

RESEARCH ARTICLE

Transition to secondary progressive multiple sclerosis: The consequences for patients and healthcare systems, a healthcare professional survey

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Funding information

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Abstract

Background and Aims: Transition to secondary progressive multiple sclerosis (SPMS) from relapsing-remitting MS (RRMS) is an expected part of the disease trajectory for most patients. However, the transition is challenging to identify due to the gradual nature of progression, and the complications of superimposed relapses, comorbidities, and natural variability in symptoms. This healthcare professional (HCP) survey sought to characterize the transition to and management of SPMS in UK clinical practice.

Methods: Telephone interviews with 20 neurologists and MS specialist nurses from England and Scotland gathered quantitative and qualitative responses. Numerical analyses and theoretical thematic methods were used to identify key emerging themes.

Results: The burden SPMS imposes on patients and caregivers was a major theme; discharge from specialist services is common, leading to a sense of abandonment. Respondents acknowledged substantial hesitancy toward identifying SPMS, predominantly due to restricted options of licensed and reimbursed disease-modifying therapies (DMTs) for SPMS compared with RRMS. Currently, HCPs continue DMTs under a label of RRMS, even after recognition of progression. This survey identified MS to be unusual in comparison with other disease areas in that reimbursement guidelines have a direct impact on clinicians' decisions around disease staging. Respondents suggested reimbursed DMTs proven to slow disability progression in SPMS will create a step-change in identifying SPMS, providing rationale to acknowledge progression earlier while removing key obstacles to identification. To aid this change, respondents identified a need for SPMS-specific diagnostic guidance, despite substantial divergence in implementation of current guidance.

Conclusions: In contrast to the current heterogeneity, a more structured and standardized approach to the identification of SPMS, along with guidelines on treatment, will ensure patients can maximally benefit as treatment options for SPMS evolve.

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KEYWORDS

disease-modifying therapies, multiple sclerosis, progressive, quality of life, symptomatic treatment

1 | INTRODUCTION

Multiple sclerosis (MS) affects 130 000 people in the United Kingdom, with 6700 people diagnosed every year.¹ Although MS is highly heterogeneous, three broad clinical phenotypes are recognized: relapsing-remitting MS (RRMS); secondary progressive MS (SPMS); and primary progressive MS (PPMS).²

SPMS is defined as a clinically progressive course, involving steadily increasing, objectively documented neurological disability independent of relapses, following on from a relapsing-remitting course. SPMS may present with or without superimposed relapses,^{2,3} and is exclusively defined by the clinically observed course.

The transition from RRMS to SPMS is ultimately observed in two-thirds of people with RRMS.^{4,5} However, the transition to SPMS remains challenging to identify as it occurs due to the gradual nature of disease progression, the fluctuations of all stages of MS, and confounders including comorbidities.² Transition is often identified retrospectively, following a period of diagnostic uncertainty.^{2,6}

As SPMS follows RRMS and is generally associated with higher levels of disability, patients with SPMS predictably have more severe neurological symptoms, lower quality of life (QoL), and increased caregiver dependence.^{5,7-9} Patients may need to undergo a further period of acceptance for their condition, since any new symptoms are likely to be permanent and deteriorate.

Various disease-modifying therapies (DMTs) are licensed and reimbursed for RRMS, however the development of effective DMTs in SPMS has faced many hurdles, with the majority of trials involving patients with progressive MS failing to demonstrate an effect on disability progression.¹⁰⁻¹⁴ Although the treatment landscape for SPMS is now changing, at the time of the survey, only one treatment option was reimbursed in the UK National Health Service (NHS) for patients with SPMS, which was not known to slow SPMS disability progression.^{10,13,15}

Through interviews with healthcare professionals (HCPs) across the United Kingdom, this survey sought to (a) investigate the transition to and management of SPMS in UK clinical practice, thereby identifying the key challenges faced by HCPs, patients, and their caregivers, to reveal the areas with greatest unmet need; (b) understand how any future licensed treatments may fit into NHS practice, and (c) explore the resource use associated with management of SPMS in the United Kingdom.

