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Köpke, S. and Giordano, A. and Veronese, S. and Christin Rahn, A. and Kleiter, I. and Basedow-Rajwich, B. and Fornari, A. and Battaglia, M. A. and Drulovic, J. and Kooij, L. and Koops, J. and Mens, J. and Meza Murillo, E. R. and Milanov, I. and Milo, R. and Patti, F. and Pekmezovic, T. and Sastre-Garriga, J. and Vosburgh, J. and Voltz, R. and Bay, J. and Oliver, David J. and Solari,

DOI

https://doi.org/10.1111/ene.13760

Link to record in KAR

https://kar.kent.ac.uk/69168/

Document Version

Author's Accepted Manuscript

european journal of neurology
the official journal of the european academy of neurology

Patient and caregiver involvement in formulation of guideline questions: Findings from the EAN Guideline on Palliative Care of People with Severe Multiple Sclerosis

Journal:	*European Journal of Neurology*
Manuscript ID	EJoN-18-0243.R2
Wiley - Manuscript type:	Original Article
Date Submitted by the Author:	n/a
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	of Neuroepidemiology
Keywords:	Multiple sclerosis < Demyelinating diseases < NEUROLOGICAL DISORDERS, Palliative care < MANAGEMENT, Best practice, Clinical practice guideline, Patient and public involvement, Online survey, Mixed methods

We thank the reviewer for his/her careful and valuable work. We believe that, by responding to his/her points, the study processes have been better detailed. This was possible as we moved the Methods, the Acknowledgements, Funding, and Conflict of interest to the Supplementary Appendix. For point 7, we did our best to match information provision and the available space.

1. *The authors state in their revised methods that they used a deductive qualitative approach, which is a very helpful clarification. If this is the case, though, then there should be a statement in the methods of [1a] a theory/hypothesis that they were testing, a testable proposition, or a model that they were seeking to support. [1b] Was there a specific type of deductive qualitative approach used, such as pattern matching? [1c] Also, if the point of the analysis was simply to identify important outcomes from the discussion and all other comments/topics raised by participants were ignored, this should be explicitly stated.*

   [1a] We now specify in the Methods (Appendix): 'As we were particularly interested in understanding patient values we thought that MS patients and their caregivers would have been more prone to discuss in a dedicated setting the guideline questions. In doing so we expected to find across the data themes mainly related to the clinical questions.'

   [1b] We did not use any specific type of deductive qualitative approach.

   [1c] We believe that the focus of the FGMs (i.e. of the qualitative analysis) is detailed in Table 5 (aims): 'Explain/discuss the process of guideline production; Identify outcomes important to patient and caregivers; Explore 'difficult' topics and taxing issues.' Note that it is further mentioned in the Discussion: 'The FGMs allowed the explanation of the process of guideline production, the identification of patient-important outcomes, and deliberation about taxing issues (Table 5)'.

2. *Edited to add – this is mentioned briefly in the discussion with the sentence, "The deductive analysis was linked to the preformed questions and themes derived from the literature and consensus, and was not aimed to produce an interpretative model" but this needs to be described in the methods. I don't feel strongly about this being mentioned as a limitation as long as the methods are clear about the intent and process of the qualitative analysis.*

   We have changed the manuscript following the reviewer's advice - Methods: 'The deductive qualitative analysis was linked to the pre-formed questions and themes derived from the literature and consensus, and was not aimed to produce an interpretative model.'

3. *The COREQ checklist mentions that in the Milan focus group, a research assistant was needed to help the disabled patients (eg in drinking, changing position). This kind of detail is important for guideline developers hoping to replicate the work that current authors have done. This "practical support" is a theme previously reported as important to patient engagement in guideline panels (Armstrong et al. Recommendations for patient engagement in guideline development panels: A qualitative focus group study of guideline-naïve patients. PLOS One 12(3):e0174329). It would be useful to add this information to the main manuscript as an example of both the resource-intensive nature of patient engagement but also how to make sure it is done well.*

   We have changed the manuscript following the reviewer's advice - Methods: 'In the Milan FGM of patients a research assistant also attended, to help participants (e.g. in drinking, changing position).'

4. *It is not clear why the UK results were excluded from the analysis (as per Table 2, text) simply because the desired number of participants was not reached. While the low response rate is unfortunate, excluding completed surveys brings in more bias than including them. Additionally, there are ethical concerns with excluding data of consented participants. Such concerns are obviously greater when patients have endured more risk for a study than a survey, but some of the ethical principles are the same. If there is a methodologic reason for excluding them, this should be stated. It makes sense that there weren't sufficient numbers to inform a by-country analysis (UK responses versus responses from other countries) but in an analysis whose primary outcome is to identify outcomes important to patients, it is not clear why patient voices were excluded?*

   As from the Methods, the guideline task force set a priori the minimum number of participants required to deem that a given country contributed to the study findings. This decision was taken besides any cross-country comparison purpose, to substantiate the countries characterized in the survey. In the UK (the second country in terms of inhabitants and number of MS patients, see Table 1) participants were 17, a value well below the threshold of 50. There is no need for a sensitive analysis to prove that inclusion of these data would not have changed the overall study findings. We do not see any ethical concern in this, and we did not want to exclude patient voices. Rather, these findings indicate that online surveys are increasingly performed by patient organizations, and careful planning is needed. The online survey was unsuccessful in the UK. Nevertheless, the results of the study will be made available to the scientific community and (via the International MS Federation and the NMSSs) to the patients.

5. *Is there a reason that partial surveys were not used for the questions for which there were responses? The reason for excluding partial surveys is not provided*.

   As reported in the Methods, the demographic section had 'a common set of multiple choice items on participant age, sex, education, status (patient or caregiver), and specific multiple choice questions for patients (time from MS diagnosis, disability level, employment status) and caregivers (relation with the MS sufferer, time from MS diagnosis, disability level, employment status of the MS sufferer)'. As we aimed to characterize participants, and to compare the findings of the patients and caregivers, we excluded from the analysis those participants who abandoned the survey without providing the key information regarding their status (and the status-specific questions). We have now specified this in the Results: 'The analysis was performed on 934 participants from seven countries who provided information on their status (MS patient or caregiver) (Table 2).' We have reported in the Table below for the reviewer the pattern of the responses of these participants. In the manuscript this finding is summarized in the Results as follows: 'High rates of agreement were obtained also from participants excluded from the analysis as they did not provide information on their status (data not shown).'

	Strongly agree	**Agree**	**Disagree**	**Strongly disagree**	**Prefer not to answer**	**Row total**
Topic	***N (%)***					
1. Symptomatic treatments	68 (43)	76 (48)	3 (2)	1 (1)	10 (6)	158
2. Multidisciplinary rehabilitation	56 (51)	51 (47)	1 (1)	0	1 (1)	109
3. Timely engagement in advance care planning	35 (44)	40 (51)	1 (1)	0	3 (4)	79

4. General palliative care	28 (45)	29 (46)	5 (8)	0	1 (1)	63
5. Specialist palliative care	21 (50)	19 (46)	1 (2)	1 (2)	0	42
6. Education/training programs for caregivers	14 (36)	17 (44)	4 (10)	0	4 (10)	39
7. Practical/emotional support to caregivers	16 (45)	13 (37)	3 (9)	0	3 (9)	35
8: Education/training in palliative care for MS HPs	14 (44)	17 (53)	0	0	1 (3)	32
9. Education/training in MS for palliative care HPs	11 (40)	15 (56)	0	0	1 (4)	27

6. *There is no information in the methods about how themes were determined for the write-in answers/comments on the survey. (This is essentially a qualitative-type analysis of write-in responses and the approach to categorizing the comments can easily be added to the methods for clarity.)*
   We have now detailed this in the Methods: 'Two researchers (AG, AF) coded the open section on additional topics independently and jointly as follows: they devised two lists of response categories, one for the interventions and one for the outcomes; additional categories identified during the coding process were included to the pertinent list; if a comment included multiple topics, it was coded it into multiple categories. A third researcher (AS) was involved in case of difficult attribution.'

7. *While the results of patient engagement are now stated more explicitly in the text and Table 5 and this is very helpful, the discussion still has no framing of the study results in the context of the broader literature. Authors identified that engaging patients impacted the questions asked for the guideline. Is this consistent with what is reported in the literature? How do these findings relate to the broader work in this field? Are results consistent with prior findings or new? The answer is that these findings are consistent with what is described previously and this should be discussed. Such a discussion will strengthen the impact of this study, as it will demonstrate that this work adds to the growing body of literature showing that engaging patients in guideline development impacts guideline development (here, specifically relating to selection of topics/questions). Setting patient-centered scope is one identified result of patient engagement in guidelines (Tong 2011 [Tong, A., et al., Consumer involvement in topic and outcome selection in the development of clinical practice guidelines. Health Expectations, 2011. 15: p. 410-423.], Diaz del Campo 2011 [Diaz Del Campo, P., et al., A strategy for patient involvement in clinical practice guidelines: methodological approaches. BMJ Qual Saf, 2011. 20(9): p. 779-84.], Brouwers 2017 [Brouwers, M.C., et al., Understanding optimal approaches to patient and caregiver engagement in the development of cancer practice guidelines: a mixed methods study. BMC Health Serv Res, 2017. 17(1): p. 186.]), as are identifying issues that may be overlooked by medical professionals (Jarrett 2004 [Jarrett, L. and P.I. Unit, A report on a study to evaluate patient/carer membership of the first NICE Guideline Development Groups. 2004], Cowl 2015 [Cowl, J., et al., Chapter 1: How to conduct public and targeted consultation, in G-I-N Public Toolkit: Patient and Public Involvement in Guidelines (2015 ed). 2012, Guidelines International Network: Pitlochry, Scotland.], van der Ham 2016 [van der Ham, A.J., N. van Erp, and J.E. Broerse, Monitoring and evaluation of patient involvement in clinical practice guideline development: lessons from the Multidisciplinary Guideline for Employment and Severe Mental Illness, the Netherlands. Health Expect, 2016. 19(2): p. 471-82.], Den Breejen 2016 [den Breejen, E.M., et al., Added value of involving patients in the first step of multidisciplinary guideline development: a qualitative interview study among infertile patients. Int J Qual Health Care, 2016. 28(3): p. 299-305.]) and selecting patient-relevant topics and outcomes (Jarrett 2004, Tong 2011, Graham 2006 [Graham, K. Patient/carer involvement in clinical guidelines: the SIGN*

experience, Scottish Intercollegiate Guidelines Network. in Presented at the conference of the Spanish HTA group. 2006. Seville, Spain.], Légaré 2011, Diaz del Campo 2011, Guyatt 2011 [Guyatt, G.H., et al., GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol, 2011. 64: p. 395-400.], Coon 2016 [Coon, J.T., et al., End-user involvement in a systematic review of quantitative and qualitative research of non-pharmacological interventions for attention deficit hyperactivity disorder delivered in school settings: reflections on the impacts and challenges. Health Expect, 2016. 19(5): p. 1084-97.]). Useful reviews that could be cited include Légaré 2011 (Légaré, F., et al., Patient and public involvement in clinical practice guidelines: A knowledge synthesis of existing programs. Med Decis Making, 2011. 31: p. E45-E74) and/or Armstrong 2018 (Armstrong, M.J., et al., Impact of patient involvement on clinical practice guideline development: a parallel group study. Implement Sci, 2018. 13:55). Regardless of the specific references chosen, there needs to be some discussion of the current work in the context of similar research to identify the contribution that this work makes to an expanding field. Such a discussion will make the current work more impactful because it will frame these results in the context of an important and expanding body of work demonstrating the value of patient engagement at the step of guideline question development. The answer is that these findings are consistent with what is described previously and this should be discussed. Such a discussion will strengthen the impact of this study, as it will demonstrate that this work adds to the growing body of literature showing that engaging patients in guideline development impacts guideline development (here, specifically relating to selection of topics/questions).

We have widened the Discussion on this regard, by adding a sentence and two references (to comply with the manuscript length limits): ‘Our findings add to the growing body of literature showing that engaging patients in guideline development is feasible, and impacts the process (here, the selection and formulation of the guideline questions) [14, 15, 17, 18].’ The references added are Légaré F et al. 2011; Armstrong MJ, et al. 2018.

Full title: Patient and caregiver involvement in formulation of guideline questions: Findings from the EAN Guideline on Palliative Care of People with Severe Multiple Sclerosis

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Total word count of the manuscript including title page, references, legends and structured abstract: 3472

Running title: Patient and caregiver involvement in the formulation of guideline questions.

Keywords: Multiple sclerosis; palliative care; best practice; clinical practice guideline; patient and public involvement; online survey; mixed methods.

ABSTRACT

Background: Patient and public involvement in clinical practice guideline development is recommended to increase guideline trustworthiness and relevance.

Objective: To engage multiple sclerosis (MS) patients and caregivers in definition of the key questions to be answered in the EAN Guideline on Palliative Care of People with Severe MS.

Methods: A mixed methods approach was used: International online survey launched by the national MS societies of eight countries, after pilot testing/debriefing on 20 MS patients and 18 caregivers; focus group meetings (FGMs) of Italian and German MS patients and caregivers.

