

# Patient and caregiver involvement in the formulation of guideline questions: findings from the European Academy of Neurology guideline on palliative care of people with severe multiple sclerosis

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**Background and purpose:** Patient and public involvement in clinical practice guideline development is recommended to increase guideline trustworthiness and relevance. The aim was to engage multiple sclerosis (MS) patients and caregivers in the definition of the key questions to be answered in the European Academy of Neurology guideline on palliative care of people with severe MS.

**Methods:** A mixed methods approach was used: an 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 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 analysed: 751 (80%) were MS patients (74% women, mean age 46.1) and 183 (20%) were 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 focus group meetings (three of MS patients, two of caregivers, and overall 35 participants) corroborated the survey findings. In addition, they allowed an explanation of the guideline production process and the exploration of patient-important outcomes and of taxing issues.

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

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## 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), sensitive to their values and preferences. Consequently, professional societies and other guideline producers have recognized the need to involve consumers in all 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, the results of this process and the main challenges encountered are described.

## 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 Appendix S1. For the FGMs, the consolidated criteria for reporting qualitative studies (COREQ) checklist is reported in Table S1 and guides are reported in Table S2.

## Results

### Expert survey

The expert survey took place in April 2017 (Fig. 1): 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 and the 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.

Based on a 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).

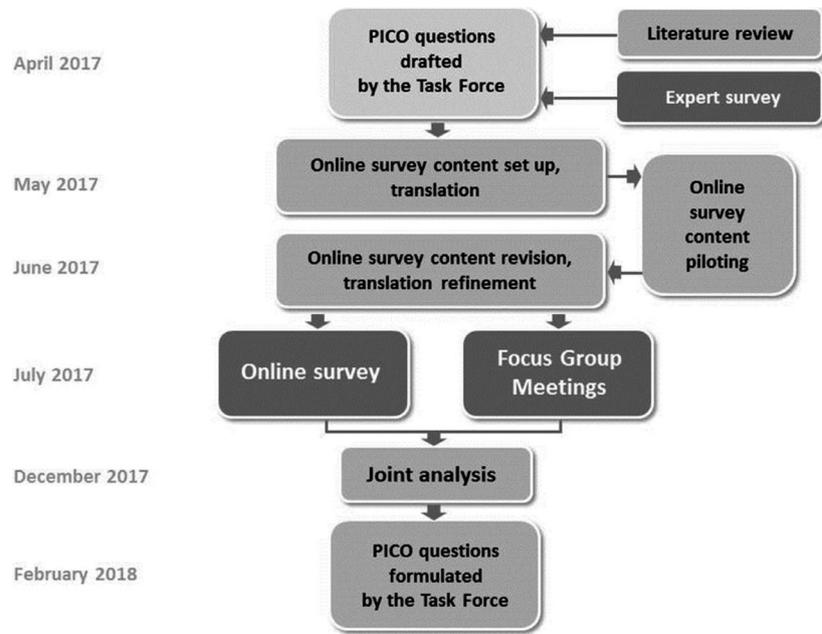
### Piloting of the international online survey

The first version of the survey was discussed in dedicated meetings of the Danish MS society (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 and the 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 to be 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).

The analysis was performed on 934 participants from seven countries who provided information on their status (MS patient or caregiver) (Tables 2 and 3). 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



**Figure 1** 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

Country	Inhabitants [12]	MS patients [13]	Prevalence [13]	Accessed the survey	Consented no. (%)	Completed no. (%)		
						Overall	Patients	Caregivers
Germany	80 × 10 <sup>6</sup>	130.000	149/10 <sup>5</sup>	227	189 (83%)	136 (72%)	118 (87%)	18 (13%)
UK	63 × 10 <sup>6</sup>	100.000	164/10 <sup>5</sup>	32	17 (53%)	17 (100%)	13 (76%)	4 (24%)
Italy	59 × 10 <sup>6</sup>	68.000	113/10 <sup>5</sup>	488	443 (91%)	388 (87%)	334 (86%)	54 (14%)
Spain	47 × 10 <sup>6</sup>	42.900	102/10 <sup>5</sup>	178	144 (81%)	98 (68%)	68 (70%)	30 (30%)
Netherlands	17 × 10 <sup>6</sup>	14.300	88/10 <sup>5</sup>	75	60 (80%)	43 (72%)	28 (65%)	15 (35%)
Bulgaria	7 × 10 <sup>6</sup>	4.250	39/10 <sup>5</sup>	145	124 (86%)	92 (75%)	77 (84%)	15 (16%)
Serbia	7 × 10 <sup>6</sup>	–	–	58	53 (91%)	53 (100%)	22 (41%)	31 (59%)
Denmark	6 × 10 <sup>6</sup>	12.800	227/10 <sup>5</sup>	179	169 (95%)	124 (73%)	104 (84%)	20 (16%)
Totals	–	–	–	1382	1199 (87%)	951 (79%)	764 (80%)	187 (20%)

MS, multiple sclerosis.

