Availability of real-world evidence (RWE) to support economic modelling in primary progressive multiple sclerosis (PPMS)

Audrey Brown[1], Alistair Curry[2], David Cork[1]
[1]SIRIUS Market Access, Newcastle upon Tyne, United Kingdom
[2]SIRIUS Market Access, London, United Kingdom. email: info@siriusmarketaccess.com

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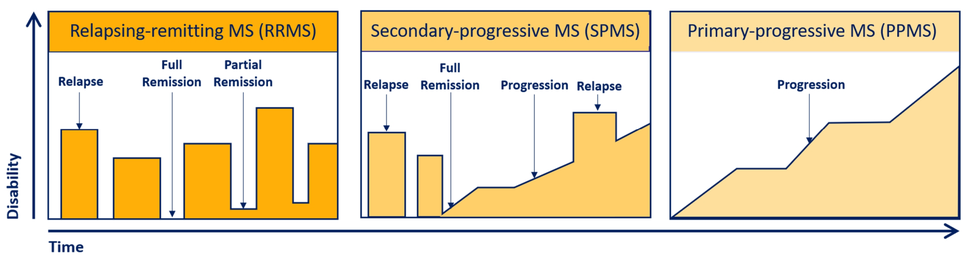
Introduction

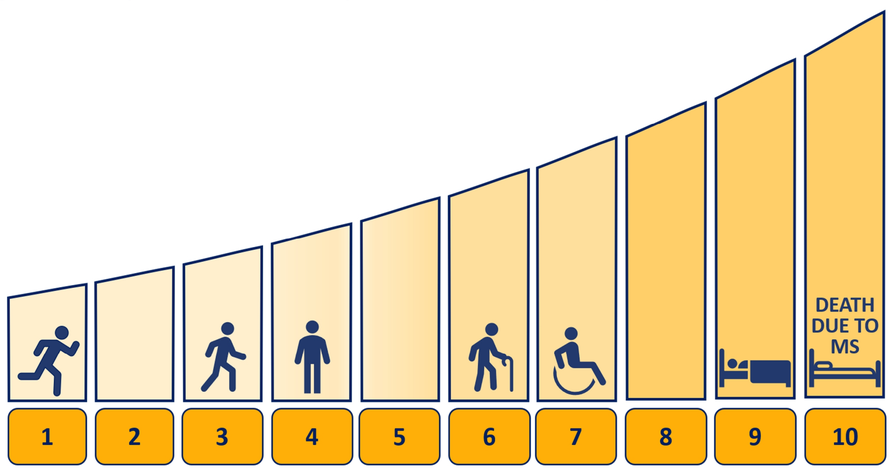
Multiple sclerosis (MS) is a chronic, neurodegenerative disease of the central nervous system. MS is classified into three subtypes; relapsing-remitting (RRMS), secondary progressive (SPMS; a progression from RRMS), and primary progressive (PPMS; no prior relapsing-remitting history), summarized in **Figure 1**[1]. Approximately 10-15% of MS patients have PPMS[2].

Figure 1: MS subtypes



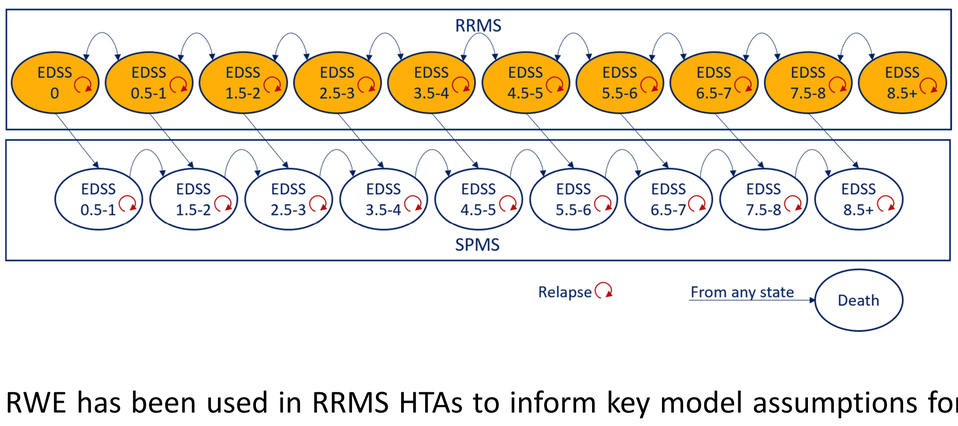
The most commonly used measure of disability in MS is the Expanded Disability Status Scale (EDSS), a physician-scored scale which categorizes a patient's level of disability from 0 (normal examination) to 10 (death due to MS, as shown in **Figure 2**[3]**.**

Figure 2: Expanded disability status scale (EDSS)



Many disease-modifying therapies (DMTs) have undergone HTA assessment and robust methodologies for cost-effectiveness modelling have been established based on EDSS health states. These models typically incorporate 10 health states for RRMS based on the level of disability, transition to SPMS, 9 SPMS health states, and death (**Figure 3**).

Figure 3: Established structure for economic modelling of RRMS and SPMS[4]



RWE has been used in RRMS HTAs to inform key model assumptions for epidemiology, baseline EDSS, annualized relapse rates, costs by EDSS state, and utilities. Transition probabilities for RRMS, RRMS to SPMS, and SPMS have been obtained from randomised controlled trials (RCTs), supplemented with RWE from the London Ontario cohort dataset.