Results: Of 1199 participants, 951 (79%) completed the whole online survey, and 934 from seven countries were analyzed: 751 (80%) were MS patients (74% women, mean age 46.1) and 183 (20%) caregivers (36% spouses/partners, 72% women, mean age 47.4). Participants agreed/strongly agreed on inclusion of the nine pre-specified topics (from 89% for ‘advance care planning’ to 98% for ‘multidisciplinary rehabilitation’), and <5% replied ‘I prefer not to answer’ to any topic. There were 569 free comments: 182 (32%) on the pre-specified topics, 227 (40%) on additional topics (16 guideline-pertinent), and 160 (28%) on outcomes. Five FGMs (three of MS patients, two of caregivers, overall 35 participants) corroborated the survey findings. In addition, they allowed the explanation of the guideline production process, the exploration of patient-important outcomes and of taxing issues.

Conclusions: MS patient and caregiver involvement was resource and time intensive, but rewarding. It was key for the formulation of the 10 guideline questions, and for the identification of patient-important outcomes.

INTRODUCTION

The incorporation of patient values into individual clinical decisions, a fundamental of shared decision making, also applies to clinical practice guideline development [1]. The ultimate aim is to address the issues that are important to health consumers (patients, caregivers, and the public) and sensitive to their values and preferences. Consequently, professional societies and other guidelines producers have recognized the need to involve consumers in all the phases of guideline development [2]. An initial and fundamental guideline phase is the formulation of the clinical questions, specifying the population, intervention, comparator, and outcomes (PICO) [3]. For complex healthcare interventions, formulating PICO questions is more challenging than for questions of drug interventions, and no guidance currently exists [4,5]. The engagement of healthcare consumers is even more important to facilitate the operational definition of these questions.

The European Academy of Neurology (EAN) has recently appointed a guideline production group (‘task force’ in the EAN guideline terminology) [6] to devise a clinical practice guideline on palliative care of people with severe multiple sclerosis (MS). The task force consists of health professionals from three disciplines (neurology, palliative care, and rehabilitation), methodologists, and patient advocates. Task force members are from nine European countries: Bulgaria, Germany, Denmark, Israel, Italy, the Netherlands, Serbia, Spain, and the UK.

The guideline PICO questions were formulated obtaining information on patient values from literature search, from expert survey, and from the direct engagement of MS patients and caregivers using a mixed methods (quantitative and qualitative) approach. Here we describe the results of this process, and the main challenges encountered.

MATERIALS AND METHODS

The construction of the international online survey, its implementation, the focus group meetings (FGMs), the ethics statement, and analyses are reported in the Appendix.

RESULTS

Expert survey

The expert survey took place in April 2017 (Figure): task force members invited health professionals to complete a questionnaire that contained an introduction, two open sections (on interventions and clinical outcome measures to be included in the guideline), and a section with respondent profession and expertise. Forty-seven health professionals from eight countries (Denmark, Germany, Italy, Israel, the Netherlands, Serbia, Spain, UK) participated. Most professionals (27) were physicians (neurologists, physiatrists, palliative care physicians), eight were nurses, six therapists (physiotherapists, psychologists, occupational therapists), three social workers, one research coordinator, one hospice coordinator, one chaplain.

[Insert Figure about here]

Based on review of the literature [7-11] and on expert survey findings, the task force agreed on a set of 14 items (‘questions’), which are reported in Table S3 (right column).

Piloting of the international online survey

The first version of the survey was discussed in dedicated meetings of the Danish MSS and the Israel MSS, and was piloted/debriefed on 20 MS patients and 18 caregivers from six European countries

(Bulgaria, Germany, Italy, the Netherlands, Serbia, UK). In the Israel MSS meeting it was agreed that a survey on MS palliative care in Israel was too premature, as the discussion of palliative care, and death and dying was felt to be particularly difficult within the Israeli culture at this time. The interrogative item format (Table S3) and the section on outcomes related to each item (not shown) were found difficult to understand, and rate; the explanation paragraph of each item was considered complex; five of the 14 items were judged too taxing. As a result, the following changes were made to the first version: an affirmative item format was used; the list of outcomes attached to each question was removed; the explanation paragraph of each item was simplified; five items were removed (Table S3).

Survey implementation, and findings

Between July and December 2017, the online survey was carried out in all the task force countries, except Israel (see above). Participation was overall good, except for the UK (Table 1).

[Insert Table 1 about here]

The analysis was performed on 934 participants from seven countries who provided information on their status (MS patient or caregiver) (Table 2). MS patients (751, 80%) outnumbered caregivers (183, 20%). Mean patient age was 46.1 years (range 19-82); 558 (74%) were women, and 428 (57%) had tertiary education (college or university degree). Notably, 49% of the patients were fully ambulatory, and 23% had been diagnosed within the last five years, with consistent figures across all the countries except the Netherlands where the MS patients were more disabled, indicating that MS patients were interested in the topic of palliative care regardless of their clinical status. Patient employment status varied, with highest unemployment in Spain and Bulgaria (14%), and lowest values in the Netherlands and Denmark (0-3%). Most of the caregivers were women (72%), their mean age was 47.4 years (range 18-77), and 64% had tertiary education. One third of the caregivers were the patient's spouse or partner. The MS patients they cared for were of similar age (p=0.39) and disease duration ($\chi 2$ 3.2; p=0.20) albeit more disabled ($\chi 2$ 48.4; p<0.001) compared to the patients who completed the survey. The median (interquartile range) survey completion time was 8 (5-10) minutes in patients and 8 (6 - 11) minutes in caregivers (p=0.07).

[Insert Table 2 about here]

Participants replying 'I prefer not to answer' were consistently few among MS patients and caregivers, highest values were found for 'advance care planning' (ACP: 4% of MS patients, and 5% of caregivers), and 'specialist palliative care'(3% of MS patients, and 4% of caregivers). Participants agreed or strongly agreed on inclusion of the nine pre-specified topics, with the lowest value for 'ACP' (89% of both patients and caregivers) and the highest value for 'multidisciplinary rehabilitation' (99% of MS patients, 97% of caregivers). These figures were close to those of the 231 participants excluded from the analysis as they did not provide information on their status (data not shown).

There were 569 free comments, categorized into four domains: guideline pre-specified topics (182 comments, 32%); additional topics, pertinent to the guideline (16 comments, 3%); additional topics, not pertinent to the guideline (211, 37%), and outcomes (160, 28%). Table 3 reports distribution of the comments across the four domains by country; details on domain contents are reported in the legend.

[Insert Table 3 about here]

One-third of the comments on pre-specified guideline topics were on symptom management and rehabilitation - it was not possible from the comments to separate rehabilitation from multidisciplinary rehabilitation, thus topics 1 and 2 were merged, followed by palliative care and specialist palliative care (23%), and by emotional and practical support for caregivers (16%).

The two guideline-pertinent additional topics were: ‘voluntary euthanasia’ (related to question 14; Table S3) proposed by 12 patients from Denmark, Germany, the Netherlands, and Italy, and three caregivers from Denmark and Germany; ‘sheltered housing/assisted living’, proposed by one German patient.

Additional topics not pertinent to the guideline population, but to MS patients at large, regarded four main domains: ’welfare’ (104/211 comments, 49%), ‘empowerment’ (54 comments, 25%), ‘disease management’ (mainly related to the MS diagnosis; 31 comments, 15%), and ‘lifestyle’ (23 comments, 11%).

Fourteen overarching outcomes were mentioned, which included patient outcomes (from patient participation and quality of life, to quality of death and dying), caregiver outcomes, care-related outcomes, and costs (Table 3).

Of 934 participants, 120 (13%) commented on the survey or on the guideline project. Of those, most participants (110, 92%) expressed appreciation of the initiative. Ten participants (8%) reported some criticisms: three patients considered the survey as not exhaustive, useless, or futile; one patient commented that topics 8 and 9 were the same; six participants criticized the patient general section of the survey.

FGM findings

Patient FGMs lasted 96, 105, and 110 minutes, two had seven participants, and one 11 participants (total n=25). The median age of the patients was 54 years (range 53–75), 19 (76%) were women, and the median EDSS was 8.0 (range 6.0–9.5). Caregiver FGMs lasted 120 and 79 minutes, both with five participants (total n=10); their median age was 56 years (range 44–86), six (60%) were women; they were the spouse (n=5), widow (n=2) or widower (n=1) of MS patients who died in the previous year, mother (n=1), and daughter (n=1). After a short introduction and ice-breaking, 30-40 minutes were dedicated to the description of the guideline, the main phases of its production, and the reasons for involving patients and caregivers from the formulation of the clinical questions. All participants considered the guideline a valuable and necessary instrument for all professionals caring for people with severe MS: physicians (included family and emergency care physicians), therapists, nurses, social workers, and formal and informal caregivers.

The FGM themes, components, and illustrative citations are reported in Table 4. Participants who had not been in touch with palliative care benefited from the explanation and discussion, as most of them thought the discipline pertained exclusively to end-of-life care and cancer (citations 1-3). This was different for participants who had experienced palliative care (citations 4,5). End-of-life issues did crop up as a key guideline topic (citations 6-10). Another theme was that of requirements for severely affected MS patients: peer socialization (citations 11, 12); and case management, expressed by both relatives and patients (citations 13, 14), who often felt overwhelmed and unsupported, for instance after discharge from hospital and rehabilitation. Outcomes encompassed symptom control (citations 1, 3, 4), quality of life (citation 3), role preservation (of both patient and caregiver – citations 15,16), participation (citation 17), competency of professionals and caregivers (citations 18, 19), quality of care (citation 5), living will (citation 7), and caregiver burden (citation 10). In Germany patients' emotional well-being and quality of life were considered the most important guideline outcomes, while unplanned hospitalizations and costs were seen as the least important.

[Insert Table 4 about here]

The main outcomes and challenges of the patient and caregiver consultation are summarized in Table 5. Based on these findings, the task force formulated the guideline questions, and detailed each PICO component (Table S4). Four of the original questions (Table S3) were deemed of lesser importance, and subsidiary to specific guideline questions: original question 6 'early palliative care' to PICO question 4; original question 8 'goal setting' to PICO questions 2, 4, 5; original question 11 'anticipation of crises' to PICO question 5; and original question 12 'best place of palliative care' to PICO questions 4, 5.

[Insert Table 5 about here]

DISCUSSION

Offering the best care possible to the highest number of patients and reducing variations in service delivery are key issues for most healthcare systems, and the main reason for producing clinical practice guidelines [13]. Involvement of health service users in clinical guideline production has long been advocated, but insufficiently undertaken, and the best ways to engage users remain unclear [14-16]. Here we report the experience of an international patient and caregiver involvement, which was time and resource intensive, and employed a mixed method. A crucial role in this process was played by the NMSSs of each participating country, and particularly by a task force member who is a MS patient and also a member of the MS International Federation, and of the Danish NMSS. She was key in bridging the issues of the MS patients to those of the health professionals and researchers. The online survey allowed participation of a geographically varied population, and by being anonymous facilitated openness and trustworthiness. However, it required proficiency with online technology, and the contents of the first survey were streamlined to improve clarity and acceptability. Findings indicated that the survey was well accepted (skipped topics were < 5%, negative comments were rare) and information-rich: MS patients and caregivers consistently agreed on the inclusion of the nine proposed topics, and provided additional proposals and comments (Table 5).

The FGMs allowed the explanation of the process of guideline production, the identification of patient-important outcomes, and deliberation about taxing issues (Table 5). The consultation process as a whole was time and resource intensive (figure). It was rewarding for the formulation of key questions that were substantiated by patients and caregivers, and also for the recognition of subsidiary topics within the guideline scope.

Limitations. The online survey contents were not linguistically validated and participation differed markedly between countries. The FGMs could be organized only in two countries; not all the pre-specified guideline topics could be discussed in the FGMs; the combination of previous and current caregivers in the same FGM was challenging (Table 5). The need for more time devoted to the task emerged, however the organization of more training for partnering was out of the reach of the task force.

CONCLUSIONS

MS patients and caregivers validated the nine questions devised by our task force (with HP input), identified additional issues related to question 14 (voluntary euthanasia, assisted suicide), sheltered housing/assisted living, case management, and client-important overarching outcomes. This led to the formulation of 10 PICO questions for this guideline. Our pre-planned approach to engage patients and caregivers from the very beginning of guideline development is in line with current recommendations [3,16]. This was demanding but attainable, also at an international level. Our findings add to the growing body of literature showing that engaging patients in guideline development is feasible, and impacts the process (here, the selection and formulation of the guideline questions) [14,15,17,18].

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Supplementary Appendix. Materials and methods, acknowledgements, funding, and conflict of interest.

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Figure legend. Flowchart and time points of the study.

Full title: Patient and caregiver involvement in formulation of guideline questions: Findings from the EAN Guideline on Palliative Care of People with Severe Multiple Sclerosis

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Total word count of the manuscript including title page, references, legends and structured abstract: 3472

Running title: Patient and caregiver involvement in the formulation of guideline questions.

Keywords: Multiple sclerosis; palliative care; best practice; clinical practice guideline; patient and public involvement; online survey; mixed methods.

ABSTRACT

Background: Patient and public involvement in clinical practice guideline development is recommended to increase guideline trustworthiness and relevance.

Objective: To engage multiple sclerosis (MS) patients and caregivers in definition of the key questions to be answered in the EAN Guideline on Palliative Care of People with Severe MS.

