the use of the disease modifying therapies (DMTs) interferon- β and glatiramer acetate for multiple sclerosis (MS) on the basis of cost-effectiveness analyses using data derived from the pivotal 2-3 year randomised controlled trials.¹ However, they recognised that uncertainties over the assumptions made in the modelling could unpredictably influence the long-term estimates of cost effectiveness. Thus in February 2002 the UK's Department of Health launched the 'Risk-sharing Scheme' (RSS)² with a circular entitled the "Cost effective provision of disease modifying therapies for people with multiple sclerosis" in collaboration with the Association of British Neurologists (ABN), the MS Trust, the MS Society and the pharmaceutical companies manufacturing interferon- β and glatiramer acetate. Between 2002 and 2005 the scheme enrolled over 5,000 MS patients initiating a DMT in the UK, with the aim of measuring their disability annually over a ten year period.

The principle In the RSS is to use a Markov model to predict, for each DMT separately, the expected movement of patients between the EDSS states both "on" and "off" treatment. For patients "off" treatment, the model uses a matrix of transition probabilities derived from the actual progressions seen in the 'natural history' comparator cohort. These transition matrices are modified for patients "on" treatment by multiplying by the hazard ratio (relative rate of disease progression) derived separately for each DMT from the pivotal randomized controlled clinical trials. The model then predicts how the distribution of patients will evolve over a 20-year horizon, starting with the actual distribution at baseline for the primary analysis RSS cohort. Comparing the average observed loss of utility (average utility-weighted disease progression) for patients in the RSS to the expected loss calculated by the Markov model for patients "on" treatment; it is calculated as follows. The *expected* 'benefit' of treatment (with a specific DMT) is the "hypothetical" difference between the expected outcome without treatment and with treatment, as calculated in each case from the Markov model. The *actual* 'benefit' of treatment is the "observed" difference between the expected outcome without treatment and the actual outcome with treatment. The 'deviation' of the actual benefit from the expected is the primary outcome measure and calculated as a percentage of the expected benefit. This measure can have negative or positive values so that a negative deviation implies that the observed benefit was greater than predicted, a positive deviation suggesting that it was worse than

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3 predicted and a value of 0 indicating that it was exactly as predicted. A positive deviation beyond the
4 level agreed (confidential and individual between each pharmaceutical company and the Department
5 of Health) would lead to a price adjustment down to achieve the target cost effectiveness. Details can
6 be found in the Health Service Circular².
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11 The original cost effectiveness model³ produced a target outcome based upon transition probabilities
12 obtained from a pre-existing natural history (DMT naive) cohort of patients from London, Ontario,
13 Canada along with hazard ratios from the pivotal randomised control trials (unpublished data provided
14 to the Department of Health by the manufacturers). Complementary quality of life data collected by
15 the MS Trust⁴ and cost data from Kobelt et al⁵ were used to populate the cost-effectiveness model.
16
17 The targets ensured that the UK's National Health Service benchmark of £36,000 (46,000 Euro /
18 56,000 US dollars) per quality adjusted life year (QALY) was reached over a 20 year projection,
19 based on a planned 10 year follow up period within the RSS with 2 yearly interim analyses. Before
20 being allowed to enter the scheme, the costs of each drug was assessed against the NICE bench
21 mark over a 20 year time horizon. Price reductions were implemented to ensure each product
22 reached the target cost per QALY using the original NICE calculations³, an average 13.7% price
23 reduction was achieved for the NHS at the outset of the Scheme.
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34 The two year analysis revealed significant inconsistencies in a number of sensitivity analyses.⁶
35 Depending on the underlying assumptions, some analyses suggested that observed disability
36 progression in the treated cohort was worse than that predicted from the historical untreated cohort
37 while others demonstrated the contrary effect. A detrimental effect of DMT did not match the
38 described effect on short term, 2-3 year, disability seen in the randomised placebo controlled trials.⁷⁻¹²
39
40 With the predetermined analytical approach (based on a discrete Markov model) appearing to
41 produce unreliable results with wide variation, a decision was made to postpone any decision on cost
42 effectiveness to allow for a reappraisal of the process and to reconsider whether the statistical models
43 and control data chosen were "fit for purpose."
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51 In retrospect, both the control data set and analysis model selected, when setting up the RSS, were
52 found to have intrinsic flaws that made them unsuitable for the task.⁶ The natural history cohort (from
53 London, Ontario, Canada) was unexpectedly found to contain retrospectively smoothed disability data
54 (rather than actual, real-time collected disability scores), censoring any improvement in EDSS.
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3 Comparing our uncensored treated cohort to data retrospectively smoothed in this way would have
4 the effect of unpredictably underestimating any treatment effect. In addition, individual-level patient
5 data were not available from the London, Ontario cohort, which prevented precise baseline matching
6 between the two cohorts, limiting our validation of the underlying (Markov) model for disease
7 progression. Furthermore, there were only 342 patients matching the ABN prescribing criteria from
8 which to generate the models.
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11 This paper outlines the development of a more appropriate analysis plan and the choice of a cohort fit
12 for the needs of the scheme. The method described will be applied in the 4 and 6 year cost-
13 effectiveness analyses. The analysis plan was approved by the scheme's independent Scientific
14 Advisory Group in December 2012 in advance of unlocking the newly collected 4 and 6 year UK Risk-
15 sharing Scheme data planned for autumn 2013.
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17