2 | METHODS

The researchers developed a protocol outlining the recruitment and interview process, which is detailed below. See the Appendix S1 for researchers' experience, training, and involvement in the interviews.

2.1 | Respondents

Recruitment was via purposive sampling using pre-defined eligibility criteria (see the Appendix S1). The process was rolling and managed in small stages, aiming for 20 confirmed respondents (approximate split of 2:1 of general or MS specialist neurologists to MS specialist nurses) and geographical balance across England, Scotland, and Wales.

2.2 | Interviews

In-depth, semi-structured, one-hour telephone interviews were performed between November 2018 and March 2019. The interview questionnaire (see the Appendix S1) was developed by S.C., S.M., and M.K. and sent to respondents prior to their interview.

2.3 | Analysis of responses

Predominantly qualitative responses were gathered. Theoretical thematic analysis methods were used to derive key emerging themes.¹⁶ Minor and major themes were proposed by SC and MD, and validated by SM and FW (see the Appendix S1). All results were grouped and anonymized for presentation of key themes, with the exception of quotations for which only respondents' roles were provided.

2.4 | Ethics statement, informed consent, and confidentiality

As market research, the survey adhered with Association of the British Pharmaceutical Industry (ABPI) and British Healthcare Business Intelligence Association (BHBIA) codes of conduct. As per the BHBIA Legal and Ethical Guidelines¹⁷ and UK Department of Health,¹⁸ and as indicated by the NHS Health Research Authority decision tool,¹⁹ approval from a Research Ethics Committee (REC) was not required. Respondents gave informed consent to participate and could withdraw from the interview at any time. The sponsor was not involved in the screening or interview process, and their identity was not disclosed to respondents.

3 | RESULTS

3.1 | Respondents

Twenty respondents were recruited, comprising nine MS specialist neurologists, who would usually be responsible for initiating prescription of

DMTs, five general neurologists, who may not be able to initiate or prescribe DMTs, and six MS specialist nurses (Figure 1). A total of 18 respondents were based in England, and 2 in Scotland. Reasons for non-participation included unresponsiveness over email and lack of experience with SPMS.

Data saturation (no new major themes identified) was reached after the first 15 interviews, confirming the sample size as appropriate.

3.2 | Major and minor themes

The major and minor themes identified are discussed below, structured around the interview questionnaire topics.

3.3 | Burden of disease

Major theme: Transition to SPMS imposes substantial burden on patients and caregivers.

All respondents emphasized the devastating impact identification of SPMS has on the home and professional life of patients and caregivers. Considerable physical challenges mean daily tasks become increasingly difficult and necessitate adaptations to patients' homes. Respondents noted that increased dependence on relatives or friends as caregivers has personal implications, being known to break family homes and increase likelihood of divorce, as well as financial implications, since most patients with SPMS cannot continue full-time employment. Last, respondents commented that patients with SPMS are more likely to suffer from social isolation and mental illnesses, further reducing their QoL.

Respondents have observed that, following the confirmation of SPMS, most patients are devastated and in denial, particularly younger patients. The uncertainty in prognosis and limited treatment options may represent a loss of control. However, a minority of patients feel relieved. These are predominantly older patients, who may have already accepted their progressive condition.

3.4 | Identification of the transition to SPMS

As per the Lublin et al criteria for defining the clinical course of MS,² SPMS is identified by a history of gradual worsening after an initial

RRMS disease course.² However, there are notable challenges in operationalizing this definition in clinical practice to reliably identify the transition to SPMS. For example, the gradual worsening of disability is complicated by superimposed fluctuations driven by factors not directly related to disease progression, including fatigue, infection, and mood disturbance.

Major theme: Notable divergence from the definitions of SPMS described in the literature (Lublin² and McDonald³) was identified.