Methods: A mixed methods approach was used: International online survey launched by the national MS societies of eight countries, after pilot testing/debriefing on 20 MS patients and 18 caregivers; focus group meetings (FGMs) of Italian and German MS patients and caregivers.

Results: Of 1199 participants, 951 (79%) completed the whole online survey, and 934 from seven countries were analyzed: 751 (80%) were MS patients (74% women, mean age 46.1) and 183 (20%) caregivers (36% spouses/partners, 72% women, mean age 47.4). Participants agreed/strongly agreed on inclusion of the nine pre-specified topics (from 89% for 'advance care planning' to 98% for 'multidisciplinary rehabilitation'), and <5% replied 'I prefer not to answer' to any topic. There were 569 free comments: 182 (32%) on the pre-specified topics, 227 (40%) on additional topics (16 guideline-pertinent), and 160 (28%) on outcomes. Five FGMs (three of MS patients, two of caregivers, overall 35 participants) corroborated the survey findings. In addition, they allowed the explanation of the guideline production process, the exploration of patient-important outcomes and of taxing issues.

Conclusions: MS patient and caregiver involvement was resource and time intensive, but rewarding. It was key for the formulation of the 10 guideline questions, and for the identification of patient-important outcomes.

INTRODUCTION

The incorporation of patient values into individual clinical decisions, a fundamental of shared decision making, also applies to clinical practice guideline development [1]. The ultimate aim is to address the issues that are important to health consumers (patients, caregivers, and the public) and sensitive to their values and preferences. Consequently, professional societies and other guidelines producers have recognized the need to involve consumers in all the phases of guideline development [2]. An initial and fundamental guideline phase is the formulation of the clinical questions, specifying the population, intervention, comparator, and outcomes (PICO) [3]. For complex healthcare interventions, formulating PICO questions is more challenging than for questions of drug interventions, and no guidance currently exists [4,5]. The engagement of healthcare consumers is even more important to facilitate the operational definition of these questions.

The European Academy of Neurology (EAN) has recently appointed a guideline production group (‘task force’ in the EAN guideline terminology) [6] to devise a clinical practice guideline on palliative care of people with severe multiple sclerosis (MS). The task force consists of health professionals from three disciplines (neurology, palliative care, and rehabilitation), methodologists, and patient advocates. Task force members are from nine European countries: Bulgaria, Germany, Denmark, Israel, Italy, the Netherlands, Serbia, Spain, and the UK.

The guideline PICO questions were formulated obtaining information on patient values from literature search, from expert survey, and from the direct engagement of MS patients and caregivers using a mixed methods (quantitative and qualitative) approach. Here we describe the results of this process, and the main challenges encountered.

MATERIALS AND METHODS

The construction of the international online survey, its implementation, the focus group meetings (FGMs), the ethics statement, and analyses are reported in the Appendix.

RESULTS

Expert survey

The expert survey took place in April 2017 (Figure): task force members invited health professionals to complete a questionnaire that contained an introduction, two open sections (on interventions and clinical outcome measures to be included in the guideline), and a section with respondent profession and expertise. Forty-seven health professionals from eight countries (Denmark, Germany, Italy, Israel, the Netherlands, Serbia, Spain, UK) participated. Most professionals (27) were physicians (neurologists, physiatrists, palliative care physicians), eight were nurses, six therapists (physiotherapists, psychologists, occupational therapists), three social workers, one research coordinator, one hospice coordinator, one chaplain.

[Insert Figure about here]

Based on review of the literature [7-11] and on expert survey findings, the task force agreed on a set of 14 items (‘questions’), which are reported in Table S3 (right column).

Piloting of the international online survey

The first version of the survey was discussed in dedicated meetings of the Danish MSS and the Israel MSS, and was piloted/debriefed on 20 MS patients and 18 caregivers from six European countries

(Bulgaria, Germany, Italy, the Netherlands, Serbia, UK). In the Israel MSS meeting it was agreed that a survey on MS palliative care in Israel was too premature, as the discussion of palliative care, and death and dying was felt to be particularly difficult within the Israeli culture at this time. The interrogative item format (Table S3) and the section on outcomes related to each item (not shown) were found difficult to understand, and rate; the explanation paragraph of each item was considered complex; five of the 14 items were judged too taxing. As a result, the following changes were made to the first version: an affirmative item format was used; the list of outcomes attached to each question was removed; the explanation paragraph of each item was simplified; five items were removed (Table S3).

Survey implementation, and findings

Between July and December 2017, the online survey was carried out in all the task force countries, except Israel (see above). Participation was overall good, except for the UK (Table 1).

[Insert Table 1 about here]

The analysis was performed on 934 participants from seven countries who provided information on their status (MS patient or caregiver) (Table 2). MS patients (751, 80%) outnumbered caregivers (183, 20%). Mean patient age was 46.1 years (range 19-82); 558 (74%) were women, and 428 (57%) had tertiary education (college or university degree). Notably, 49% of the patients were fully ambulatory, and 23% had been diagnosed within the last five years, with consistent figures across all the countries except the Netherlands where the MS patients were more disabled, indicating that MS patients were interested in the topic of palliative care regardless of their clinical status. Patient employment status varied, with highest unemployment in Spain and Bulgaria (14%), and lowest values in the Netherlands and Denmark (0-3%). Most of the caregivers were women (72%), their mean age was 47.4 years (range 18-77), and 64% had tertiary education. One third of the caregivers were the patient's spouse or partner. The MS patients they cared for were of similar age (p=0.39) and disease duration ($\chi2$ 3.2; p=0.20) albeit more disabled ($\chi2$ 48.4; p<0.001) compared to the patients who completed the survey. The median (interquartile range) survey completion time was 8 (5-10) minutes in patients and 8 (6 - 11) minutes in caregivers (p=0.07).

[Insert Table 2 about here]

Participants replying 'I prefer not to answer' were consistently few among MS patients and caregivers, highest values were found for 'advance care planning' (ACP: 4% of MS patients, and 5% of caregivers), and 'specialist palliative care'(3% of MS patients, and 4% of caregivers). Participants agreed or strongly agreed on inclusion of the nine pre-specified topics, with the lowest value for 'ACP' (89% of both patients and caregivers) and the highest value for 'multidisciplinary rehabilitation' (99% of MS patients, 97% of caregivers). These figures were close to those of the 231 participants excluded from the analysis as they did not provide information on their status (data not shown).

There were 569 free comments, categorized into four domains: guideline pre-specified topics (182 comments, 32%); additional topics, pertinent to the guideline (16 comments, 3%); additional topics, not pertinent to the guideline (211, 37%), and outcomes (160, 28%). Table 3 reports distribution of the comments across the four domains by country; details on domain contents are reported in the legend.

[Insert Table 3 about here]

One-third of the comments on pre-specified guideline topics were on symptom management and rehabilitation - it was not possible from the comments to separate rehabilitation from multidisciplinary rehabilitation, thus topics 1 and 2 were merged, followed by palliative care and specialist palliative care (23%), and by emotional and practical support for caregivers (16%).

The two guideline-pertinent additional topics were: ‘voluntary euthanasia’ (related to question 14; Table S3) proposed by 12 patients from Denmark, Germany, the Netherlands, and Italy, and three caregivers from Denmark and Germany; ‘sheltered housing/assisted living’, proposed by one German patient.

Additional topics not pertinent to the guideline population, but to MS patients at large, regarded four main domains: ’welfare’ (104/211 comments, 49%), ‘empowerment’ (54 comments, 25%), ‘disease management’ (mainly related to the MS diagnosis; 31 comments, 15%), and ‘lifestyle’ (23 comments, 11%).

Fourteen overarching outcomes were mentioned, which included patient outcomes (from patient participation and quality of life, to quality of death and dying), caregiver outcomes, care-related outcomes, and costs (Table 3).

Of 934 participants, 120 (13%) commented on the survey or on the guideline project. Of those, most participants (110, 92%) expressed appreciation of the initiative. Ten participants (8%) reported some criticisms: three patients considered the survey as not exhaustive, useless, or futile; one patient commented that topics 8 and 9 were the same; six participants criticized the patient general section of the survey.

FGM findings

Patient FGMs lasted 96, 105, and 110 minutes, two had seven participants, and one 11 participants (total n=25). The median age of the patients was 54 years (range 53–75), 19 (76%) were women, and the median EDSS was 8.0 (range 6.0–9.5). Caregiver FGMs lasted 120 and 79 minutes, both with five participants (total n=10); their median age was 56 years (range 44–86), six (60%) were women; they were the spouse (n=5), widow (n=2) or widower (n=1) of MS patients who died in the previous year, mother (n=1), and daughter (n=1). After a short introduction and ice-breaking, 30-40 minutes were dedicated to the description of the guideline, the main phases of its production, and the reasons for involving patients and caregivers from the formulation of the clinical questions. All participants considered the guideline a valuable and necessary instrument for all professionals caring for people with severe MS: physicians (included family and emergency care physicians), therapists, nurses, social workers, and formal and informal caregivers.

The FGM themes, components, and illustrative citations are reported in Table 4. Participants who had not been in touch with palliative care benefited from the explanation and discussion, as most of them thought the discipline pertained exclusively to end-of-life care and cancer (citations 1-3). This was different for participants who had experienced palliative care (citations 4,5). End-of-life issues did crop up as a key guideline topic (citations 6-10). Another theme was that of requirements for severely affected MS patients: peer socialization (citations 11, 12); and case management, expressed by both relatives and patients (citations 13, 14), who often felt overwhelmed and unsupported, for instance after discharge from hospital and rehabilitation. Outcomes encompassed symptom control (citations 1, 3, 4), quality of life (citation 3), role preservation (of both patient and caregiver – citations 15,16), participation (citation 17), competency of professionals and caregivers (citations 18, 19), quality of care (citation 5), living will (citation 7), and caregiver burden (citation 10). In Germany patients' emotional well-being and quality of life were considered the most important guideline outcomes, while unplanned hospitalizations and costs were seen as the least important.

[Insert Table 4 about here]

The main outcomes and challenges of the patient and caregiver consultation are summarized in Table 5. Based on these findings, the task force formulated the guideline questions, and detailed each PICO component (Table S4). Four of the original questions (Table S3) were deemed of lesser importance, and subsidiary to specific guideline questions: original question 6 'early palliative care' to PICO question 4; original question 8 'goal setting' to PICO questions 2, 4, 5; original question 11 'anticipation of crises' to PICO question 5; and original question 12 'best place of palliative care' to PICO questions 4, 5.

[Insert Table 5 about here]

DISCUSSION

Offering the best care possible to the highest number of patients and reducing variations in service delivery are key issues for most healthcare systems, and the main reason for producing clinical practice guidelines [13]. Involvement of health service users in clinical guideline production has long been advocated, but insufficiently undertaken, and the best ways to engage users remain unclear [14-16]. Here we report the experience of an international patient and caregiver involvement, which was time and resource intensive, and employed a mixed method. A crucial role in this process was played by the NMSSs of each participating country, and particularly by a task force member who is a MS patient and also a member of the MS International Federation, and of the Danish NMSS. She was key in bridging the issues of the MS patients to those of the health professionals and researchers. The online survey allowed participation of a geographically varied population, and by being anonymous facilitated openness and trustworthiness. However, it required proficiency with online technology, and the contents of the first survey were streamlined to improve clarity and acceptability. Findings indicated that the survey was well accepted (skipped topics were < 5%, negative comments were rare) and information-rich: MS patients and caregivers consistently agreed on the inclusion of the nine proposed topics, and provided additional proposals and comments (Table 5).

The FGMs allowed the explanation of the process of guideline production, the identification of patient-important outcomes, and deliberation about taxing issues (Table 5). The consultation process as a whole was time and resource intensive (figure). It was rewarding for the formulation of key questions that were substantiated by patients and caregivers, and also for the recognition of subsidiary topics within the guideline scope.

Limitations. The online survey contents were not linguistically validated and participation differed markedly between countries. The FGMs could be organized only in two countries; not all the pre-specified guideline topics could be discussed in the FGMs; the combination of previous and current caregivers in the same FGM was challenging (Table 5). The need for more time devoted to the task emerged, however the organization of more training for partnering was out of the reach of the task force.

CONCLUSIONS

MS patients and caregivers validated the nine questions devised by our task force (with HP input), identified additional issues related to question 14 (voluntary euthanasia, assisted suicide), sheltered housing/assisted living, case management, and client-important overarching outcomes. This led to the formulation of 10 PICO questions for this guideline. Our pre-planned approach to engage patients and caregivers from the very beginning of guideline development is in line with current recommendations [3,16]. This was demanding but attainable, also at an international level. Our findings add to the growing body of literature showing that engaging patients in guideline development is feasible, and impacts the process (here, the selection and formulation of the guideline questions) [14,15,17,18].

Supporting Information

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Figure legend. Flowchart and time points of the study.

Table 1. Characteristics of the 751 multiple sclerosis patients and 183 caregivers who completed the online survey, overall and by country. For some variables, few data are missing. MS, multiple sclerosis.