18 **Methods**

19 Identification of a new multiple sclerosis natural history dataset

20
21 **The Scientific Advisory Group undertook a detailed examination of all the available dataset through**
22 **literature reviews, expert opinion, discussion with the clinical leads for the RSS and discussion with**
23 **the Sylvia Lawry Centre for Multiple Sclerosis Research, Germany (<http://www.slcmr.net>).** Selection
24 criteria included availability of Expanded Disability Status Scale (EDSS) score measurements and
25 access to the unprocessed (actual) scores (i.e. no data smoothing or other data manipulation). Other
26 factors considered were size of the database, prospective data collection and length of follow-up, and
27 the broader setting such as a close match to the UK in terms of the health system and MS prevalence
28 in the underlying population. **Whilst no single perfect dataset existed** the British Columbia Multiple
29 Sclerosis (BCMS) database, Canada (est. 1980) was identified as the best natural history comparator
30 cohort for our purposes.^{13,14} In this dataset – as in the RSS – actual EDSS scores were recorded
31 prospectively. It is estimated to capture 80% of the BC MS population^{15,16} and as such is considered
32 representative of the wider MS population. EDSS scores were recorded by MS specialist neurologists
33 after a face-to-face consultation with the patient; this typically occurred at the annual MS clinic visit.
34 Patient data was not truncated if secondary-progressive MS was reached; i.e. all relapse-onset MS
35 patients and their respective EDSS scores were considered eligible. By 2004, the database had
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records for over 5900 patients spanning 28 years (>25,000 cumulative years) of prospective follow-up. Until 1996 DMTs were not widely available in British Columbia.

Patient and data selection from the BCMS database.

In order to generate relevant data for our needs, patients were only selected from the BCMS database if they fulfilled the 2001 Association of British Neurologists (ABN) criteria for interferon- β and glatiramer acetate (IFN- β /GA) use (adapted from Appendix IV Health Service Circular 2002/004), defined as: EDSS \leq 6.5; \geq 18 years old; two relapses in the last 2 calendar years.

Baseline for each patient was the 'first eligibility date,' meaning the first date at which a patient fulfilled the ABN eligibility criteria. Only patients with definite MS (Poser criteria¹⁷) and a minimum of two EDSS scores at least 9 months apart were considered.

In order to be comparable with the RSS data the following adjustments and selection were applied:

1) EDSS scores taken during a relapse or when disability was affected by other factors considered largely unrelated to MS (e.g. hip fracture) were excluded.

2) For the original discrete Markov model (see below) as well as visual presentation of the yearly descriptive data (see under results), annual EDSS scores were needed. However, as is typical in clinical practice, not all visits / EDSS assessments occurred at exactly yearly intervals and the exclusion of some EDSS scores (e.g. due to a relapse or hip fracture) also affected the availability of a yearly score. Therefore, data was selected such that only EDSS scores one year apart (+/- three calendar months) were considered. See appendix 1 for further details.

3) For the continuous Markov model, (see below) all eligible EDSS scores were used regardless of their measurement interval i.e. no yearly data selection, as in (2), was needed.

4) All patient data was truncated to the end of 1995 (i.e. the last full year in which the DMTs were not widely available in BC Although initially it was planned to truncate individual patient profiles only once a DMT was initiated (in order to maximise the number of EDSS assessments), even when this extended past 1995 when treatment would have been available). It became apparent that this

introduced a bias into the data, likely related to 'indication bias,' whereby patients 'doing well' would be less likely to start a DMT.

Analysis

The primary purpose of the analytical work was to find the best statistical model able to predict EDSS progression in a natural history cohort based on entry demographic and clinical data. The following models were applied in the current study and their performances were critically evaluated.

a) The discrete Markov model¹⁸ as in the original 2 year analysis⁶ i.e. disability scores (EDSS) had to be measured at discrete, fixed time points.

b) A continuous Markov model allowing for EDSS scores to be collected at **any time, i.e. at any** unevenly spaced time intervals, as is typical in clinical practice.¹⁹ Such a model also allowed covariates to be included. This model allows for more complete use of EDSS scores collected at irregular time intervals both in the BCMS and RSS cohorts.

With regard to the "MS course" (i.e. relapsing remitting vs. secondary progressive) as a potential covariate, we did not distinguish between these disease states when developing the Markov models because secondary progressive MS is simply a later stage of the relapsing remitting form of the disease and the transition has considerable overlap.

Predicting outcomes in the continuous Markov model (b)

A multi-state model algorithm ('R' library 'msm'¹⁹) allows the EDSS distribution to be predicted at any time t . See appendix 2 for further details).

To keep computations feasible, only integer EDSS values were used and fractional values rounded down (i.e. EDSS 1.5 was scored as 1, 2.5 was scored as 2 etc.). Moreover, 'msm' as a tool for *multi-state modelling* requires a consecutive numbering of (disease) states, starting with "1". Therefore the (rounded down) EDSS 0 became 'state 1', EDSS 1 'state 2' etc., leading to the ten EDSS 'states' (1–10) representing EDSS 0–9. Transition probability and intensity matrices as the output of these models were then used to predict disease progression in terms of EDSS as follows.

Covariates considered in the models

The selection of potential covariates by the scientific advisory group was based upon; (a) those which were reliably and consistently recorded in both the BCMS and the RSS database and (b) *a priori* knowledge of those associated with the outcome of disability progression. As a result, sex, age at MS symptom onset, as well as disease duration and disability (EDSS) – combined into a Multiple Sclerosis Severity Score (MSSS)²⁰ were tested in the continuous Markov model with up to two covariates. In addition, for the more promising models an alternative model was considered with dichotomous covariates (split at the median) replacing the continuous variables. This has the advantage that the resulting model can be formulated as the aggregate of a small number of discrete Markov models, so computations can be carried out without requiring special software, especially since the EDSS values in the RSS have been collected at strict yearly intervals, as opposed to the BCMS data which was based on routine clinical practice, and therefore do not necessitate a continuous model.