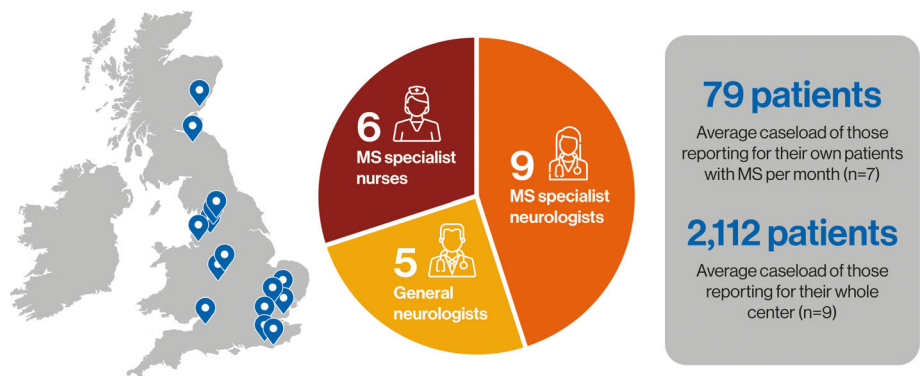
The majority (13/20) of respondents indicated that their clinic does not use any standardized approach to identify the transition to SPMS. Although respondents agreed that the decision to label a patient as SPMS is based on assessment in clinic, this could be highly subjective and is likely not based on the same consistent criteria across clinics.

MS affects several functional domains, and the Expanded Disability Status Scale (EDSS) has known limitations in the holistic evaluation of patients. However, amongst the respondents, mobility remains the strongest predictor of SPMS, since it would be highly unlikely for a patient with SPMS to not have experienced deterioration in their walking ability. Some respondents appeared to associate, whether consciously or not, SPMS with higher EDSS levels seen with advanced MS; they considered any patient who was wheelchair-bound to definitely be labelled as SPMS. Although SPMS correlates with higher EDSS states, it is not defined by and does not define these higher levels of disability.

Beyond mobility, some respondents discussed the absence of magnetic resonance imaging (MRI) activity as a marker of SPMS transition, in direct contradiction to the Lublin criteria,² where progression is considered independently of activity (ie, clinical relapse or appearance of new lesions on MRI).

The use of the term "relapsing progressive MS" varies across literature and guidelines: the NHS England Treatment Algorithm for MS DMTs²⁰ provides criteria for treatment of this phenotype, whereas the Lublin criteria² recommend the term to be dropped as it is believed to be vague and overlapping with other MS subtypes. Our survey therefore included a question on the term "relapsing progressive MS" to explore its use in UK clinical practice. However, there was similarly no consensus on use of the term amongst our respondents, with 9/20 respondents using the term and 11/20 choosing not to; there was no theme in preference between type of HCP. Some respondents considered the term to have clinical value, bridging the

FIGURE 1 Geographical spread, demographics, and caseload of respondents. Nurses and neurologists are grouped in the map to preserve anonymity. MS, multiple sclerosis



gap between relapsing and progressive patients, providing an option for maintaining treatment with DMTs in difficult-to-define progressive patients. Other respondents however considered the term to be ill-defined, with terms mentioning “activity” to be more helpful.

These notable divergences between respondents' working definitions of the transition to SPMS meant a consensus for an “identifiable transition point” for RRMS to SPMS was challenging to identify from the responses.

Major theme: There is considerable hesitancy and caution around identifying SPMS.

All respondents recognized that the transition to SPMS is considered with a patient over several appointments, with an average timeframe of 15 months (range from 3 months to 5 years). This results from both the prolonged time required for HCPs to have absolute confidence in the SPMS transition, and the interval between neurologist appointments (typically 6 months) when decisions are made.

Furthermore, a proportion of patients still recorded as RRMS may in fact have transitioned to progressive disease. Respondents estimated that an average of 12% of patients with RRMS should truly be classified as SPMS, highlighting the caution in identifying SPMS. When presented with a list of factors influencing this hesitancy, the respondents ranked them as shown in Figure 2.