Country	**Inhabitants**	**MS patients**	**Prevalence**	**Accessed the survey**	**Consented no. (%)**	**Completed no. (%)**		
						Overall	*Patients*	*Caregivers*
Germany	80 * 10^6	130.000	149 / 10^5	227	189 (83%)	136 (72%)	118 (87%)	18 (13%)
The UK	63 * 10^6	100.000	164 / 10^5	32	17 (53%)	17 (100%)	13 (76%)	4 (24%)
Italy	59 * 10^6	68.000	113 / 10^5	488	443 (91%)	388 (87%)	334 (86%)	54 (14%)
Spain	47 * 10^6	42.900	102 / 10^5	178	144 (81%)	98 (68%)	68 (70%)	30 (30%)
The Netherlands	17 * 10^6	14.300	88 / 10^5	75	60 (80%)	43 (72%)	28 (65%)	15 (35%)
Bulgaria	7 * 10^6	4.250	39 / 10^5	145	124 (86%)	92 (75%)	77 (84%)	15 (16%)
Serbia	7 * 10^6	–	–	58	53 (91%)	53 (100%)	22 (41%)	31 (59%)
Denmark	6 * 10^6	12.800	227 / 10^5	179	169 (95%)	124 (73%)	104 (84%)	20 (16%)
Totals	–	–	–	1382	1199 (87%)	951 (79%)	764 (80%)	187 (20%)

Table 2. Characteristics of the eight countries that participated to the online survey [8, 15] and survey participation. UK was excluded from the analysis as participation was sub-threshold.

Characteristic (patients)	**Germany (n=118)**	**Italy (n=334)**	**Spain (n=68)**	**Netherlands (n=28)**	**Bulgaria (n=77)**	**Serbia (n=22)**	**Denmark (n=104)**	**Totals (n=751)**
	No (%)							
Women	81 (69%)	252 (75%)	54 (79%)	19 (78%)	55 (71%)	16 (73%)	81 (78%)	558 (74%)
Age, mean (SD) years	42.8 (11.6)	46.2 (11.9)	44.7 (9.8)	53.1 (8.7)	43.9 (10.2)	45.8 (12.8)	50.4 (9.4)	46.1 (11.4)
Tertiary education	62 (53%)	157 (47%)	49 (72%)	13 (46%)	44 (57%)	13 (59%)	90 (87%)	428 (57%)
Time from diagnosis:								
< 5 years	41 (35%)	77 (24%)	21 (31%)	6 (21%)	20 (26%)	6 (27%)	22 (22%)	193 (26%)
5-10 years	31 (27%)	81 (25%)	18 (26%)	10 (36%)	22 (29%)	3 (14%)	28 (27%)	193 (26%)
> 10 years	44 (38%)	166 (51%)	29 (43%)	12 (43%)	35 (45%)	13 (59%)	52 (51%)	351 (48%)
Disability level:								
Fully ambulatory	57 (50%)	180 (55%)	32 (47%)	5 (19%)	27 (35%)	12 (55%)	46 (45%)	359 (49%)
Reduced walking	37 (32%)	92 (28%)	26 (38%)	9 (33%)	31 (41%)	8 (36%)	38 (37%)	241 (33%)
Chair/bed-bound	21 (18%)	53 (16%)	10 (15%)	13 (48%)	18 (24%)	2 (9%)	19 (18%)	136 (18%)
Employment:								
Unemployed	5 (4%)	33 (10%)	9 (13%)	0	11 (14%)	1 (5%)	3 (3%)	62 (8%)
Employed, full time	33 (28%)	132 (40%)	18 (27%)	3 (11%)	26 (34%)	8 (36%)	9 (9%)	229 (31%)
Employed, part time	22 (19%)	58 (18%)	3 (5%)	2 (7%)	10 (13%)	1 (5%)	22 (22%)	118 (16%)
Student/homemaker	12 (10%)	37 (11%)	3 (5%)	3 (11%)	7 (9%)	2 (9%)	3 (3%)	67 (9%)
Sick leave/retired	40 (34%)	33 (10%)	31 (48%)	18 (67%)	23 (30%)	9 (41%)	41 (40%)	195 (26%)
Age retired	5 (4%)	36 (11%)	1 (2%)	1 (4%)	0	1 (5%)	23 (23%)	67 (9%)

Characteristic (caregivers)	Germany (n=18)	Italy (n=54)	Spain (n=30)	Netherlands (n=15)	Bulgaria (n=15)	Serbia (n=31)	Denmark (n=20)	Totals (n=183)
					No (%)			
Women	13 (72%)	37 (69%)	25 (83%)	13 (87%)	8 (53%)	18 (58%)	18 (90%)	132 (72%)
Age, mean (SD) years	43.7 (13.2)	47.0 (13.4)	41.6 (12.4)	58.4 (12.7)	52.5 (9.7)	44.2 (13.8)	53.8 (12.7)	47.4 (13.6)
Tertiary education	11 (61%)	26 (48%)	19 (66%)	6 (40%)	12 (80%)	24 (77%)	18 (90%)	116 (64%)
Relationship:								
Spouse/partner	6 (33%)	29 (54%)	10 (33%)	7 (47%)	4 (29%)	5 (16%)	5 (25%)	65 (36%)
Parent	2 (11%)	8 (15%)	6 (21%)	1 (6%)	3 (21%)	0	8 (40%)	30 (17%)
Son/daughter	4 (22%)	7 (13%)	4 (14%)	1 (6%)	0	3 (10%)	2 (10%)	18 (10%)
Other relative	4 (22%)	5 (9%)	2 (7%)	6 (40%)	4 (29%)	9 (29%)	2 (10%)	32 (18%)
Friend	1 (6%)	2 (3%)	3 (11%)	0	1 (7%)	14 (45%)	3 (15%)	24 (13%)
Other	1 (6%)	3 (6%)	4 (14%)	0	2 (14%)	0	0	10 (6%)
Women patient	9 (53%)	29 (54%)	15 (56%)	6 (40%)	5 (42%)	18 (58%)	10 (53%)	92 (53%)
Patient age, mean (SD) years	48.5 (17.2)	47.2 (12.8)	46.6 (13.0)	55.57 (10.2)	45.4 (13.4)	44.4 (11.1)	43.9 (13.3)	47.0 (13.1)
Time from diagnosis:								
< 5 years	3 (18%)	11 (22%)	6 (24%)	2 (13%)	2 (13%)	9 (29%)	3 (15%)	36 (21%)
5-10 years	5 (29%)	12 (24%)	7 (28%)	0	4 (27%)	8 (26%)	7 (35%)	43 (25%)
> 10 years	9 (53%)	28 (54%)	12 (48%)	13 (87%)	9 (60%)	14 (45%)	10 (50%)	95 (54%)
Disability level:								
Fully ambulatory	5 (29%)	21 (40%)	6 (24%)	0	5 (33%)	13 (43%)	5 (25%)	55 (32%)
Reduced walking	4 (24%)	11 (21%)	9 (36%)	1 (7%)	4 (27%)	10 (33%)	5 (25%)	44 (25%)
Chair/bed-bound	8 (47%)	20 (38%)	10 (40%)	14 (93%)	6 (40%)	7 (23%)	10 (50%)	75 (43%)
Employment:								
Unemployed	1 (6%)	9 (18%)	2 (8%)	3 (20%)	2 (13%)	2 (6%)	2 (10%)	21 (12%)
Employed, full time	4 (23%)	14 (26%)	3 (13%)	0	2 (13%)	8 (26%)	0	31 (18%)
Employed, part time	2 (12%)	2 (4%)	1 (4%)	0	1 (7%)	3 (10%)	3 (15%)	12 (7%)
Student/homemaker	0	7 (14%)	4 (16%)	0	1 (7%)	4 (12%)	1 (5%)	17 (10%)
Sick leave/retired	9 (53%)	11 (22%)	13 (55%)	8 (53%)	7 (47%)	13 (42%)	10 (50%)	71 (39%)
Age retired	1 (6%)	8 (16%)	1 (4%)	4 (27%)	2 (13%)	1 (3%)	4 (20%)	21 (12%)

SD, standard deviation.

Table 3. Comments of multiple sclerosis (MS) patients and caregivers categorized into four domains, overall and by country. Domain contents are reported in the legend.

Country	Pre-specified topics[1]	New topics, guideline-pertinent[2]	New topics, non-pertinent[3]	Outcomes[4]	Row total
			No (%)		
Germany	51 (28%)	10 (62%)	41 (19%)	46 (29%)	148 (26%)
Italy	56 (31%)	1 (6%)	100 (47%)	54 (34%)	211 (37%)
Spain	30 (16%)	0	36 (17%)	31 (19%)	97 (17%)
Netherlands	12 (7%)	2 (12%)	9 (4%)	5 (3%)	28 (5%)
Bulgaria	14 (8%)	0	2 (1%)	6 (4%)	22 (4%)
Serbia	4 (2%)	0	9 (4%)	4 (2%)	17 (3%)
Denmark	15 (8%)	3 (20%)	14 (7%)	14 (9%)	46 (8%)
Column total	182 (100%)	16 (100%)	211 (100%)	160 (100%)	569

1. Symptoms management and multidisciplinary rehabilitation (topics 1 and 2): 59/182 comments (33%); palliative care (topics 4 and 5) 41 (23%); emotional and practical support for caregivers (topic 7): 29 (16%); advance care planning (topic 3): 19 (10%); education for caregivers (topic 6): 18 (10%); education and training in palliative care for MS health professionals (topic 8): 9 (5%); education and training in MS for palliative care professionals (topic 9): 7 (4%).
2. 'Voluntary euthanasia': 15/16 comments; 'sheltered housing/assisted living': one comment.
3. 'Welfare' (104/211 comments, 49%): access/coordination of care/services (43, 20%), rights (28, 13%), employment (13, 6%), economic support for MS patients and caregivers (13, 6%), housing and environmental adaptations (7, 3%); 'Empowerment' (54 comments, 25%): MS information for patients, relatives, caregivers, and health professionals (49, 23%), decisional autonomy (4, 2%); 'Disease management' (31 comments, 15%): competent professionals (15, 7%), patient emotional support (11, 5%), relative emotional support (5, 2%); 'Lifestyle' (23 comments, 11%): diet (8, 4%), sexuality (8, 4%), and leisure (7, 3%).
4. 'Patient participation' (36/160 comments, 22%), 'Functioning' (21, 13%), 'Symptom burden' (17, 11%), 'Emotional wellbeing' (14, 9%), 'Advance directive/living will' (14, 9%), 'Service coordination' (10, 6%), 'Caregiver emotional wellbeing' (10, 6%), 'Quality of life' (8, 5%), 'Quality of death/dying' (8, 5%), 'Satisfaction with care/services' (8, 5%), 'Patient-clinician relationship' (5, 3%), 'Caregiver burden' (4, 2%), 'Complicated bereavement' (3, 2%), 'Costs' (2, 1%).

Table 4. The focus group meeting themes, components, and illustrative citations. Citations 1, 3-5, 7 and 10 also pertain to the theme ‘outcomes’ and to the following components: ‘symptom burden’ (cit. 1, 3, 4), ‘quality of life’ (cit. 4), ‘satisfaction with care/service’ (cit. 5), ‘living will’ (cit. 7) and ‘caregiver burden’ (cit. 10) . MS is multiple sclerosis; EDSS is expanded disability status scale.

Theme	**Component**	**Citation**
Palliative care	Theoretical	*1. I think it's irrelevant whether I have MS or cancer […] What matters to me is to be kept free of pain and all is done to obtain this, so that you feel well then.* [Woman with MS, Hamburg] *2. The word palliative medicine does not scare me anymore, as now I know what it means. I see it as a way to receive protection, if it works as it should do...* [Man with MS, Berg] *3. When she accepted the PEG [Percutaneous endoscopic gastrostomy] [...], she began to breathe better, to have less secretions, and to talk much better. At some point she jokingly said ‘Hey guys, I’m going to stand up, I’m going to be healed!’ But I’ve no idea whether it was palliative or curative…* [73 year old widower of a MS patient who recently died, at age 70, Milan]
	Experiential	*4. If you continue to suffer the difficulties, the pain, the immobility and everything, it’s so hard to carry on with your daily life. So to me, it’s key to have a somewhat dignified life. [My husband] had massive drooling as he could not swallow the saliva... [The palliative physician] prescribed Scopolamine patches, and the drooling stopped. He no longer appeared or felt soaked all the time, he was definitely better: At least that problem was manageable*. [51 year old widow of a MS patient who recently died, at age 54, Milan] *5. I just experienced* [home palliative service] *with my mom who died last year of a kidney cancer. We lived together, just the two of us. In the hospital often you're just a number [...]. Here you have these people alongside who can help you, even if only to talk and to deal with these issues, a doubt or something, it is so important… You feel like being at the center of care*. [58 year old MS woman, EDSS 8.5, Milan]
End of life	Discussion about choices	*6. I live alone with three caregivers: one for the day, one for the night and the third for two weekends a month. But I wonder what will happen to me when things will be more difficult. All decisions and things that one has to make, that is, when you are no longer able to settle on… what do you do?* [59 year old MS woman, EDSS 9.0, Milan] *7. We have to have a reasonable living will, which shows where we are, yes, with my thoughts and everything behind it and then properly formulated.* [Woman with MS, Hamburg] *8. This is the question that I always ask myself, what will happen next, how do I know when the time has come? Well, I must admit I had thought to go to Switzerland to... That is, there will be a*