Critical evaluation of the models was performed using the following validation techniques, with the goal being to identify the most appropriate model to represent the natural progression of MS. See appendix 3 for further details.

- 1) Transition probabilities derived from the complete eligible, BCMS natural history data were applied to the baseline data to predict outcomes over the subsequent 10 years to assess how well it matched the observed data from which the model was derived.
- 2) The BCMS dataset was repeatedly randomly divided into two subsets of equal size, with one half only being used to derive transition probabilities (as in #1). The probabilities derived from this half were then applied to the baseline characteristics of the second half, generating a model whose goodness of fit could be judged against the actual, observed 10 year disability data of this second half.

Measuring Goodness of Fit

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3 Goodness of fit was assessed via visual inspection of the graphical displays as well as numerically.
4 These included progression over time (mean EDSS profiles) for the cohort as a whole as well as
5 comparisons with the proportions in a particular EDSS state over time.
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9 For the numerical assessment a classical mean square prediction error (weighted root mean square
10 over years of the prediction error in the average quantity shown, weighted by the number of patients
11 contributing data in the given year) and the likelihood, resulting from the maximum likelihood
12 algorithm were calculated for each of the covariate models to allow comparison.
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17 This study was approved by the University of British Columbia's Clinical Research Ethics Board (H08-
18 01544)
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20 21 **Results**

22 Data Description

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25 The baseline demographics showed the BCMS and RSS cohorts to be remarkably well matched.
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27 Patient characteristics are shown in table 1.
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31 The natural history BCMS comparator dataset comprised of 898 patient profiles with 7335 EDSS
32 scores providing 6357 transitions between consecutive EDSS states, i.e 6357 'events' where EDSS
33 values were recorded at consecutive visits. In any given "transition," a patient's EDSS could increase,
34 decrease or stay the same
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38 Discrete Markov model

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40 When applying the discrete Markov model to the BCMS reference data, the goodness of fit was
41 unsatisfactory, underestimating EDSS in earlier years and overestimating in later years (see figure 1).
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43 Consequently, the discrete Markov model was no longer considered appropriate, and development of
44 a continuous Markov model was pursued.
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48 Continuous Markov models

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50 The following continuous 10 state Markov models (EDSS 0 to 9), with and without covariates, were
51 evaluated:
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- 54 1. Model without covariates
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- 3 2. One covariate model with age at onset*
- 4 3. One covariate model with MSSS* at baseline
- 5 4. One covariate model with disease duration* at baseline
- 6 5. One covariate model with sex
- 7 6. Two covariate model: sex and age at onset*
- 8 7. Two covariate model: MSSS* at baseline and age at onset*
- 9 8. Two covariate model: disease duration* at baseline and age at onset*
- 10 - *two variants were implemented: continuous (original) data and a 'binary' version with the
- 11 median used for categorisation.
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17 There was a systematic deviation **with a slight overestimation when the continuous Markov model**

18 **without covariates was applied (figure 2). Hence this model was** not considered further.

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22 After validation was repeated for all covariate models (table 2), it was noted that inclusion of a second

23 covariate did not reveal any additional benefits. With one covariate, the model with "age at onset" as a

24 binary covariate (**median: 28 years**) was selected because it displayed the smallest -2 log likelihood

25 and minimal EDSS prediction error, see table 2. Further, the goodness of fit was acceptable when

26 comparing the predicted and observed EDSS profiles, as shown in Figure 3a. A more detailed

27 comparison of observed and expected proportions 'per EDSS state' is shown in Figure 3b which

28 confirmed that no systematic deviations were present which might otherwise have been **cancelled out**

29 **when only looking at an average EDSS profile.** It was concluded that only random fluctuation

30 remained, and a systematic deviation was no longer visible. When comparing figure 1 with figures 2

31 or 3 it should be noted that the former is based on the *annual* EDSS data which were obtained as

32 described in Appendix 1 while figures 2 and 3 show the EDSS at any time t , i.e. not necessarily when

33 an observation was recorded (**while the continuous Markov model takes into account all observations**

34 **at any time t it is not straightforward to define what the 'observed EDSS' at any time t is in a graphic**

35 **representation;** for details on how to define and calculate what is the observed EDSS at a given time

36 see Appendix 2).

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50 Using this 'best' model, transition probabilities were extracted from half of the BCMS cohort and

51 applied to the other half. This gave good predictions, with the mean EDSS profiles (observed versus

52 predicted) being similar to each other and to those of the entire cohort.

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3 In summary, the continuous Markov model with a single covariate - onset age - was considered the
4 model of choice to be used in future RSS analysis. The respective transition matrices are presented in
5 Table 3.
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9 **Discussion**