3.5 | Treatment for patients with SPMS

Major theme: HCPs' use of DMTs for transitioning disease phenotypes tends to follow one of two approaches.

Respondents noted substantial hesitancy in DMT discontinuation, particularly in patients with disease activity who may still experience clinical benefit for their relapses. Respondents aligned with one of two approaches:

1. Confirming SPMS, however continuing DMT until there is strong evidence of no inflammation or relapses

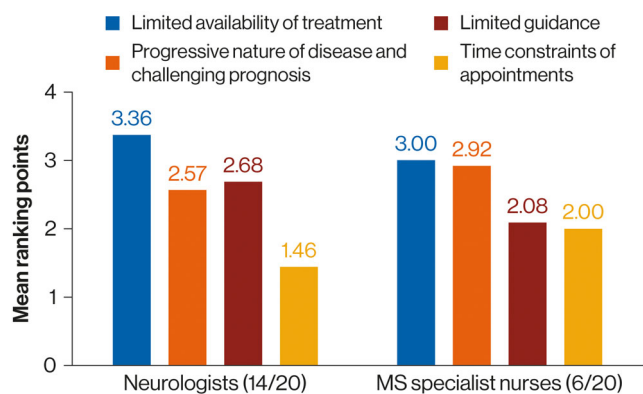


FIGURE 2 Mean ranking points for influence on the hesitancy toward identifying patients as SPMS. Ranked as first most influential factor: 4 points; ranked as second most influential factor: 3 points; ranked as third most influential factor: 2 points; ranked as fourth most influential factor: 1 point. The four factors were provided in the questionnaire to the respondents. SPMS, secondary progressive multiple sclerosis

According to respondents, approximately 30% of patients with suspected or identified SPMS are prescribed DMTs. On average, respondents' patients will have been prescribed two DMTs prior to transition to SPMS, and this is increasing in parallel to the greater availability of new DMTs. The respondents noted there may be a minor bias toward older DMTs (ie, injectables), since current patients whose disease is transitioning to SPMS are likely in their 40s or 50s, been diagnosed with MS prior to the introduction of oral therapies, and subsequently never been escalated.

2. Allowing the decision to identify SPMS to be driven by whether patients may still benefit from their DMT

Other respondents discussed that the formal identification of SPMS, and hence potential discontinuation of DMT, may be postponed until there is strong evidence of disability progression in absence of disease activity. Nevertheless, patients with SPMS are usually taken off their DMT once there is certainty that they no longer have RRMS and therefore are no longer eligible for, or benefitting from, treatment. The timespan to reach certainty of SPMS and consider DMT discontinuation varies considerably between patients, however is generally considered to be 1 to 2 years by the respondents.

Major theme: Availability of licensed and reimbursed treatments could create a step-change in the identification and management of SPMS in the NHS.

All respondents indicated the availability of “further licensed DMTs for SPMS” (not further defined in questionnaire) would change current UK clinical practice. This would provide clear clinical rationale for identifying SPMS earlier, removing the deterrent and increasing HCPs' confidence to confirm SPMS; some respondents emphasized that the impact on clinical practice would be dependent on the availability of significant clinical evidence of the DMT for delaying disease progression. The HCPs also believed that DMTs for SPMS would reduce patients' anxiety associated with progression, and would provide rationale for opening extra clinics, preventing patients' sense of neglect.

3.6 | Improving the pathway for patients with SPMS

Minor theme: Respondents highlighted the need for robust and practical guidelines and treatment algorithms.

When asked how they would improve the pathway for patients with SPMS, respondents highlighted an unmet need for bodies such as the National Institute for Health and Care Excellence (NICE) to provide guidelines on identification of and treatment for SPMS (Figure 3).

When directly asked if further guidelines would be of benefit, fewer prescribing respondents (5/9 MS specialist neurologists) agreed compared with respondents unable to prescribe DMTs, where 10/11 general neurologists and MS specialist nurses agreed further guidelines were needed.