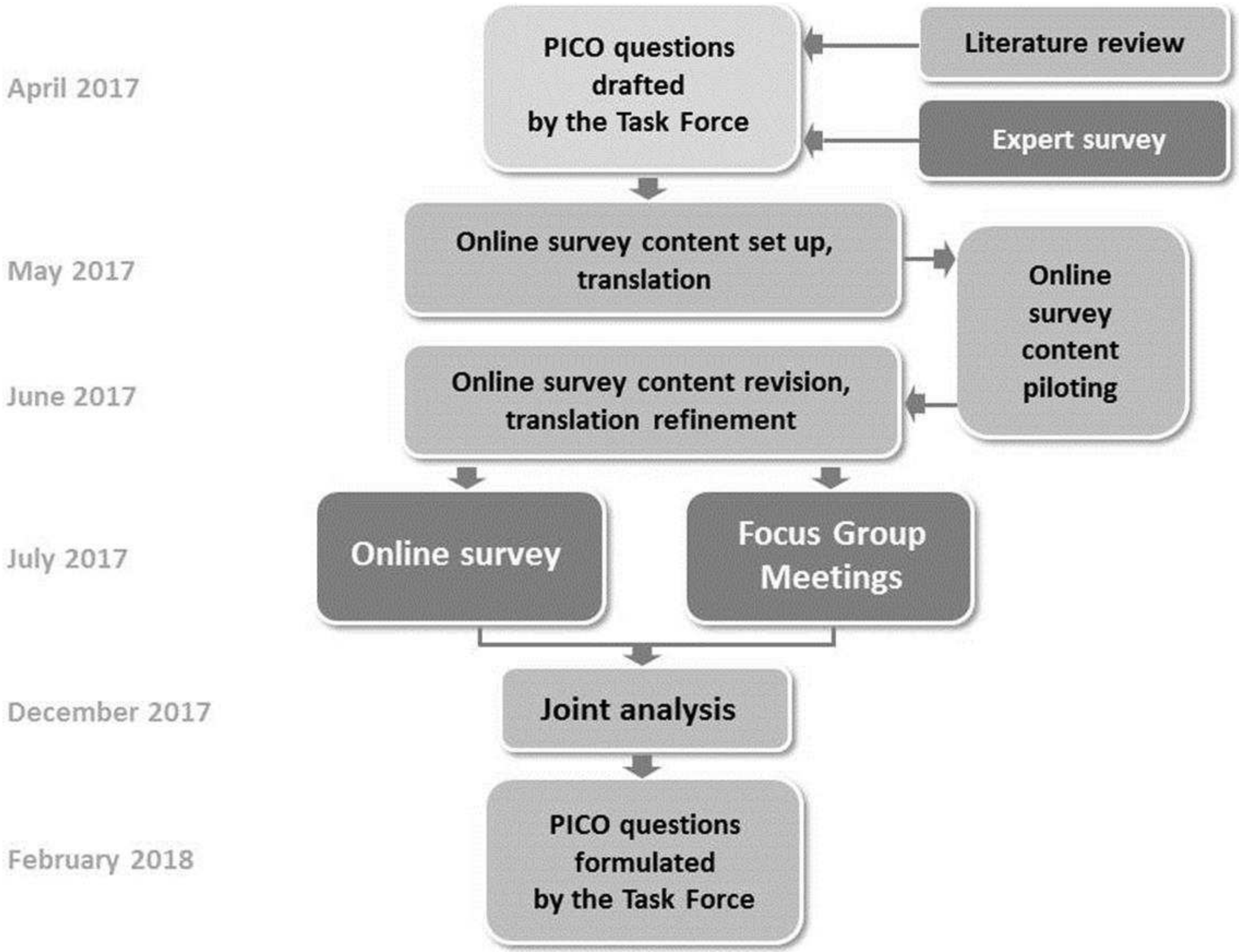
		time when […] and then how do I decide, how do I understand that the time has come to end my life? Fear of the future, what will happen? End-of-life choices? Hastening death? It's something I can't talk about with my husband, because he says that these are arguments that he does not want to go into. But I do keep thinking about this. [53 year old MS woman, EDSS 8.5, Milan].
	Medically assisted suicide	*9. She asked me repeatedly to be brought to Lugano, rather than to Zurich, to do... , we tried to convince her of the meaningfulness of her life, even in such disastrous conditions, and I must say that two psychologists helped her to accept to stay alive.* [73 year old widower of a MS patient who recently died, at age 70, Milan]
	Voluntary euthanasia	*10. [Euthanasia] should not be hushed up, but should simply be discussed. But just with the difficulty that the bandwidth may become very large and it could become just too easy and comfortable, so that some people could feel pressed to reduce relatives' burden or: ask as they are thinking: I'm just a millstone around your neck.* [Woman with MS, Hamburg]
Requirements	Peer socialization	*11. During my hospitalizations and outpatient visits, I have been in contact with other patients, we've shared our stories. Over time there have been no friendships, say, with these people, but I am well aware that discussing these issues is indeed something that helps. Absurdly, right now that I have more physical difficulties, I would need more meetings and discussions, but I don't know how to do that, I don't know who to turn to, I do not know...* [53 year old MS woman, EDSS 8.5, Milan] *12. Having conversations can be good, because I get a lot of energy from it. One should not always stand there... so 'empty'... and that's why I always like to have the opportunity to talk more. With other patients, you just sit together and take your time.* [Woman with MS, Berg]
	Case management	*13. I need someone to help me, someone just to ask to.* [Woman with MS, Berg] *14. I was blamed by my family doctor because I turned my anger on him in an occasion, [my husband] had been admitted to the emergency ward, and I felt a bit abandoned. And then I realized that it was not the family doctor who had that [case management] role. Anyway, I felt so alone…*[51 year old widow of a MS patient who recently died, at age 54, Milan] .
Outcomes	Role preservation	*15. It's really a huge loss, because as a university teacher not being able to walk is not a problem, not being able to use your hands is more a problem, but if you can't even talk is a rip off, that is because one has so much to say and can't say, that is, one has to reduce sentences to short ones and this is a real handicap.* [58 year old MS woman, EDSS 8.5, Milan] *16. But I wanted that my son was exempted from doing the bladder catheterization [to her mom].* [73 year old widower of a MS patient who recently died, at age 70, Milan]
	Participation	*17. I got here with a transport for disabled persons. But if on a Sunday I want to go out, to say, to*

		a dinner with friends, the transport for disabled persons is not easy to find [...] With public transportation it t can happen that I get there and then the platform does not work. At that point I give up and go back home. I feel helpless with these small and trivial things. [53 year old MS woman, EDSS 8.0, Milan]
	Competent professionals/ caregivers	*18. We teamed up. In the last period I have to say that we set up a caregiving company, we have been supported by a foundation that provided us great home care. I hired a paid caregiver, who I educated about procedures, such as the intermittent catheterization, managing the respirators, and basically, she worked with me and my son and we all worked together on 24 hours.* [73 year old widower of a MS patient who recently died, at age 70, Milan] *19. So perhaps it was hard to make the paid caregiver understand that [my husband] preferred to listen to the radio, rather than watch television. To her [the paid caregiver] no, one had to watch television... I also missed the training, because I always learned everything when it happened... , that is, first you have to understand what the problem is.* [51 year old widow of a MS patient who recently died, at age 54, Milan]

Table 5. The purposes, outcomes and challenges of the international online survey and focus group meetings. MS is multiple sclerosis: QOL is quality of life.

	Literature review/expert consultation	**International online survey**	**Focus group meetings**
Aims	- Identify topics that represent opportunities for quality improvement within the guideline scope. - Involve guideline users.	- Involve a geographically and clinically varied population of patients and caregivers via the national MS Societies. - Anonymous, free expression of participants' views and preferences.	- Involve severely affected MS patients, and caregivers of such patients. - Involve caregivers of recently deceased patients. - Explain/discuss the process of guideline production. - Identify outcomes important to patient and caregivers. - Explore 'difficult' topics and taxing issues.
Outcomes	- Draw up of 14 clinical questions.	- Over 88% of participants agreed/strongly agreed on inclusion in the guideline of each of the nine pre-specified topics. - Consistent findings between MS patients and caregivers. - Identification of 14 outcomes important to the patients and caregivers via 160 free comments. - Identification of 15 free comments on voluntary euthanasia.	- Patients need to discuss about end of life choices, medical assisted suicide, and voluntary euthanasia. - Identification of seven outcomes, related to the guideline questions: symptom burden, participation, QOL, living will, role preservation (of the patient and caregiver), caregiver burden, quality of care.

Challenges	- None identified.	- Variable participation across the countries, negligible in the UK (excluded from analysis). - Selection of online-proficient and well-educated participants (57% of the patients and 64% of the caregivers had college or university degree). - Time and resource consuming (survey set up, translation into the target languages, piloting, revision, conduction, and analysis; Figure).	- Performed in only two of the nine guideline task force countries. - The combination of previous and current caregivers in the same meeting was challenging. - Not all the pre-specified guideline topics could be discussed. - Not a pre-planned action (no dedicated resources).


April 2017
PICO questions drafted by the Task Force
Literature review
Expert survey
May 2017
Online survey content set up, translation
Online survey content piloting
June 2017
Online survey content revision, translation refinement
July 2017
Online survey
Focus Group Meetings
December 2017
Joint analysis
February 2018
PICO questions formulated by the Task Force

Supplementary Appendix.

MATERIALS AND METHODS

Construction of the international online survey, its implementation, the focus group meetings (FGMs), the ethics statement, and analyses.

The task force devised a set of guideline questions based on review of the literature and expert consultation.

Construction of the international online survey

The preliminary survey structure consisted of six parts: an introduction to the aims of the consultation, with explanations on guideline, and palliative care; a consent page; a section with a set of guideline questions, each with a structured, short explanation of the population, intervention, and outcomes, followed by the statement: 'Please express whether you agree/disagree on including this question in the guideline' on a four-point Likert scale (strongly agree/agree/disagree/strongly disagree), plus a 'I prefer not to answer' option; an open section for additional topics to be included (up to a maximum of six topics); a demographic section with a common set of multiple choice items on participant age, sex, education, status (patient or caregiver), and specific multiple choice questions for patients (time from MS diagnosis, disability level, employment status) and caregivers (relation with the MS sufferer, time from MS diagnosis, disability level, employment status of the MS sufferer); an open section for comments on the survey or on the guideline project.

The survey was devised in English, translated into the target languages by appointed task force members with help from the National MS Societies (NMSSs), and then it was discussed at dedicated meetings at the Danish and Israel NMSSs, and piloted/debriefed on MS patients in

Bulgaria, Germany, Italy, Serbia, the Netherlands, and the UK. The final version of the survey was then produced, translated, and hosted at the University of Hamburg, Eppendorf (EFS Survey® software, compliant with HIPAA regulations). The survey was CHERRIES-compliant [7], except for one checklist item as it was not possible to customize a completeness check, giving respondents the opportunity to review and change their responses at the end of survey completion.

Survey implementation

An invitation letter, with an email contact to receive further information, and the survey link was posted on the NMSS websites. NMSS invitation via the social media was also envisaged. Each invitation was scheduled to limit overlap with other NMSS surveys. The invitation was posted for 2-4 weeks, and feedback on participation was provided to the NMSS on a weekly basis. The pre-specified minimum number of participants was 50 in countries with ≥ 40 million inhabitants, and 20 in countries with < 40 million inhabitants [8]. The survey was anonymous to promote openness and trustworthiness and could be accessed only once from a given IP address, to prevent multiple entries from the same user. Completion time was recorded. After survey closure, the open section text was translated into English by the appointed task force members with help from the NMSSs. Two researchers (AG, AF) coded the open section on additional topics independently and jointly as follows: they devised two lists of response categories, one for the interventions and one for the outcomes; additional categories identified during the coding process were included to the pertinent list; if a comment included multiple topics, it was coded it into multiple categories. A third researcher (AS) was involved in case of difficult attribution. We excluded from the analysis those cases in which, in the demographic section, it was not specified whether the participant was a person with MS or a caregiver.

Focus Group Meetings (FGMs)

We addressed the guideline questions using a qualitative approach, inviting severely affected MS patients and caregivers who were interested in palliative care to participate in FGMs. The caregiver FGMs also included caregivers of MS patients who had died in the preceding 1-5 years. The FGMs were held in parallel to the online survey in clinical settings in Milan (Foundation C. Besta) and Berg (Marianne-Strauß-Klinik). In Hamburg they took place in a local patient self-help organization. In Milan and Hamburg participants were MS outpatients, and patients' relatives; in Berg they were MS inpatients, residents of the clinic nursing home and patients' relatives. As the contents of the first version of the survey were streamlined to improve clarity and acceptability, a further FGM objective was to consider the removed topics. Four FGMs were planned, two of severely affected MS patients, and two of caregivers. Each FGM had 5 to 10 participants with two moderators (SV and AS in Italy, SK, ACR, and BBR in Germany). In the Milan FGM of patients a research assistant also attended, to help participants (e.g. in drinking, changing position). One moderator (facilitator) engaged participants, promoted exchange, modulated conflicts, ensuring the topics were adequately covered and allowing sufficient time for exploration of pertinent issues arising. The co-moderator helped the moderator, took notes, oversaw the audio recording and otherwise assisted as necessary. The facilitator first explained the purpose of the meeting, encouraged participants to introduce themselves, then explained the technical elements of guideline development (in Milan, aided by a power point presentation). After discussion of each guideline question the facilitator summarized major points arising, and asked whether all concerns had been fully aired. He then explored additional topics, and related outcomes. In Germany each participant rated outcome importance on a questionnaire at the end of the FGM. The consolidated criteria for reporting qualitative studies (COREQ) checklist is reported in Table S1; the FGM guides (produced by SK and revised by SV and AS) are reported in Table S2.