23% had been diagnosed within the last 5 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) min in patients and 8 (6–11) min in caregivers ( $P = 0.07$ ).

Participants replying ‘I prefer not to answer’ were consistently few amongst MS patients and caregivers; highest values were found for ‘advance care planning’ (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 ‘advance care planning’ (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

**Table 2** Characteristics of the eight countries that participated in the online survey and survey participation: patients

Characteristic (patients)	Germany ( <i>n</i> = 118)	Italy ( <i>n</i> = 334)	Spain ( <i>n</i> = 68)	Netherlands ( <i>n</i> = 28)	Bulgaria ( <i>n</i> = 77)	Serbia ( <i>n</i> = 22)	Denmark ( <i>n</i> = 104)	Totals ( <i>n</i> = 751)
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%)

Values are given as number (%). The UK was excluded from the analysis as participation was sub-threshold [13].

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 4 reports the distribution of comments across the four domains by country; details on domain contents are reported in the footnotes.

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; and ‘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 4).

Of 934 participants, 120 (13%) commented on the survey or on the guideline project. Of these, 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 min; two had seven participants and one had 11 participants (total *n* = 25). The median age of the patients was 54 years (range 53–75); 19 (76%) were women, and the median Expanded Disability Status Scale was 8.0 (range 6.0–9.5). Caregiver FGMs lasted 120 and 79 min, 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

**Table 3** Characteristics of the eight countries that participated in the online survey [8,15] and survey participation: caregivers

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)
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%)

Values are given as number (%). The UK was excluded from the analysis as participation was sub-threshold [13].

**Table 4** Comments of multiple sclerosis (MS) patients and caregivers categorized into four domains, overall and by country

Country	Pre-specified topics <sup>a</sup> No. (%)	New topics, guideline-pertinent <sup>b</sup>	New topics, non-pertinent <sup>c</sup>	Outcomes <sup>d</sup>	Row total
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

<sup>a</sup>Symptoms management and multidisciplinary rehabilitation (topics 1 and 2), 59/182 comments (32%); 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), nine (5%); education and training in MS for palliative care professionals (topic 9), seven (4%). <sup>b</sup>Voluntary euthanasia, 15/16 comments; sheltered housing/assisted living, one comment. <sup>c</sup>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, 26%): 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%), leisure (7, 3%). <sup>d</sup>Patient participation (36/160 comments, 22%), functioning (21, 13%), symptom burden (17, 11%), emotional well-being (14, 9%), advance directive/living will (14, 9%), service coordination (10, 6%), caregiver emotional well-being (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 5** The focus group meeting themes, components and illustrative citations

Theme	Component	Citation
Palliative care	Theoretical	<p>1. <i>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.</i> [Woman with MS, Hamburg]</p> <p>2. <i>The word palliative medicine does not scare me any more, as now I know what it means. I see it as a way to receive protection, if it works as it should do ...</i> [Man with MS, Berg]</p> <p>3. <i>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 an MS patient who recently died, at age 70, Milan]</i></p>
	Experiential	<p>4. <i>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 an MS patient who recently died, at age 54, Milan]</i></p> <p>5. <i>I just experienced [home palliative service] with my mum 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 centre of care. [58-year-old MS woman, EDSS 8.5, Milan]</i></p>
End of life	Discussion about choices	<p>6. <i>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 are 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]</i></p> <p>7. <i>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.</i> [Woman with MS, Hamburg]</p> <p>8. <i>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]</i></p>
	Medically assisted suicide	<p>9. <i>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 an MS patient who recently died, at age 70, Milan]</i></p>
	Voluntary euthanasia	<p>10. <i>[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.</i> [Woman with MS, Hamburg]</p>
Requirements	Peer socialization	<p>11. <i>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 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]</i></p> <p>12. <i>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.</i> [Woman with MS, Berg]</p>
	Case management	<p>13. <i>I need someone to help me, someone just to ask to.</i> [Woman with MS, Berg]</p> <p>14. <i>I was blamed by my family doctor because I turned my anger on him on 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 an MS patient who recently died, at age 54, Milan]</i></p>

(continued)

Table 5 (Continued)