10 This paper outlines the successful identification of a more suitable natural history cohort for the UK
11 MS risk-sharing scheme, with the British Columbia, Canada dataset now replacing the London,
12 Ontario, Canada cohort in the RSS analysis plan. The analytical work is based on a Markov model
13 which has been frequently used for ordinal data from relapsing (remitting) diseases, especially
14 MS.^{21,22,23}
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22 Further, because use of the British Columbian data has now allowed access to a richer dataset,
23 including full access to original, 'real-time' disability (EDSS) assessments, as well as individual
24 patient-level, we have been able to explore and develop more appropriate approaches. Specifically,
25 we were able to employ more advanced statistical models, making use of all the available data and
26 including clinically relevant patient-level characteristics as covariates in order to identify the most
27 accurate predictive model to be applied to the RSS. Finally, we observed that to minimize 'indication
28 bias' in relation to initiation of a DMT in the natural history cohort (British Columbia), censoring (data
29 truncation) was more appropriate at the population (rather than individual) level.
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37 Findings from our validation procedures indicate future feasibility with respect to obtaining reliable
38 cost-effectiveness results in the upcoming 6 year RSS analyses. For instance, visualisation of the
39 predicted and observed outcomes in the final model showed almost perfect overlap, with a one-
40 covariate model, with no additional improvements from introducing further covariates. In addition, the
41 final model was able to predict accurately the MS disease course (disability) in half of the cohort
42 (randomly selected) having obtained the transition probabilities from the other half. These
43 observations along with the baseline comparability of the BCMS and the RSS cohorts suggest the
44 transition probabilities from the BCMS cohort within this model can be used to predict the untreated
45 progression of patients in the RSS.
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55 An additional strength of this continuous model is the ability to include all valid disability (EDSS)
56 assessments, regardless of their exact timing, maximising data usage. We acknowledge the potential
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3 limitations of using of a historical control from a geographically discrete population. It is possible that
4 the natural history of MS has changed over time or that the BCMS population is not representative of
5 a UK one. However, in British Columbia, it has been previously shown that disability progression (as
6 measured by the EDSS) has not substantially changed overtime (1980-2009²⁴). Further, we have
7 previously shown that the use of a 'contemporary' untreated control cohort – i.e. where patients are
8 potentially eligible for a DMT in an era when the DMTs are readily available, but remain untreated - is
9 subject to indication bias and thus a historical control cohort, with data collected pre-DMT use, is likely
10 to be more appropriate.²⁵ Although we are proposing using a dataset from Canada (as was the
11 original RSS natural history dataset) and cannot rule out differences between the BCMS patients and
12 the UK RSS cohort, we are reassured that the baseline features are comparable except baseline
13 EDSS, but in the underlying Markov model we calculate the transition probabilities between EDSS
14 'states', and different baseline EDSS distributions would only matter if baseline EDSS as such had a
15 prognostic value, which doesn't seem to be the case when we were looking at the rates of EDSS
16 progression stratified by EDSS at baseline. In addition, the underlying ethnicity of the two jurisdictions
17 was similar; around the time of the cohort selection in British Columbia, 30.2% of the population self-
18 identified as British and within the wider BCMS database, >90% were Caucasian,^{26,27} which is
19 comparable to the UK cohort. Both cohorts may have enrolled a small number of patients with
20 neuromyelitis optica (we estimate this to be less than 0.5% of the total²⁸) because the availability of
21 the antibody assay occurred after 2007 (and after enrolment to the RSS scheme). An additional
22 limitation is the potential for different ways of measuring the EDSS scores between the BCMS and the
23 UK RSS cohorts because of changes in how the EDSS is interpreted over time and also because of
24 differences in the physicians performing the assessments.

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Observational studies, such as the RSS, provide a pragmatic approach when assessing drug effectiveness in a disease such as MS. Because MS disability accrues over decades, the cost effectiveness of disease modifying treatments cannot be assessed by short-term randomised controlled trials. However, observational studies are not without their own unique challenges.

Identifying and validating models to predict the untreated outcome of treated cohorts is a crucial step to measuring the long-term benefits of MS treatments. MS is the commonest cause of progressive disability in the western world, thus identification of treatments that might significantly impact long-

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3 term disability outcomes in MS could have major cost and quality of life benefits. Additionally, any
4 models developed here would be readily transferable to other chronic diseases.
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8 The current model described here will form the basis for calculating the drug cost per QALY and for
9 informing decisions on price adjustment in order to deliver the treatments cost effectively to UK MS
10 patients in an ongoing manner. The model will be used to calculate the Hazard Ratio at which each
11 product delivers efficacy against the NICE agreed cost per QALY and should any product fall short
12 price reductions will be implemented by the DH.
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18 Further work on repeated measures modelling, testing the models on other untreated appropriate MS
19 datasets and identifying sensitivity analyses (such as the effect of drop outs, switching to a different
20 class of DMT and the effects of treatments on backward transitions, i.e. disability improvements) are
21 also planned.
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3 All authors 1) made substantial contributions to the conception and design, acquisition of data, or
4 analysis and interpretation of data 2) were involved in drafting the article or revising it critically for
5 important intellectual content and 3) were involved in the final approval of the version to be published.
6
7
8 JP is a clinical lead for the UK risk sharing scheme, inputs into the scientific advisory panel, was
9 involved in the identification of the alternative dataset, interpretation of the analysis and was involved
10 in the drafting and revising of the manuscript. TB is the senior statistician in the scheme and the
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14 advisory panel, was involved in the identification of the alternative dataset, interpretation of the
15 analysis and was involved in the drafting and revising of the manuscript, MD is a clinical lead for the
16 UK risk sharing scheme, inputs into the scientific advisory panel, was involved in the interpretation of
17 the analysis and was involved in the drafting and revising of the manuscript, CD is a department of
18 health advisor for the scheme, inputs into the scientific advisory panel, and was involved in the
19 analysis of the data, its interpretation and was involved in the drafting and revising of the manuscript.
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Table 1: Characteristics of patients reaching the Association of British Neurologists criteria in the British Columbia MS database after 1980 (the ‘natural history’ untreated comparator cohort) and the Risk-sharing Scheme cohort.