Ethics statement

The guideline protocol was approved by the ethics committee of the Foundation C. Besta (ref. no. 34, 2016). The qualitative study (i.e. FGMs) was approved by the ethics committee of the Foundation C. Besta (ref. no. 43, 2017), and by the ethics committee of the University of Lübeck (ref. no. 17-307, 2017).

Statistical analysis

The analyses were performed comparing responses obtained from the patients and the caregivers. Those participants who did not provided information about their status (patient or caregiver) were excluded from the analysis.

Categorical variables were summarized as numbers and percentages, and compared by χ2 or Fisher's exact test; continuous variables were summarized as means and SD or medians with interquartile ranges, and compared by ANOVA or Wilcoxon rank-sum test. Normality and equality of variance assumptions were tested using Shapiro-Wilk's and Bartlett's tests, respectively.

Qualitative analysis

Each FGM transcript was analyzed by moderators using thematic analysis (deductive approach) [3]. As we were particularly interested in understanding patient values we thought that MS patients and their caregivers would have been more prone to discuss in a dedicated setting the guideline questions. In doing so we expected to find across the data themes mainly related to the clinical questions. The deductive qualitative analysis was linked to the pre-formed questions and themes derived from the literature and consensus, and was not aimed to produce an interpretative model. The two moderators analyzed the transcripts independently; then, analyses produced by each moderator were compared, and a consensus report was produced. In Italy the report was submitted to meeting participants for review (respondent validation). The FGM reports were then translated into English, and a joint report produced.

References

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ACKNOWLEDGEMENTS, FUNDING, AND CONFLICT OF INTEREST

Acknowledgements

This is a joint initiative of the EAN, the European Association for Palliative Care (EAPC), the European Network for Best Practice and Research in MS Rehabilitation (RIMS), and has been endorsed by the European Committee for Treatment and Research in MS (ECTRIMS), and by the MS International Federation (MSIF). We are indebted to the persons with MS, the caregivers, and the health professionals who provided their valuable input. We also thank the Bulgarian Movement Disorders and MS Society, the Bulgarian MS Patient Association, the Danish MS Society, the Dutch MS Society, the German MS Society, the Israel MS Society, the Italian MS Society, the Serbian MS Society, the Spanish MS Society, and the UK MS Society.

Funding

The guideline was funded by the EAN, and by the Foundation of the Italian MS Society (FISM grant nr. 2017/S/2). Travel expenses (two people participating to a task force meeting) were covered by the RIMS.

Conflict of interest

Dr. Drulovic serves on scientific advisory boards for Bayer Schering Pharma, Merck Serono, TEVA, Sanofi Genzyme and received speaker honoraria from Merck Serono, Teva, Bayer Schering, Sanofi Genzyme, Medis; and has also received research grant support from the Ministry of Education and Science, Republic of Serbia (project no. 175031). She is the principal investigator in clinical trials for Merck Serono, Teva, Biogen Idec, Roche, Sanofi Genzyme, Celgene, outside the submitted work. Dr. Pekmezovic received speaker honoraria from Teva, Roche, Medis, Gedeon Richter; and has also received research grant support from the Ministry of Education, Science and Technological Development of the Republic of Serbia (projects no. 175087 and 175090), outside the submitted work. Dr. Voltz reports personal fees from Prostrakan, Pfizer, MSD Sharp&Dome, AOK, grants from TEVA/EffenDys, Otsuka, DMSG/Hertie Stiftung, outside the submitted work. Dr. Solari reports grants from Italian MS Foundation (FISM), European Academy of Neurology, during the conduct of the study; she serves as board member for Merck Serono, Novartis; she received personal fees from Almirall, Excemed, Genzyme, Merck Serono, Teva, outside the submitted work. All the other authors have nothing to declare.

Table S1. Consolidated Criteria for Reporting Qualitative Studies (COREQ) checklist. Items 30-32 were not completed as they do not imply the provision of information but a judgment on the analysis. N.R. = not reported; N.A. = not applicable.

Topic	**Description/Paper quotation**	**Section where reported in paper**
Domain 1: Research team and reflexivity		
Personal characteristics		
1. Interviewer/facilitator	'Each FGM had […] two moderators (SV and AS in Italy, SK, ACR, and BBR in Germany). One moderator (facilitator) engaged participants, promoted exchange, modulated conflicts, ensuring the topics were adequately covered and allowing sufficient time for exploration of pertinent issues arising. The co-moderator helped the moderator, took notes, oversaw the audio recording and otherwise assisted as necessary.'	Appendix
2. Credentials	MD (SV, BBR, AS), PhD in health sciences (SK), MSc (ACR)	N.R.
3. Occupation	SV was head of Research Unit at the Palliative Care Department, Fondazione FARO, Turin; AS was head of the Neuroepidemiology Service, Foundation IRCCS Istituto Neurologico C. Besta, Milan; Italy. SK was head of the Nursing Research Unit, Institute of Social Medicine and Epidemiology, University of Lübeck, Lübeck; ACR was research fellow at the Institute of Neuroimmunology and Multiple Sclerosis, University Medical Center Hamburg-Eppendorf; BBR was staff neurologist and palliative physician at the Marianne-Strauß-Klinik, Berg; Germany.	N.R.
4. Gender	Two moderators were men (SV, SK), and three were women (AS, ACR, BBR).	N.R.
5. Experience & training	AS, SV, SK, ACR were experienced in qualitative research. BBR was trained by SK for the purpose of this study.	N.R.
Relationship with participants		
6. Relationship established	Patient FGMs: AS was the treating neurologist of one patient, and BBR of 11 patients. Caregiver FGMs: SV had been the referring palliative physician of one patient. BBR was the treating neurologist of 5 patients whose caregivers participated in the FGM. The other moderators did not have any relationship with participants before the FGM.	N.R.
7. Participant knowledge of the interviewer	See description of item 6 above.	-
8. Interviewer characteristics	SK, SV, ACR were part of the EAN Guideline Task Force. ACR and BBR were part of the Patient Consultation Panel of the Task Force. These characteristics and reasons for doing the research were communicated to the participants of the FGM prior to the survey.	N.R.

Domain 2: Study design		
Theoretical framework		
9. Methodological orientation & Theory	'Each FGM transcript was analyzed by moderators using thematic analysis (deductive approach) .'	Appendix
Participant selection		
10. Sampling	We used a purposive approach to select participants: 'We addressed the guideline questions using a qualitative	Appendix

	approach, inviting severely affected MS patients and caregivers who were interested in palliative care to participate in FGMs. The caregiver FGMs also included caregivers of MS patients who had died in the preceding 1-5 years. The FGMs were held in Italy (Foundation C. Besta, Milan) and Germany (University Medical Center, Hamburg; Marianne-Strauß-Klinik, Berg) in parallel to the online survey. In Milan and Hamburg participants were MS outpatients, and patients' relatives; in Berg they were MS inpatients, residents of the clinic nursing home and patients' caregivers.'	
11. Method of approach	Eligible participants were first identified by the centre physician, who informed them of study aims and procedures face-to-face or by telephone, and asked them to provide informed consent to participate in the FGM. Consenting participants were then contacted by the FGM moderator or by a research assistant, who further detailed the FGM procedure, and checked participant's availability on the scheduled date/time. Before the FGM, each participant signed in the informed consent.	N.R.
12. Sample size	'Four FGMs were planned, two of severely affected MS patients, and two of caregivers. Each FGM had 5 to 10 participants with two moderators.'	Appendix
13. Non-participation	Of 29 patients contacted 4 refused to participate for the following reasons: difficulty in coming to the center (n=2), uneasy about sharing their personal views (n=2). Of 16 caregivers contacted 6 refused to participate for the following reasons: unavailable on the scheduled date (n=2), uneasy about sharing their personal views (n=2), caregiving duties (n=1), would have participated but only if together with a relative (n=1).	N.R.
Setting		
14. Setting of data collection	'The FGMs were held in parallel to the online survey in clinical settings in Milan (Foundation C. Besta) and Berg (Marianne-Strauß-Klinik). In Hamburg they took place in a local patient self-help organization. In Milan and Hamburg participants were MS outpatients, and patients' relatives; in Berg they were MS inpatients, residents of the clinic nursing home and patients' relatives.'	Appendix
15. Presence of non-participants	In the Milan FGM of patients one research assistant was present in the meeting room at disposal of the disabled patients who needed help (e.g. in drinking, changing position). No additional participants were present in the German FGMs.	N.R.
16. Description of sample	'Patient FGMs […] The median age of the patients was 54 years (range 53–75), 19 (76%) were women, and the median EDSS was 8.0 (range 6.0–9.5). Caregiver FGMs […] 'their median age was 56 years (range 44–86), six (60%) were women; they were the spouse (n=5), widow (n=2) or widower (n=1) of MS patients who died in the previous year, mother (n=1), and daughter (n=1)'.	Results
Data collection		
17. Interview guide	'[…] the FGM guides (produced by SK and revised by SV and AS) are reported in Table S2.'	Table S2
18. Repeat interviews	No FGM was repeated.	N.R.
19. Audio/visual recording	'The co-moderator helped the moderator, took notes, oversaw the audio recording and otherwise assisted as necessary.'	Appendix
20. Field notes	'The co-moderator helped the moderator, took notes, oversaw the	Appendix

	audio recording and otherwise assisted as necessary.'	
21. Duration	'Patient FGMs lasted 96, 105, and 110 minutes, […]'. 'Caregiver FGMs lasted 120 and 79 minutes, […]'.	Results
22. Data saturation	We did not consider the achievement of data saturation. FGMs were added to the online survey (protocol amendment) to address the importance of the guideline PICOs qualitatively, and to explore sensible themes that were not included in the survey. The number of FGMs was pre-set to 4, based on the available resources and the project timeline.	N.R.
23. Transcripts returned	'A report of this analysis was submitted to meeting participants for review (respondent validation).'	Appendix

Domain 3: Analysis and findings		
Data analysis		
24. Number of data coders	SV and AS analyzed the Italian FGMs. SK, ACR and BBR analyzed the German FGMs.	N.R.
25. Description of the coding tree	Each FGM transcript was analyzed by moderators using thematic analysis (deductive approach) [3]. The two moderators analyzed the transcripts independently; then, analyses produced by each moderator were compared, and a consensus report was produced. In Italy the report was submitted to meeting participants for review (respondent validation). The FGM reports were then translated into English, and a joint report produced.	Appendix
26. Derivation of themes	See description of item 25 above (deductive approach). The deductive analysis was linked to the pre-formed questions and themes derived from the literature and consensus, and was not aimed to produce an interpretative model.	- Discussion
27. Software	Not used.	N.R.
28. Participant checking	'After discussion of each guideline question the facilitator summarized major points arising, and asked whether all concerns had been fully aired. […] In Italy the report of this analysis was submitted to meeting participants for review (respondent validation).'	Appendix
Reporting		
29. Quotations presented	Illustrative quotations were presented in the manuscript. Quotations are identified by a short description of the participant (patient or caregiver, age, city).	Table 4
30. Data & findings consistent	–	
31. Clarity of major themes	–	
32. Clarity of minor themes	–	

Table S2. Focus group meeting guides. MS is multiple sclerosis.