FIGURE 3 Respondent quotations highlighting the need for clearer and widely adopted guidelines to ease the transition to SPMS. MS, multiple sclerosis; SPMS, secondary progressive multiple sclerosis

Major theme: Substantial changes in healthcare resource use are acknowledged during and after the transition to SPMS.

Respondents commented that specialist clinics have limited capacity to see patients who are not prescribed DMTs. The majority (13/20) of respondents acknowledged that patients with SPMS are seen less by neurologists and specialist nurses compared with patients with RRMS, since the treatable nature of RRMS necessitates more frequent monitoring appointments.

Following discontinuation of DMT, respondents noted that tertiary referral centers may discharge patients with SPMS to a general neurology service in a different center, leading to a feeling of abandonment or neglect. Compared to patients with RRMS, patients with SPMS are therefore seen more frequently in primary care and by allied HCPs for symptom management, which is individualized to patients' specific needs and aims to maintain QoL for as long as possible.

Patients with SPMS experiencing a relapse are reviewed in the same manner as patients with RRMS (eg, access to a nurse helpline, relapse clinic, steroid treatment). The majority (17/20) of respondents indicated reinitiating DMTs in patients with relapsing SPMS would be a possibility. Opinions were mixed on whether this would be the patient's previous DMT, or a more highly active second-line therapy. Nevertheless, all other potential causes of sudden decline would be excluded first.

Many respondents found it difficult to provide numerical or quantifiable responses to the frequency and length of appointments and social care; as such, the results from the healthcare resource use question have not been reported.

4 | DISCUSSION

A striking issue emerging early in this research was the marked divergence in respondents' definitions of SPMS, and varying responses to the use of and challenges in defining subgroups of SPMS, or of MS in general. This is not unique to the United Kingdom, and indeed, at one extreme, the US Food and Drug Administration (FDA) has recently moved away from distinguishing RRMS and SPMS in prescribing information, instead using the term "relapsing forms of MS (RMS)."²¹⁻²³ Lublin et al²⁴ published a clarification on the Lublin 2014 clinical course descriptor for MS, to address these discrepancies emerging

from regulatory communications of recently approved DMTs. Together with the heterogeneity observed across our respondents' definitions of SPMS, this indicates how clinical practice may shift away from current categorization of MS subtypes, toward a continuous dual assessment of disease "activity" and "progression," incorporating radiological and clinical measures in both. Even in this evolving picture, however, there will always be a point when the onset of clinical progression independent of relapse can be recognized and, based on trial evidence, this may continue to dictate a change in therapeutic strategy.

Respondents' emphasis for further guidelines should be interpreted with caution considering the notable divergence in aligning with current guidelines for the identification of SPMS; there is a clear need for further consensus, however given HCPs' conflicting interpretations of current guidance, it is unclear if further guidelines would truly improve clinical practice or lead to further heterogeneity in their use. Respondents discussed their hesitancy in identifying the transition to SPMS, which is most influenced by the limited availability of licensed and reimbursed treatments. This diagnostic challenge may be unique to MS; very few other diagnoses are likely as heavily influenced by a lack of available treatment options. Considering this uncertainty and hesitancy of HCPs to identify the transition to SPMS, introduction of stricter definitions may negatively impact patients who are subsequently withdrawn from their current RRMS treatment. This may explain the lower proportion of prescribing respondents, compared to non-prescribers, who agreed further guidelines would be of benefit, given prescribing HCPs may be influenced to a greater extent by the limited DMT options following transition to SPMS. Nevertheless, with the increasing availability of further licensed and reimbursed DMTs for SPMS, clearer guidelines and improved alignment in their use by HCPs could work to ensure new DMTs reach those patients in greatest need.