Theme	Component	Citation
Outcomes	Role preservation	15. <i>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.</i> [58-year-old MS woman, EDSS 8.5, Milan]
	Participation	16. <i>But I wanted that my son was exempted from doing the bladder catheterization [to her mom].</i> [73-year-old widower of a MS patient who recently died, at age 70, Milan] 17. <i>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 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.</i> [53-year-old MS woman, EDSS 8.0, Milan]
	Competent professionals/caregivers	18. <i>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.</i> [73-year-old widower of a MS patient who recently died, at age 70, Milan] 19. <i>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.</i> [51-year-old widow of an MS patient who recently died, at age 54, Milan]

EDSS, Expanded Disability Status Scale; MS, multiple sclerosis. Citations 1, 3–5, 7 and 10 also pertain to the theme 'outcomes' and to the following components: symptom burden (citations 1, 3, 4), quality of life (citation 4), satisfaction with care/service (citation 5), living will (citation 7) and caregiver burden (citation 10).

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 min was 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 the professionals caring for people with severe MS: physicians (including 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 5. 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), competence 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, whilst unplanned hospitalization and costs were seen as the least important.

The main outcomes and challenges of the patient and caregiver consultation are summarized in Table 6. 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.

## Discussion

Offering the best care possible to the highest number of patients and reducing variations in service

**Table 6** Purposes, outcomes and challenges of the international online survey, and focus group meetings

	Literature review/expert consultation	International online survey	Focus group meetings
Aims	<ul style="list-style-type: none"> <li>Identify topics that represent opportunities for quality improvement within the guideline scope</li> <li>Involve guideline users</li> </ul>	<ul style="list-style-type: none"> <li>Involve a geographically and clinically varied population of patients and caregivers via the national MS societies</li> <li>Anonymous, free expression of participants' views and preferences</li> </ul>	<ul style="list-style-type: none"> <li>Involve severely affected MS patients, and caregivers of such patients</li> <li>Involve caregivers of recently deceased patients</li> <li>Explain/discuss the process of guideline production</li> <li>Identify outcomes important to patients and caregivers</li> <li>Explore 'difficult' topics and taxing issues</li> </ul>
Outcomes	<ul style="list-style-type: none"> <li>Draw up 14 clinical questions</li> </ul>	<ul style="list-style-type: none"> <li>Over 88% of participants agreed/strongly agreed on inclusion in the guideline of each of the nine pre-specified topics</li> <li>Consistent findings between MS patients and caregivers</li> <li>Identification of 14 outcomes important to the patients and caregivers via 160 free comments</li> <li>Identification of 15 free comments on voluntary euthanasia</li> </ul>	<ul style="list-style-type: none"> <li>Patients need to discuss about end-of-life choices, medical-assisted suicide and voluntary euthanasia</li> <li>Identification of seven outcomes related to the guideline questions: symptom burden, participation, quality of life, living will, role preservation (of the patient and caregiver), caregiver burden, quality of care</li> </ul>
Challenges	<ul style="list-style-type: none"> <li>None identified</li> </ul>	<ul style="list-style-type: none"> <li>Variable participation across the countries, negligible in the UK (excluded from analysis)</li> <li>Selection of online-proficient and well-educated participants (57% of the patients and 64% of the caregivers had college or university degree)</li> <li>Time and resource consuming (survey setup, translation into the target languages, piloting, revision, conduction and analysis; Figure 1)</li> </ul>	<ul style="list-style-type: none"> <li>Performed in only two of the nine guideline task force countries</li> <li>The combination of previous and current caregivers in the same meeting was challenging</li> <li>Not all the pre-specified guideline topics could be discussed</li> <li>Not a pre-planned action (no dedicated resources)</li> </ul>

MS, multiple sclerosis.

delivery are the key issues for most healthcare systems and the main reason for producing clinical practice guidelines [14]. 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 [15–17]. Here, the experience of an international patient and caregiver involvement is reported, which was time and resource intensive and employed a mixed method. A crucial role in this process was played by the National Multiple Sclerosis Society of each participating country, and particularly by a task force member who was an MS patient and also a member of the MS International Federation, and of the Danish national MS society. 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 6).

The FGMs allowed the explanation of the process of guideline production, the identification of patient-important outcomes, and deliberation about taxing issues (Table 6). The consultation process as a whole was time and resource intensive (Fig. 1). 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 6). 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

Multiple sclerosis patients and caregivers validated the nine questions devised by our task force (with health professional 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 [3,17]. 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) [15,16,18,19].

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### Disclosure of conflict of interests

Dr Drulovic serves on scientific advisory boards for Bayer Schering Pharma, Merck Serono, TEVA, Sanofi Genzyme; 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 the 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.

### Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

**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 judgement on the analysis. N.R., not reported; N.A., not applicable.

**Table S2.** Focus group meeting guides.

**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.

**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.

**Appendix S1. Materials and methods.****References**

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