Focus group meeting guide - MS patients

1. Introduction, organisational issues		
Introduction of facilitators and participants	Introduction and information on the group interview	Background, MS experience, duration, audio-recording, data protection, ethics, etc.
Short introduction to the topic	Why are we here?	*"We want to develop a guideline for the care of people with severe MS. The guideline should help patients, carers, and physicians to make good decisions on care […]"*
Longer introduction to the topic & the method	• What are clinical practice guidelines? • What is the role of clinical practice guidelines? • What has been done already? (i.e. online survey & discussions among experts) • What is a focus group and why do we consider it relevant here? • How do we define "severe MS"? What is palliative care? Is it all about dying? • At the end: Example question from the online survey; what could a recommendation look like	• Graphical presentation (guideline development & layout) • Example recommendation (from the online survey): *Topic 6: Education and training programs for family members and caregivers of patients with severe MS. Education and training programs (e.g. classes, booklets, CDs) directed to help the caregiving role of family members and caregivers of patients with severe MS* → It could look like: Training programmes are beneficial for caregivers of people with severe MS (strong recommendation) → It could also look like: Training programmes could be

		considered for caregivers of people with severe MS (weak recommendation) • short Power Point presentation / or flipchart
2. Interventions		
Introduction participants & first round	Introduction round	Name, reason to take part
Questions on interventions (list of topics)	• Introduction of topics 1-3 from the survey (5 min. discussion about inclusion in the guideline)	Introduce topics 1-3: “*Please take a look at these interventions for people with severe MS. Should each of these be included in the guideline?” “Do you see any problems/barriers/challenges?”*
	• Introduction of topics 4-6 from the survey (5 min. discussion about inclusion in the guideline)	Introduce topics 4-6: *“Now please look at these three topics. Should all of them be included in the guideline?” “Do you see any problems/barriers/challenges?”*
	• Introduction of topics 7-9 from the survey	Introduce topics 7-9: “*And finally, 3 more interventions for people with severe MS. Should each of these be included in the guideline?” Do you see any problems/barriers/challenges?”*
	• 5 min. discussion about inclusion in the guideline	
	• Missing topics	Are there any additional topics that you would include in this guideline?
3. Outcomes - caregivers		
Discussion of outcomes of interventions for caregivers	• Which outcomes are important for caregivers of people with severe MS?	Introducing list of outcomes: *“For caregivers of people with severe MS, what would be relevant outcomes to show how successful any of these interventions are?”* *“Are there any additional outcomes caregivers of people with severe MS might consider important in this context?”*

		Record additional outcomes on flipchart.
4. Outcomes - people with MS		
Short discussion on adjustments of outcomes for people with severe MS	• Which outcomes are important for people with severe MS?	*“Do you think people with severe MS would consider different outcomes to be relevant indicators of success for any of these interventions?”* In case new outcomes are mentioned: Record on flipchart (in different colour)
5. End-of-life care		
Interventions & outcomes caregiver Interventions & outcomes people with MS	• Final round especially addressing end of life care and dying.	*“We have talked a lot about interventions that could support people with MS and their carers and what results you would prefer from these interventions. We´d now like to take a final focus on topics that cover issues of dying and bereavement and are hence particularly sensitive.”* Introduce each of the following questions, step by step: *1) For patients with severe MS and their caregivers what are the benefits of a proactive, anticipation of crises approach?* *2) For patients with severe MS and their caregivers which is the best place of (palliative) care?* *3) For patients with severe MS, what are the benefits of discussing with health professionals their wish of hastening death?* After each question*: “Should this question be included in the guideline?” “Do you see any problems/barriers/challenges?”*

		"Are there any additional particularly sensitive aspects/questions to be included in this guideline?" (record on flip chart)
Feedback	Question for further feedback, concerns	*"Any open issues?"*
Questionnaire (in Germany only)	Ask participants to fill in questionnaire on baseline data and rating of relevance of outcomes	*"As a final request, we would like to ask you to fill in this anonymous questionnaire asking for a few details about yourself and for your personal rating of each outcome regarding its relevance."*
Send-off	Information that the facilitators can be contacted in the future (phone/ email) for further questions.	

Focus group meeting guide - Caregivers of MS patients

1. Introduction, organisational issues		
Introduction of facilitators and participants	Introduction and information on the group interview	Background, MS experience, duration, audio-recording, data protection, ethics, etc.
Short introduction to the topic	Why are we here?	*"We want to develop a guideline for the care of people with severe MS. The guideline should help patients, carers, and physicians to make good decisions on care."*
Longer introduction to the topic & the method	• What are clinical practice guidelines? • What has been done already? (Online survey & discussions among experts) • What is a focus group and why do we consider it relevant here? • How do we define "severe MS"? What is palliative care? Is it all about dying? • At the end: Example question from survey, what could a recommendation look like	• Graphical presentation (guideline development & layout) • Example recommendation (from online survey): *Topic 6: Education and training programs for family members and caregivers of patients with severe MS. Education and training programs (e.g. classes, booklets, CDs) directed to help the caregiving role of family members and caregivers of patients with severe MS* → It could look like: Training programmes are beneficial for caregivers of people with severe MS (strong recommendation) → It could also look like: Training programmes could be considered for caregivers of people with severe MS (weak recommendation) • Short Power Point presentation /or flipchart

2. Interventions		
Introduction participants & first round	Introduction round	Name, reason to take part, how long affected by MS, informal caregiver
Questions on interventions (list of topics)	• Introduction of topics 1-3 from the survey (5 min. discussion about inclusion in the guideline)	Introduce topics 1-3: "*Please take a look at these interventions for people with severe MS. Should each of these be included in the guideline?" "Do you see any problems/barriers/challenges?"*
	• Introduction of topics 4-6 from the survey (5 min. discussion about inclusion in the guideline)	Introduce topics 4-6 : *"Now please look at these three topics. Should all of them be included in the guideline?"* *"Do you see any problems/barriers/challenges?"*
	• Introduction of topics 7-9 from the survey • 5 min. discussion about inclusion in the guideline	Introduce topics 7-9: "*And finally, 3 more interventions for people with severe MS. Should each of these be included in the guideline?" Do you see any problems/barriers/challenges?"*
	• Missing topics	Are there any additional topics that you would include in this guideline?
3. Outcomes – people with MS		
Discussion of outcomes of interventions for people with MS	• Which outcomes are important for people with severe MS?	Introducing list of outcomes: *"For people with severe MS, what would be relevant outcomes to show how successful any of these interventions are?"* *"Are there any additional outcomes people with severe MS might consider important in this context?"* Record additional outcomes on flipchart.
4. Outcomes caregivers		
Short discussion on adjustments of outcomes for caregivers of people with	• Which outcomes are important for caregivers of	*"Do you think caregivers of people with severe MS would consider different outcomes to*

severe MS	people with severe MS?	*be relevant indicators of success for any of these interventions?"* In case new outcomes are mentioned: Record on flipchart (in different colour)
5. End-of-life care		
Interventions & outcomes – people with MS Interventions & outcomes - caregiver	• Final round especially addressing end of life care and dying.	*"We have talked a lot about interventions that could support people with MS and their carers and what results you would prefer from these interventions. We´d now like to take a final focus on topics that cover issues of dying and bereavement and are hence particularly sensitive."* Introduce each of the following questions, step by step: *4) For patients with severe MS and their caregivers what are the benefits of a proactive, anticipation of crises approach?* *5) For patients with severe MS and their caregivers which is the best place of (palliative) care?* *6) For patients with severe MS, what are the benefits of discussing with health professionals their wish of hastening death?* After each question: *"Should this question be included in the guideline?" "Do you see any problems/barriers/challenges?"* *"Are there any additional particularly sensitive aspects/questions to be included in this guideline?"* (record on flip chart)

Feedback	Question for further feedback, concerns	*"Any open issues?"*
Questionnaire (in Germany only)	Ask participants to fill in questionnaire on baseline data and rating of relevance of outcomes	*"As a final request, we would like to ask you to fill in this anonymous questionnaire asking for a few details about yourself and for your personal rating of each outcome regarding its relevance."*
Send-off	Information that the facilitators can be contacted in the future (phone/ email) for further questions.	

Table S3. The nine items ('topics') of the online survey (left column) are listed in the survey order. The 14 items ('questions') of the first version are reported in the right column, for comparison. Items 10-14 correspond to the removed items. MS is multiple sclerosis.

Item no.	**Second (final) version**	**First version**
1	*Topic 1:* Symptomatic treatments for patients with severe MS. A symptomatic treatment is any treatment (medicinal product, complementary and alternative medicine) that eases the MS symptoms (for example pain, fatigue, spasticity) without addressing the basic cause of the disease.	*Question 13:* For patients with severe MS what are the benefits of symptomatic treatments? *Who:* Patients with progressive MS and complex needs. *What:* Any treatment (medicinal products, complementary and alternative medicines) that eases the MS symptoms (e.g. pain, fatigue, spasticity) without addressing the basic cause of the disease.
2	*Topic 2:* Multidisciplinary rehabilitation for patients with severe MS. Multidisciplinary rehabilitation is a coordinated intervention, in two or more disciplines (for example physiotherapy, orthotics, psychology, urology, sexology). The goal of multidisciplinary rehabilitation is to reduce patient symptoms, improve functional independence and social participation.	*Question 2:* For patients with severe MS what are the benefits of multidisciplinary rehabilitation? *Who:* Patients with progressive MS and complex needs. *What:* Coordinated intervention, delivered by two or more disciplines (e.g. nursing, physiotherapy, occupational therapy, speech therapy, orthotics, dietetics, social work, psychology, neuropsychology, urology, sexology) in conjunction with physician consultation (neurologist or rehabilitation medicine physician), which aims to limit patient symptoms, and enhance functional independence and maximize participation.
3	*Topic 3:* Timely engagement in advance care planning for patients with severe MS. In advance care planning the patient and his/her physician establish future goals of care in the end-of-life phase, based on shared discussion and on the patient values and preferences. Advance care planning can lead to an advance directive, which is a written statement about a person's preferences regarding future medical decisions.	*Question 3:* For patients with progressive MS what are the benefits of early engagement in advance directives / advance care planning? *Who:* Patients with progressive MS. *What:* Advance directives, advance care planning, and end of life choices are individually tailored processes of discussion between a patient and his or her healthcare provider regarding concerns, goals, preferences, prognosis and future care,

		activated when the patient is in a relatively stable disease phase.
4	*Topic 4:* Palliative care for patients with severe MS. Palliative care is a way of caring that includes the consideration of all aspects of a person – his/her physical, emotional, social and spiritual needs. This is a comprehensive approach to care for anyone who has a serious illness and has increasing needs. Palliative care is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life.	*Question 1:* For patients with severe MS what are the benefits of palliative care? *Who:* Patients with progressive MS and complex needs. *What:* Palliative care is a comprehensive approach to care for anyone who has a serious illness and has increasing needs. It represents a way of caring that includes the consideration of all aspects of a person – his/her physical, emotional, social and spiritual needs.
5	*Topic 5:* Specialist palliative care (hospice care) for patients with severe MS in unstable, deteriorating or dying phase of the disease. Specialist palliative care (hospice care) is a specific model of (palliative) care for patients affected by progressive relentless diseases. It is usually provided in hospice or at home, but can be offered in other settings (e.g. in hospital or care homes). It is aimed at reducing suffering, improving quality of life and enable planning for the end of life. It can also provide support and education to carers, reducing long term issues in bereavement.	*Question 7:* For patients with severe MS what are the benefits of specialist palliative care (hospice care) in unstable, deteriorating or dying phase of the disease? *Who:* Patients with progressive MS in unstable, deteriorating or dying phase. *What:* Specialist palliative care (hospice care) is a specific model of multidisciplinary care aimed at providing help in different settings (mainly at home or in hospice, but can be offered in hospital or care homes) to patients affected by progressive relentless diseases. It is aimed at reducing suffering, improving residual quality of life and planning the end of life. It can also provide support and education to carers, preventing pathological bereavement.
6	*Topic 6:* Education and training programs for family members and caregivers of patients with severe MS. Education and training programs (e.g. classes, booklets, compact disks) directed to help the caregiving role of family members and caregivers of patients with severe MS.	*Question 4:* For caregivers of patients with severe MS what are the benefits of education and training interventions? *Who:* Caregivers (informal, such as family and friends or formal, such as paid helpers) of patients with progressive MS and complex needs. *What:* Education and training programs (e.g. classes, booklets, CDs) to help the caregiving role.
7	Topic 7: Practical and emotional support to	*Question 5:* For caregivers of patients with

	family members and caregivers of patients with severe MS. The provision of practical support (e.g. advice, help with daily living needs/housework, respite care) and emotional support (e.g. counseling, support groups) to family members and caregivers of patients with severe MS.	severe MS does the provision of support provide benefits for them? *Who:* Caregivers (informal, such as family and friends or formal, such as paid helpers) of patients with progressive MS and complex needs, including caregivers of recently deceased MS patients. *What:* Practical and emotional support, included bereavement support.
8	*Topic 8:* Education and training in palliative care for MS health providers, such as neurologists, physiatrists, nurses, psychologists.	*Question 9:* For MS health professionals what are the benefits of training and education in palliative care? *Who:* MS health professionals (e.g. neurologists, physiatrists, nurses, psychologists, therapists). *What:* Training and education programs in palliative care.
9	*Topic 9:* Education and training in MS care for palliative care health providers, such as palliative care physicians, nurses, psychologists.	*Question 10:* For palliative care health professionals what are the benefits of training and education in MS care? *Who:* Palliative care health professionals (e.g. palliative care physicians, nurses, psychologists). *What:* Training and education programs in MS care.
10		*Question 6:* For patients with severe MS should palliative care be considered early in the disease trajectory? *Who:* Patients with progressive MS and complex needs. *What:* Palliative care is a way of caring that includes the consideration of all aspects of a person – his/her physical, emotional, social and spiritual needs. This is a comprehensive approach to care for anyone who has a serious illness and has increasing needs.
11		*Question 8:* For patients with severe MS and their caregivers does the setting of goals of treatment lead to benefit?

		Who: Patients and caregivers (informal, such as family and friends or formal, such as paid helpers) of patients with progressive MS and complex needs. *What:* Goal setting, sometimes referred to as goal planning, is the formal process whereby a health professional or team together with the patient and/or his family negotiate goals that are patient-specific, relevant, achievable and realistic.
12		*Question 11:* For patients with severe MS and their caregivers what are the benefits of a proactive, anticipation of crises approach? *Who:* Patients with progressive MS and complex needs, and their caregivers (informal, such as family and friends or formal, such as paid helpers). *What:* A proactive, anticipation of crises care approach, like the "Just in case kit" – a box containing easy to use and clearly explained prescriptions and drugs for controlling shortness of breath episodes. This approach can be used for other symptoms or episodes occurring at patient home, helping to avoid hospitalization.
13		*Question 12:* For patients with severe MS and their caregivers which is the best place of (palliative) care? *Who:* Patients with progressive MS and complex needs, and their caregivers (informal, such as family and friends or formal, such as paid helpers). *What:* Palliative care delivered at home, on an outpatient basis, respite care, special housing, or hospice admission.
14		*Question 14.* For patients with severe MS, what are the benefits of discussing with health professionals their wish of hastening death? *Who:* Patients with progressive MS and complex needs. *What:* Open discussion of the wish to

	hasten death, a reaction to a suffering which can occur in patients with life-threatening conditions.