| Baseline (eligible for DMT) | BCMS (1980-1995*) | RSS full cohort RSS analysis cohort** |
|--|-------------------------|--|
| N | 898 | 5610 4138 |
| Females: n (%) | 666 (74.2%) | 4162 (74.2%) 3125 (75.5%) |
| Age at baseline, years: mean (SD; range) [years] | 37.2 (9.32; 18 - 69) | 39.4 (9.05; 15 - 73) 38.4 (8.58; 18 - 73) |
| Age at onset of MS, years: mean (SD; range) | 29.3 (8.65; 3 - 61) | 30.5 (8.52; 5 - 68) 30.5 (8.38; 5 - 68) |
| Disease duration at baseline, years: mean (SD; range) [years] | 7.9 (6.89; 0.2 to 38.9) | 8.8 (7.47; 0 - 46) 7.7 (6.62; 0 - 41) |
| SPMS documented at baseline# n (%) | 141 (15.7%) | 772 (13.8%) - |
| Relapses in the last two-years prior to eligibility: median (quartiles) | 2 (2 - 3) | 3 (2 - 3) 3 (2 - 3) |
| First eligible EDSS: median (quartiles; range) | 2 (1, 3.5; 0-6.5) | 3.5 (2.0, 5.0; 0 - 8.0) 3.0 (2.0, 4.0; 0 - 6.5) |

‘Eligibility’ refers to the first time a patient fulfilled the ABN criteria

**data was truncated to 1995 in the final models to minimize DMT exposure in the cohort*

*** “analysis cohort” is the subset of patients eligible for the analysis (e.g., treated patients, at least one post-baseline EDSS available etc.)*

#all were still DMT eligible

RSS=Risk-sharing Scheme ; BCMS=British Columbia MS database; SD=standard deviation;
EDSS=Expanded disability status score ; DMT=disease modifying treatment

Table 2: “Goodness of fit” statistics for the ten state* disability (EDSS) Markov models

| Description of each ten-state ¹ disability model | Minus 2 log likelihood ² x 1,000 | Prediction errors (years) | |
|---|---|---------------------------|---------------------------------|
| | | Cells | 1-10) ³ EDSS Utility |
| No covariates | 17.152 | 2.20 | 0.24 0.022 |
| One covariate models | | | |
| Age at onset, binary | 17.458 | 1.39 | 0.09 0.009 |
| Age at onset, continuous | 17.599 | 1.58 | 0.13 0.007 |
| MSSS at baseline, binary | 17.460 | 1.41 | 0.10 0.008 |
| MSSS at baseline, continuous | 17.457 | | |
| Disease duration, binary | 17.462 | 1.33 | 0.10 0.009 |
| Disease duration, continuous | 17.557 | | |
| Sex | 17.470 | 1.32 | 0.10 0.008 |
| Two covariates models | | | |
| Sex and age at onset, binary | 17.603 | 1.51 | 0.14 0.007 |
| Sex and age at onset, continuous | 17.618 | | |
| Age at onset and MSSS, binary | 17.609 | 1.53 | 0.14 0.007 |
| Age at onset and MSSS, continuous | 17.618 | | |
| Age at onset and disease duration, binary | 17.603 | 1.52 | 0.14 0.007 |
| Age at onset and disease duration, continuous | 17.618 | | |

¹the ten disability states refer to EDSS 0 to 9, i.e. EDSS 0 is “state 1”, EDSS 1 is “state 2” etc.

²log likelihood statistic as calculated by ‘msm’ module, see Jackson¹⁹ for details; lower values implying a better model (to be compared within each class of models, e.g. one-covariate and two-covariate models)

EDSS= Expanded disability status score ; MSSS= Multiple sclerosis status score

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3 ³Prediction errors, averaged over years 1-10, for (a) the EDSS distribution in individual cells, (b)
4 average EDSS, (c) average utility (see definitions in the appendix 3, comparing the values predicted
5 by the model with the “observed” values using the method of midpoint interpolation (see appendix 2).
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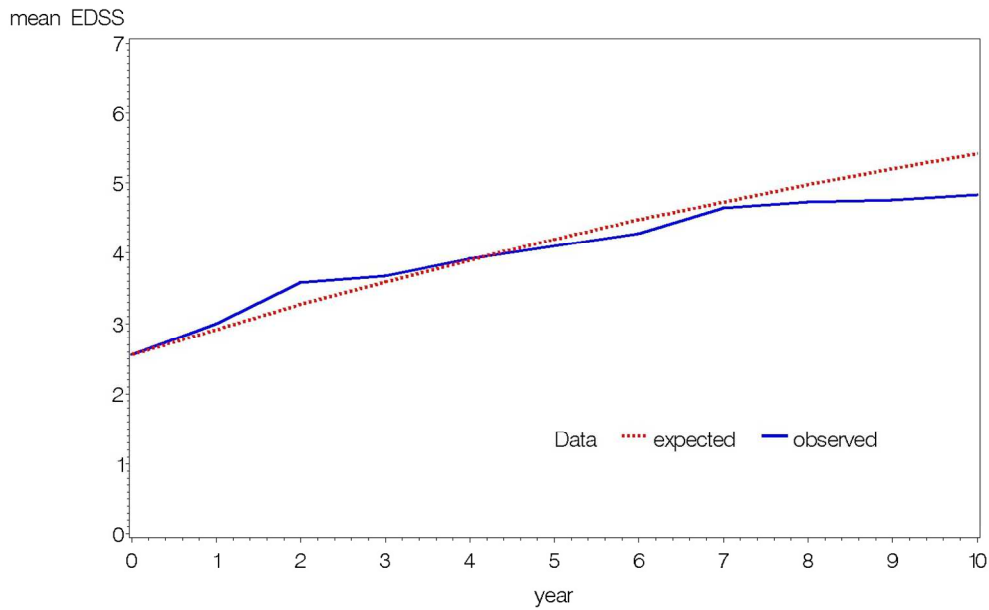
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9 Primary goodness of fit statistic is -2 log likelihood; prediction errors have only been calculated for the
10 binary versions of the individual models except for the “final” model with age at onset as covariate
11 where prediction errors have been calculated for both versions.
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Table 3: Transition matrices for the ten state disability (EDSS) Markov model with “age at onset” as binary covariate and annual transition probabilities