Objectives and methods

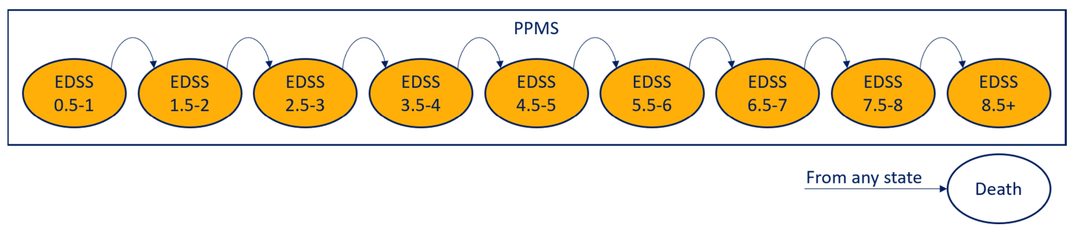
New treatments for PPMS are in development and HTAs are in process or due soon. As of April 2018, one HTA has been published in the US for PPMS by the Institute for Clinical and Economic Review (ICER)[4].

The objective of this study is to review the real-world evidence used in the cost-effectiveness models developed for the ICER assessment of DMTs in MS with particular focus on the model developed for PPMS.

Results

The main aim of the ICER review was to assess the clinical-effectiveness and lifetime cost-effectiveness of DMTs for treatment of MS. Evidence for clinical-effectiveness of DMTs in PPMS is limited and was taken from two RCTs examining rituximab (OLYMPUS) and ocrelizumab (ORATORIO). Cost-effectiveness was based solely on ocrelizumab. Cost-effectiveness in PPMS was modelled based on 10 health states, EDSS 1-9, and death (**Figure 4**). EDSS scores could increase, or stay the same but were assumed not to decrease over each 1-year transition cycle. Progression to death could occur from any state.

Figure 4: Markov model structure for PPMS



The sources of evidence used in the ICER assessment are shown in **Table 1** along with a summary of whether RWE is available to support the assumptions made in the ICER model.

Table 1: Summary of PPMS assumptions in ICER model and RWE

Assumption	Source of evidence	Comment
Assumed mean age at onset of PPMS is 42 years.	Natural history study of PPMS based on data from the British Columbia MS database[5].	For population-based PPMS cohorts, the mean (SD) age at symptom onset was 36.2 (11.0) years and diagnosis age was 44.5 (10.0) years. No statistically significant difference in diagnosis age was reported for SPMS and PPMS[6].
EDSS distribution of PPMS patients entering the model based on RCT data.	Baseline characteristics of PPMS patients entering ORATORIO clinical trial[7].	Data from the ORATORIO trial consistent with other clinical trials in the PPMS population.
Transition probabilities for PPMS assumed to be equal to SPMS.	Transition probabilities for RRMS and SPMS based on data from the DEFINE[8] and CONFIRM[9] clinical trials and the London Ontario cohort dataset[10].	Data from the MSBase registry indicates heterogeneity in the rate of disability accumulation in PPMS, identifying patients with a mild, moderate, and severe disease trajectory[11]. Variability in disease progression has also been reported by studies analysing a PPMS cohort from the British Columbia MS database[5]. Data from the CLIMB study, a longitudinal prospective study, indicate that disease progression is significantly faster in the PPMS than the relapsing-onset population (includes both RRMS and SPMS patients) ($p<0.001$ for all timepoints)[12]. In comparing PPMS with SPMS in another population cohort study, time to EDSS 4, 6, and 8 was significantly longer in PPMS compared with SPMS (8.1 vs. 4.3, and 9.6 vs. 6.3 years, to EDSS 4 and 6 respectively, both $p<0.0001$; 20.7 vs. 17.1 years, $p<0.01$ to EDSS 8)[13].
In the absence of available data, utilities for PPMS were assumed to be the same as for SPMS.	Utility data for RRMS based on DEFINE and CONFIRM clinical trials. SPMS utilities derived from a UK survey[14].	Analysis of utility values collected from a prospective cohort study indicate that utility is comparable across EDSS states between SPMS and PPMS populations[15].
Costs per EDSS state assumed to be the same for RRMS, SPMS, and PPMS.	EDSS state-specific costs calculated based on data from a survey of NARCOMS participants[16].	Analysis of health care utilization using the NARCOMS registry reported similar rates of hospital admissions and emergency department visits in SPMS and PPMS. Health care utilization was significantly higher compared with the RRMS cohort ($p<0.0001$, for both)[6] which may affect costs per EDSS state.

Conclusions

The limited availability of RWE for PPMS led to assumptions of equivalence to SPMS. While RWE suggests that utilities and rates of health care resource utilization for SPMS and PPMS are comparable across similar disability levels, natural history studies suggest that rates of disease progression differ not only between the two populations but also within the PPMS population. This will have an impact on transition probabilities in any economic model developed.

RWE supports assumptions of equivalence between SPMS and PPMS for some but not all economic model parameters. HTA agencies such as NICE, conducting future assessments, may require PPMS-specific RWE or validation of the assumptions used in economic model development.

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