Table S4. The 10 clinical questions formulated by the task force after completion of the consultation, each detailed in terms of population, intervention, comparator, outcomes, and setting. Outcomes reported in bold are those identified by patients and caregivers.
ADL is activity of daily living; CCT is controlled clinical trial; EDSS is expanded disability status scale; MS is multiple sclerosis; QOL is quality of life; RCT is randomized controlled trial.

1. For patients with severe MS what are the effects of symptomatic treatments on patient outcomes, caregiver outcomes, and costs?	
Population	Patients with primary or secondary progressive MS and complex needs, EDSS > 6.0, and specific disabling symptoms (as e.g. fatigue, pain, incontinence, spasticity)
Intervention	Any symptomatic treatment targeting one or more of the specified disabling symptoms
Comparator	Usual/standard care, placebo, other symptomatic treatment option
Outcomes (max 7)	**1. Symptom burden** **2. ADL/participation** **3. QOL** 4. Unplanned hospitalizations/hospital deaths 5. Costs **6. Caregiver burden** 7. **Caregiver QOL**
Setting	Any (e.g. home, hospital, care home, hospice)
Exclusion	1. Pediatric MS population 2. Mixed patient population with MS patients < 50%, or MS data not available 3. Severe MS patients (see ‘population’ above) < 50%, or data not available 4. Published before database inception or after December 2017 5. Language other than English, Spanish, Danish, German, Dutch, Italian, Bulgarian, Serbian, Hebrew
Study type	Systematic reviews RCTs CCTs

2. For patients with severe MS what are the effects of multidisciplinary rehabilitation on patient outcomes, caregiver outcomes, and costs?	
Population	Patients with primary or secondary progressive MS and complex needs, EDSS > 6.0
Intervention	”A coordinated intervention, delivered by two or more disciplines in conjunction with physician consultation (neurologist or rehabilitation medicine physician), which aims to limit patient symptoms, and enhance functional independence and maximise participation. The multiple disciplines include nursing, physiotherapy, occupational therapy, speech therapy, orthotics, dietetics, social work, psychology or neuropsychology” [Khan F, et al. Multidisciplinary rehabilitation for adults with multiple sclerosis. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD006036]
Comparator	Usual/standard care, other form of rehabilitation, other pharmacological or non-pharmacological intervention (e.g. education, training)
Outcomes (max 7)	**1. Symptom burden** **2. ADL** **3. Participation** **4. QOL** **5. Costs** **6. Caregiver burden** 7. **Caregiver QOL**
Setting	In-patient, out-patient, home-based, community-based
Exclusion	1. Pediatric MS population 2. Mixed patient population with MS patients < 50%, or MS data not available 3. Severe MS patients (see ‘population’ above) < 50%, or data not available 4. Published before database inception or after December 2017 5. Language other than English, Spanish, Danish, German, Dutch, Italian, Bulgarian, Serbian, Hebrew
Study type	Systematic reviews RCTs CCTs

3. For patients with severe MS what are the effects of advance care planning on patient outcomes, caregiver outcomes, and costs?	
Population	Patients with primary or secondary progressive MS and complex needs, EDSS > 6.0, or patient-caregiver dyads
Intervention	Advance care planning (ACP) is any process that enables individuals to identify their values, reflect upon the meanings and consequences of serious illness scenarios, define goals and preferences for future medical treatment and care, and discuss these with family and health-care providers. ACP addresses individuals' concerns across the physical, psychological, social, and spiritual domains. It encourages individuals to identify a personal representative and to record and regularly review any preferences, so that their preferences can be taken into account should they, at some point, be unable to make their own decisions [e.g. Rietjens JAC, et al. Definition and recommendations for ACP: an international consensus supported by the EAPC. Lancet Oncol 2017; 18: e543–51]
Comparator	Usual/standard care
Outcomes (max 7)	**1. Patient QOL** **2. Unwanted hospitalizations/treatments**, hospital deaths **3. Completion of advance directive/living will** **4. Consistency of care with patient goals and preferences (respect of end of life choices)** **5. Caregiver burden** **6. Caregiver QOL and mood** 7. Costs
Setting	Any (in-patient, out-patient, home, care home, hospice)
Exclusion	1. Pediatric MS population 2. Mixed patient population with MS patients < 50%, or MS data not available 3. Severe MS patients (see 'population' above) < 50%, or data not available 4. Published before database inception or after December 2017 5. Language other than English, Spanish, Danish, German, Dutch, Italian, Bulgarian, Serbian, Hebrew
Study type	Systematic reviews RCTs CCTs Observational studies Qualitative studies

4. For patients with severe MS what are the effects of general palliative care on patient outcomes, caregiver outcomes, and costs?	
Population	Patients with primary or secondary progressive MS and complex needs, EDSS > 6.0, or patient-caregiver dyads
Intervention	General palliative care is provided by primary care professionals and specialists treating patients with life-threatening diseases who have good basic palliative care skills and knowledge. Professionals who are involved more frequently in palliative care, such as oncologists or geriatric specialists, but do not provide palliative care as the main focus of their work, still may have acquired special education and training in palliative care and may provide additional expertise. [Radbruch L, Payne S and the Board of Directors of the EAPC. White Paper on standards and norms for hospice and palliative care in Europe: part 1. European Journal of Palliative Care 2009; 16(6):278-289]
Comparator	Usual/standard care
Outcomes (max 7)	**1. Symptom burden** **2. QOL** **3. Unplanned hospitalizations/treatments**, hospital deaths 4. Quality of death/dying 5. Costs **6. Caregiver burden/mood symptoms/QOL** 7. Complicated bereavement
Setting	Any (e.g. home, hospital, care home, hospice)
Exclusion	1. Pediatric MS population 2. Mixed patient population with MS patients < 50%, or MS data not available 3. Severe MS patients (see 'population' above) < 50%, or data not available 4. Published before database inception or after December 2017 5. Language other than English, Spanish, Danish, German, Dutch, Italian, Bulgarian, Serbian, Hebrew
Study type	Systematic reviews RCTs CCTs Observational studies Qualitative studies

5. For patients with severe MS what are the effects of specialist palliative care on patient outcomes, caregiver outcomes, and costs?

Population	Patients with primary or secondary progressive MS and complex needs, EDSS > 6.0, or patient-caregiver dyads
Intervention	Specialist palliative care describes services whose main activity is the provision of palliative care […] Specialist palliative care services require a team approach, combining a multiprofessional team with an interdisciplinary mode of work. Team members must be highly qualified and should have their main focus of work in palliative care. [Radbruch L, Payne S and the Board of Directors of the EAPC. White Paper on standards and norms for hospice and palliative care in Europe: part 1. European Journal of Palliative Care 2009; 16(6):278-289]
Comparator	Usual/standard care, non-specialist palliative care
Outcomes (max 7)	**1. Symptom burden** **2. QOL** 3. **Unplanned hospitalizations/treatments**, hospital deaths 4. Quality of death/dying 5. Costs **6. Caregiver burden/mood symptoms/QOL** 7. Complicated bereavement
Setting	Any (e.g. home, hospital, care home, hospice)
Exclusion	1. Pediatric MS population 2. Mixed patient population with MS patients < 50%, or MS data not available 3. Severe MS patients (see 'population' above) < 50%, or data not available 4. Published before database inception or after December 2017 5. Language other than English, Spanish, Danish, German, Dutch, Italian, Bulgarian, Serbian, Hebrew
Study type	Systematic reviews RCTs CCTs Observational studies Qualitative studies

6. For caregivers of patients with severe MS what are the effects of education and training programs on patient outcomes, caregiver outcomes, and costs?	
Population	Primary caregivers (informal or formal) of patients with primary or secondary progressive MS and complex needs, EDSS > 6.0
Intervention	Structured education and training program on caregiving in general and specifically for a person with MS (classes, web-based, booklet, etc.)
Comparator	No education/training, low intensity program (e.g. information leaflet), usual care
Outcomes (max 7)	**1. Caregiver burden** **2. Caregiver QOL** 3. Bereavement issues / complicated bereavement **4. MS patient symptom burden** **5. MS patient ADL/participation/QOL** 6. Costs **7. Unplanned hospitalizations**
Setting	Any (home, hospital, care home, hospice)
Exclusion	1. Pediatric MS population 2. Mixed patient population with MS patients < 50%, or MS data not available 3. Severe MS patients (see 'population' above) < 50%, or data not available 4. Published before database inception or after December 2017 5. Language other than English, Spanish, Danish, German, Dutch, Italian, Bulgarian, Serbian, Hebrew
Study type	Systematic reviews RCTs CCTs Observational studies Qualitative studies

7. For caregivers of patients with severe MS what are the effects of practical and emotional support interventions on patient outcomes, caregiver outcomes, and costs?

Population	Primary caregivers (informal or formal) of patients with primary or secondary progressive MS and complex needs, EDSS > 6.0, including caregivers of patients deceased over the previous 6 months
Intervention	Structured, practical (e.g. advice, help with daily living needs/housework, respite care) and/or emotional support (e.g. counselling, support groups, involvement with specialist MS nurse or professional or volunteer), included bereavement support
Comparator	No support, low intensity intervention (e.g. information leaflet)
Outcomes (max 7)	**1. Caregiver burden** **2. Caregiver QOL** 3. Bereavement issues/complicated bereavement 4. MS patient symptom burden 5. MS patient ADL/participation/QOL **6. Service/care satisfaction** 7. Costs
Setting	Any (home, hospital, care home, hospice)
Exclusion	1. Pediatric MS population 2. Mixed patient population with MS patients < 50%, or MS data not available 3. Severe MS patients (see 'population' above) < 50%, or data not available 4. Published before database inception or after December 2017 5. Language other than English, Spanish, Danish, German, Dutch, Italian, Bulgarian, Serbian, Hebrew
Study type	Systematic reviews RCTs CCTs Observational studies Qualitative studies

8. For MS health professionals what are the effects of education and training in palliative care on professional outcomes, patient outcomes, caregiver outcomes, and costs?	
Population	Health professionals (e.g. physicians, nurses, psychologists, therapists) directly caring for MS patients
Intervention	Structured education and training program in palliative care (classes, web-based, booklet, etc.)
Comparator	No education/training, low intensity program (e.g. information leaflet)
Outcomes (max 7)	1. Professional skills in palliative care 2. Professional skills in shared decision-making/informed choices 3. Professional wellbeing including burnout reduction/prevention 4. MS patient QOL **5. MS patient symptom burden** 6. MS caregiver burden and QOL 7. Costs
Setting	Any
Exclusion	1. Pediatric MS population 2. Mixed patient population with MS patients < 50%, or MS data not available 3. Severe MS patients (see 'population' above) < 50%, or data not available 4. Published before database inception or after December 2017 5. Language other than English, Spanish, Danish, German, Dutch, Italian, Bulgarian, Serbian, Hebrew
Study type	Systematic reviews RCTs CCTs Observational studies Qualitative studies

9. For specialist palliative care health professionals what are the effects of education and training in MS on professional outcomes, patient outcomes, caregiver outcomes, and costs?	
Population	Specialist palliative care (hospice) health professionals (e.g. physicians, nurses, psychologists, therapists, social workers)
Intervention	Structured education and training program in MS (classes, web-based, booklet, etc.)
Comparator	No education/training, low intensity program (e.g. information leaflet)
Outcomes (max 7)	1. Professional's skills in MS care 2. Professional's skills in MS communication and shared decision making 3. Professional wellbeing including burnout reduction/prevention 4. MS patient QOL **5. MS patient symptom burden** **6. MS caregiver burden and QOL** 7. Costs
Setting	Any
Exclusion	1. Pediatric MS population 2. Mixed patient population with MS patients < 50%, or MS data not available 3. Severe MS patients (see 'population' above) < 50%, or data not available 4. Published before database inception or after December 2017 5. Language other than English, Spanish, Danish, German, Dutch, Italian, Bulgarian, Serbian, Hebrew
Study type	Systematic reviews RCTs CCTs Observational studies Qualitative studies

10. For patients with severe MS what are the effects of discussing with health professionals their wish to hasten death on patient outcomes and caregiver outcomes?	
Population	Patients with primary or secondary progressive MS and complex needs, EDSS > 6.0, or patient-caregiver dyads
Intervention	Open, structured or unstructured discussion of one or more of the following: the patient wish to hasten death; the explicit expression of a wish to die; a request for euthanasia or physician-assisted suicide.
Comparator	Usual/standard care
Outcomes (max 7)	**1. Patient QOL** **2. Patient emotional wellbeing** 3. Patient-health professional relationship **4. Satisfaction with care/services** 5. Completion of advance care planning 6. Caregiver emotional wellbeing
Setting	Any (in-patient, out-patient, home, care home, hospice)
Exclusion	1. Pediatric MS population 2. Mixed patient population with MS patients < 50%, or MS data not available 3. Severe MS patients (see ‘population’ above) < 50%, or data not available 4. Published before database inception or after December 2017 5. Language other than English, Spanish, Danish, German, Dutch, Italian, Bulgarian, Serbian, Hebrew
Study type	1. Systematic reviews 2. RCTs 3. CCTs 4. Observational studies 5. Qualitative studies