| age at onset < 28 yrs | | | | | | | | | | | |
|-----------------------|---|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| to EDSS | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | |
| from EDSS | 0 | 0.68704 | 0.21102 | 0.07195 | 0.02236 | 0.00434 | 0.00136 | 0.00176 | 0.00012 | 0.00003 | 0.00000 |
| | 1 | 0.06122 | 0.67867 | 0.16643 | 0.06462 | 0.01698 | 0.00474 | 0.00667 | 0.00052 | 0.00014 | 0.00001 |
| | 2 | 0.01692 | 0.12656 | 0.59550 | 0.17291 | 0.04537 | 0.01842 | 0.02190 | 0.00182 | 0.00054 | 0.00005 |
| | 3 | 0.00620 | 0.05215 | 0.11647 | 0.54386 | 0.09452 | 0.05730 | 0.11480 | 0.01070 | 0.00366 | 0.00035 |
| | 4 | 0.00176 | 0.02251 | 0.06617 | 0.12107 | 0.48737 | 0.10090 | 0.16644 | 0.02621 | 0.00690 | 0.00067 |
| | 5 | 0.00055 | 0.00562 | 0.02915 | 0.05936 | 0.09153 | 0.47268 | 0.28098 | 0.03961 | 0.01910 | 0.00143 |
| | 6 | 0.00012 | 0.00141 | 0.00447 | 0.02516 | 0.03208 | 0.04241 | 0.72834 | 0.11509 | 0.04566 | 0.00525 |
| | 7 | 0.00001 | 0.00016 | 0.00052 | 0.00260 | 0.00730 | 0.00419 | 0.12197 | 0.68145 | 0.16286 | 0.01895 |
| | 8 | 0.00000 | 0.00001 | 0.00004 | 0.00030 | 0.00057 | 0.00053 | 0.01884 | 0.05747 | 0.86099 | 0.06124 |
| | 9 | 0.00000 | 0.00000 | 0.00000 | 0.00002 | 0.00004 | 0.00004 | 0.00178 | 0.00596 | 0.17090 | 0.82125 |
| age at onset ≥ 28 yrs | | | | | | | | | | | |
| to EDSS | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | |
| from EDSS | 0 | 0.69537 | 0.20294 | 0.07251 | 0.02170 | 0.00422 | 0.00137 | 0.00175 | 0.00011 | 0.00003 | 0.00000 |
| | 1 | 0.05826 | 0.69501 | 0.15783 | 0.06088 | 0.01638 | 0.00458 | 0.00643 | 0.00048 | 0.00013 | 0.00001 |
| | 2 | 0.01586 | 0.12133 | 0.60789 | 0.16796 | 0.04458 | 0.01849 | 0.02159 | 0.00174 | 0.00052 | 0.00004 |
| | 3 | 0.00594 | 0.04960 | 0.12006 | 0.54422 | 0.09109 | 0.05845 | 0.11649 | 0.01030 | 0.00355 | 0.00030 |
| | 4 | 0.00165 | 0.02214 | 0.06660 | 0.11519 | 0.48935 | 0.10388 | 0.16811 | 0.02580 | 0.00671 | 0.00056 |
| | 5 | 0.00052 | 0.00533 | 0.02942 | 0.05866 | 0.08736 | 0.48695 | 0.27310 | 0.03880 | 0.01883 | 0.00102 |
| | 6 | 0.00012 | 0.00133 | 0.00444 | 0.02497 | 0.03069 | 0.04080 | 0.74069 | 0.10897 | 0.04377 | 0.00423 |
| | 7 | 0.00001 | 0.00015 | 0.00052 | 0.00247 | 0.00727 | 0.00385 | 0.11684 | 0.69269 | 0.16061 | 0.01559 |
| | 8 | 0.00000 | 0.00001 | 0.00004 | 0.00029 | 0.00055 | 0.00050 | 0.01881 | 0.05574 | 0.90340 | 0.02066 |
| | 9 | 0.00000 | 0.00000 | 0.00000 | 0.00002 | 0.00004 | 0.00003 | 0.00176 | 0.00568 | 0.17414 | 0.81832 |

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Transition probabilities obtained from the BCC dataset using the discrete Markov model were then applied to the baseline EDSS of the same cohort, projected over 10 years to produce a predicted mean EDSS outcome (red) and compared to the observed mean EDSS course of the cohort (blue).
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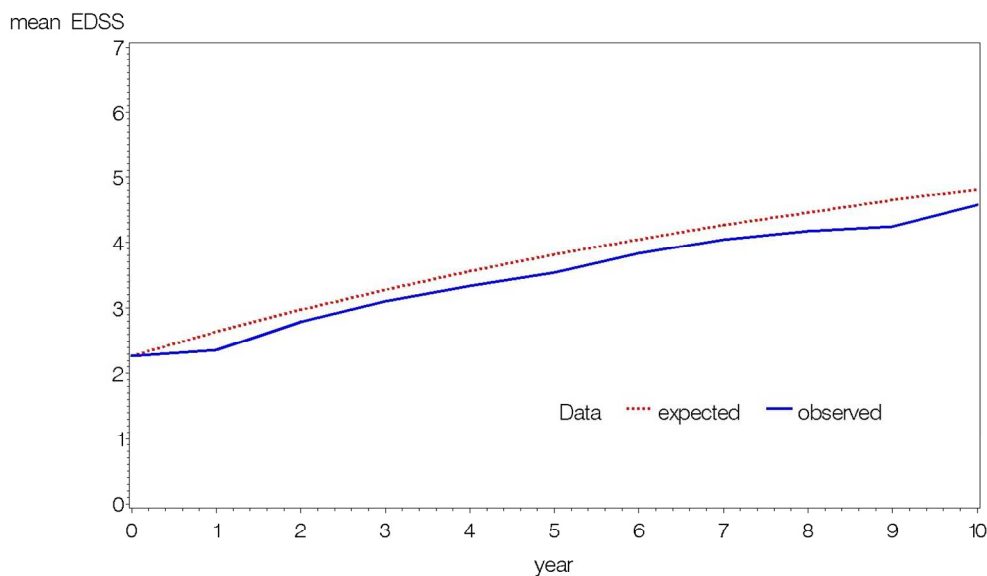