Previously reported studies have indicated that per patient per year costs for SPMS are £30 000 greater than for RRMS.^{25,26} The respondents in our survey also noted substantial changes in the healthcare resource use between patients with RRMS and SPMS; 13/20 respondents noted that patients with SPMS are seen less compared with patients with RRMS, however, the respondents may have taken a siloed view to healthcare, referring to only neurologist-led services or DMT-associated appointments, rather than also considering

symptomatic therapy and allied HCP appointments. Aside from the formal identification of SPMS, these changes in healthcare resource use could also be associated with generally worsening disability along with the discontinuation of DMTs.

4.1 | Strengths

Two previous patient and HCP surveys on the transition to SPMS captured responses from one region in South Wales.^{7,27} Our research aimed to capture responses from multiple NHS Trusts, to present an overview of SPMS management practices more applicable across the whole of the United Kingdom. From the 20 respondents, 18 centers were represented across Scotland and England; this geographical balance minimized any selection bias. The predominantly qualitative approach supported a more in-depth understanding of the complexity of SPMS practices than would have been possible using a solely quantitative method. Additionally, this survey highlights new and distinctive features of MS not captured in the previous surveys, such as the direct impact of reimbursement guidelines on clinicians' decisions around diagnosis and disease staging.

4.2 | Limitations

Due to some lack of responsiveness in the early recruitment phase, a risk of response bias cannot be completely excluded. No respondents were successfully recruited in NHS Wales, and recruitment methods did not target respondents from Northern Ireland. Nevertheless, the two previous qualitative studies conducted in Wales presented similar themes to those identified in our interviews.^{7,27}

Since the questionnaire predominantly focused on qualitative responses, several respondents did not provide numerical responses to specific questions; any figures quoted in this paper are therefore based on small sample sizes of the total 20 respondents.

5 | CONCLUSION

The findings from this survey emphasize the substantial heterogeneity across England and Scotland in HCPs' approaches to defining and identifying the transition to SPMS, which could contribute to the confusion and sense of neglect experienced by patients through this time, as highlighted by respondents. Additionally, this survey has identified a distinctive feature of MS care, compared with other disease areas: in reverse of standard practice of receiving a diagnosis and subsequently prescribing appropriate treatment, disease staging for patients with MS is directly impacted by reimbursement guidelines and availability of treatment. Given the evolving evidence base in SPMS, there is a clear need to address the current heterogeneity in clinical practice, ultimately through a more structured and standardized approach to phenotyping MS and consensus guidelines on treatment to ensure patients can maximally benefit as the treatment options for SPMS evolve.

ACKNOWLEDGMENTS

The authors would like to thank the neurologists and nurses who participated in an interview, and also the market research agencies who were contracted to recruit respondents.

FUNDING

This project was funded by Novartis Pharmaceuticals UK, who contracted Costello Medical to undertake the work.

CONFLICT OF INTEREST

Stephen Maxwell Montgomery and Fern Amy Woodhouse are employees of Costello Medical, who were contracted by Novartis Pharmaceuticals UK to undertake the work. Sophie Clare Laura Caseby was also an employee of Costello Medical at the time of the study. Michel Anton Kroes is an employee of Novartis Pharmaceuticals UK and a Novartis shareholder. Martin Edward Duddy has received honoraria for advisory boards, speaker's fees, research funding, and expenses to attend educational events from Novartis, Biogen, Celgene/Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Sanofi Genzyme, and TG Therapeutics.

AUTHOR CONTRIBUTIONS

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All authors have read and approved the final version of the manuscript.

The corresponding author had access to all of the anonymised data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

The corresponding 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.

PRIOR PRESENTATION

This manuscript has not been published elsewhere. Results from this survey have been presented as a poster at the MS Trust Conference 2019 (Hinckley, England, November 3–5, 2019).

DATA AVAILABILITY STATEMENT

The anonymized data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Caseby SCL, Woodhouse FA, Montgomery SM, Kroes MA, Duddy ME. Transition to secondary progressive multiple sclerosis: The consequences for patients and healthcare systems, a healthcare professional survey. *Health Sci Rep*. 2022;5:e474. doi:10.1002/hsr2.474