Figure 2: Transition probabilities obtained from the BCC dataset using the continuous Markov model were then applied to the baseline EDSS of the same cohort, projected over 10 years to produce a predicted mean EDSS outcome (red) and compared to the observed mean EDSS course of the cohort (blue).
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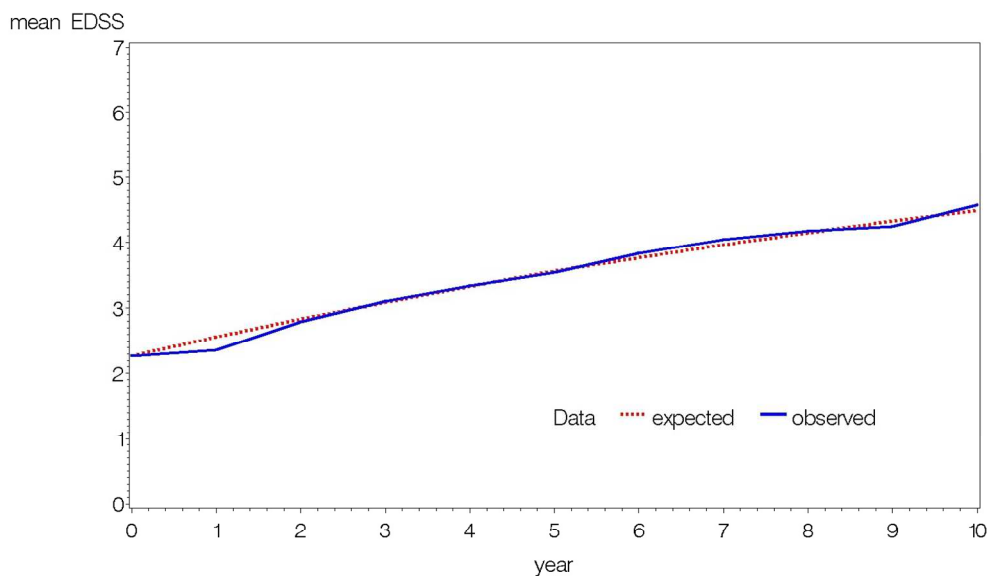
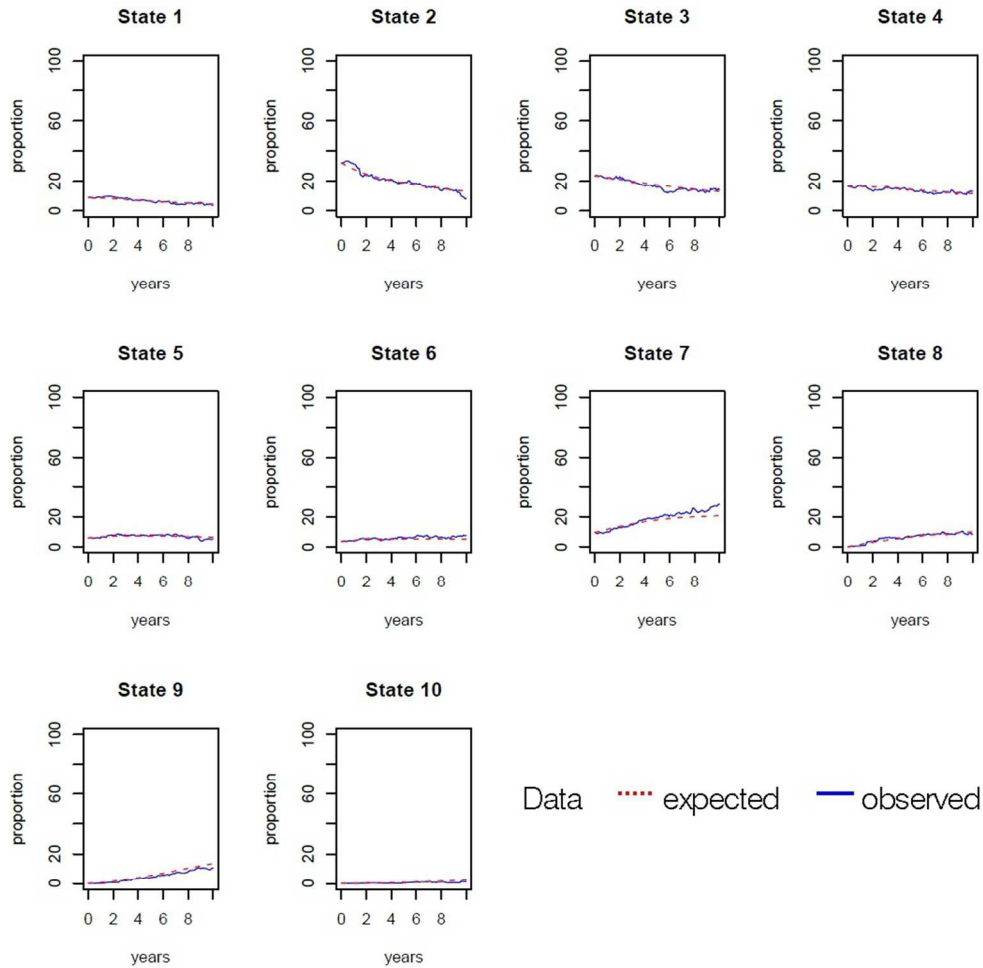


Figure 3: Transition probabilities obtained from the BCC dataset using the continuous Markov model with one covariate "age at onset" (binary version) were then applied to the baseline EDSS of the same cohort, projected over 10 years to produce a predicted outcome (red) compared to the observed course of the cohort (blue):

- a) Mean EDSS shown in the predicted and actual cohorts
- b) The proportion of patients predicted to be in each of the 10 EDSS states over time (state 1; EDSS 0, state 2; EDSS 1 and 1.5, state 3; EDSS 2.0 and 2.5, state 4; EDSS 3.0 and 3.5, state 5; EDSS 4.0 and 4.5, state 6; EDSS 5.0 and 5.5, state 7; EDSS 6.0 and 6.5, state 8; EDSS 7.0 and 7.5, state 9; EDSS 8.0 and 8.5, state 10; EDSS 9.0 and 9.5).

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Appendix 1 EDSS data extraction from the BCMS database

For the discrete Markov model and for tabular display of annual data the EDSS data were extracted and processed as follows. If the baseline EDSS fell when it was not the 'usual' yearly visit period, then subsequent EDSS scores could be lost. To maximize the number of EDSS transitions per patient, but keeping the yearly (+/- three calendar months) interval, EDSS scores were also 'individualized' as follows: the baseline EDSS became the baseline year, within that year, we searched to find the optimal new, individualized baseline for which the patient would, over the coming years have the most number of yearly EDSS scores. For some patients, this new individualized baseline date would not coincide with a clinic visit and would therefore not have an EDSS score present. When a baseline EDSS was required (e.g. for the discrete Markov model), data was also 'shifted' such that each patient would have a baseline EDSS. This lag between baseline ('eligibility') and EDSS was considered consistent with clinical practice in that it is not unusual to have a lag time between a patient becoming eligible for treatment and actual treatment initiation.

Appendix 2 Algorithms to forecast EDSS distributions at any given time

The 'msm' algorithm allows the EDSS distribution to be forecasted at any time t .¹⁹ To define what is the actual EDSS at a given time t (i.e. not necessarily when an observation was recorded) 'msm' offered two variants: (i) the last observation carried forward (LOCF) for each individual patient, and (ii) a 'midpoint interpolation' algorithm in which the EDSS state for a given patient at time t was taken as the score closest in time to the actually observed EDSS. Suppose an individual was observed in EDSS states S_{r-1} and S_r at two consecutive times t_{r-1} and t_r , and we wanted to estimate "observed" proportions at a time t between t_{r-1} and t_r . LOCF then meant that individuals were assumed to be in state S_{r-1} at time t , the same state as they were at t_{r-1} . Midpoint interpolation meant if $t \leq (t_{r-1} + t_r) / 2$, the midpoint of t_{r-1} and t_r , the state at t was assumed to be S_{r-1} , otherwise S_r . Option (i) would be more appropriate if EDSS values were always measured immediately after each transition. Option (ii) would be more appropriate if EDSS values were measured at mixed time intervals ('fixed or random'). Option (ii) was considered to mimic the clinical setting more closely and is also appears more applicable in progressive diseases.¹⁹ Therefore all results presented in this paper were based on this 'midpoint interpolation' approach.

For the continuous Markov model we limited the range of transitions which can be regarded as 'instantaneous' to +/- 3, which meant that at any time t an instantaneous progression (or improvement) into another EDSS state was only possible when not exceeding three consecutive states (an instantaneous transition from 1 to 2, 3, or 4 was possible, for example, whereas 1 to 5 was not). This restriction was recommended to avoid computationally inefficient modelling of hazard rates which were virtually 0.

Appendix 3 Validation of the models

The following validation techniques were applied when evaluating the different Markov models.

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3 The most straightforward method for the discrete Markov model consisted of applying the transition
4 matrix (and the 2nd, 3rd etc. power) to the vector of the baseline EDSS distribution in the BCMS
5 reference database, calculating the forecasted EDSS distribution for t=1, 2, 3... years and comparing
6 against the actual EDSS. A similar validation was performed in the continuous Markov model, as
7 described by Jackson.¹
8
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10 As a second validation we divided the BCMS dataset randomly into two subsets of equal size, using
11 one half to derive the model separately for the two subgroups, and then assessing the goodness of
12 fit in the other half of the dataset. Although Jackson¹⁹ emphasises that “Assessing the goodness of
13 fit of this class of models [...] is worth further research” we decided to use a classical mean square
14 prediction error (weighted root mean square over years of the prediction error in the average
15 quantity shown, weighted by the number of patients contributing data in the given year) to compare
16 competing models. Moreover, the computed likelihood itself as a result of the maximum likelihood
17 algorithm was used to rank the different one and two covariate models.
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Correction

Palace J, Bregenzer T, Tremlett H, *et al.* UK multiple sclerosis risksharing scheme: a new natural history dataset and an improved Markov model. *BMJ Open* 2014;4:e004073. The fifth author's name was misspelt in this paper. The correct spelling of this author's name is Feng Zhu.

BMJ Open 2014;4:e004073corr1. doi:10.1136/bmjopen-2013-004073corr1