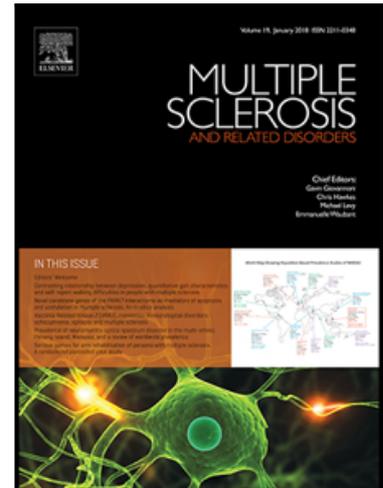


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Identifying unanswered questions and setting the agenda for future systematic research in Multiple Sclerosis. A worldwide, multi-stakeholder Priority Setting project



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Identifying unanswered questions and setting the agenda for future systematic research in Multiple Sclerosis. A worldwide, multi-stakeholder Priority Setting project

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Declarations of interest: none

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Headings:

- International stakeholders identified an evidence-based “gap-map” in MS care.
- A survey was translated into 12 languages and disseminated via MS web channels.
- Over 1000 people provided input into prioritizing topics.
- This multi stakeholder priority setting exercise offers a worldwide perspective.
- Among the five most urgent research questions is the role of MRI in predicting disease progression.

Abstract

Background

Eliciting the research priorities of people affected by a condition, carers and health care professionals can increase research value and reduce research waste. The Cochrane Multiple Sclerosis and Rare Disease of CNS Group, in collaboration with the Cochrane Neurological Sciences Field, launched a priority setting exercise with the aim of prioritizing pressing questions to ensure that future systematic reviews are as useful as possible to the people who need them, in all countries, regardless of their economic status.

Method

Sixteen high priority questions on different aspects of MS were developed by members of a multi-stakeholder priority setting Steering Group (SG). In an anonymous online survey translated into 12 languages researchers, clinicians, people with MS (PwMS) and carers were asked to identify and rank, 5 out of 16 questions as high priority and to provide an explanation for their choice. An additional free-text priority research topic suggestion was allowed.

Results

The survey was accessible through MS advocacy associations' social media and Cochrane web pages from October 20, 2020 to February 6, 2021. 1.190 responses (86.73% of all web contacts) were evaluable and included in the analysis. Responses came from 55 countries worldwide, 7 of which provided >75% of respondents and 95% of which were high and upper-middle income countries. 58.8% of respondents live in the EU, 23% in the Americas, 8.9% in the Western Pacific, 2.8% in the Eastern Mediterranean and 0.3% in South Eastern Asia. About 75% of the respondents were PwMS. The five research questions to be answered with the highest priority were: Question (Q)1 "Does MRI help predict disability worsening of PwMS?" (19.9%), Q5 "What are the benefits and harms of treating PwMS with one disease-modifying drug compared to another?" (19.3%), Q3 "Does multidisciplinary care by teams of different social and health professionals improve health outcomes and experiences for PwMS?" (11.9%), Q16 "Does psychological health affect disease progression in PwMS?" (9.2%) and Q10 "What are the benefits and harms of exercise for PwMS?" (7.2%). The multivariable logistic regression analysis indicated a significant influence of geographic area and income level on the ranking of Q1 and a marginal for Q16 as top a priority after accounting for the effect of all other predictors. Approximately 50% of the respondents indicated that they had an important additional suggestion to be considered.

Conclusion

This international collaborative initiative in the field of MS offers a worldwide perspective on the research questions perceived as pivotal by a geographically representative sample of multiple stakeholders in the field of MS. The results of the survey could guide the prioritization of research on pharmacological and non-pharmacological interventions which could be meaningful and useful for PwMS and carers, avoiding the duplication of efforts and research waste. High quality systematic reviews elicited by priority setting exercises may offer the best available evidence and inform decisions by healthcare providers and policy-makers which can be adapted to the different realities around the world.

1. Introduction

Cochrane promotes evidence-informed health decision making for clinical practice and health policy by producing high quality, relevant, accessible systematic reviews (SRs). SRs summarize the best available evidence by pooling the results of individual studies to answer specific research questions about the benefits and harms of healthcare interventions (www.cochrane.org).

The usefulness of SRs in providing better health care is optimal when clinical research is aligned with the needs, expectations and values of people affected by the condition [Liberati 2011, Crowe et al. 2015]. Research priority setting facilitates greater consistency between research and the needs of those it affects most [Bero et al. 2012, Nasser et al. 2013, Turner et al. 2020,]. Many Cochrane Review Groups adopt a systematic approach to identifying priority topics for SRs, involving the public, those affected by the condition, carers and their representatives, health care professionals, policy-makers and other health decision-makers (Chalmers et al. 2014, Tong et al. 2019).

The Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Group (MSCRG) coordinates the preparation, maintenance, and dissemination of SRs on the diagnosis, treatment and rehabilitation of people with MS (<https://ms.cochrane.org>).

An initial MSCRG international priority-setting survey was started in July 2014. PwMS, healthcare professionals and MS Societies were invited to answer a questionnaire in order to identify priority research questions. The Cochrane Priority Review List 2015/16 was developed by the “James Lind Alliance (JLA) MS Priority Setting Partnership” to ensure consistency between research topics, needs and expectations of people affected by MS and the aims of health care professionals. The results of the survey informed the identification of topics for five new SRs and for one SR to be updated (Tramacere et al. 2015, Filippini et al. 2017, Jagannath et al. 2010, Heine et al. 2015, Köpke et al. 2018, Parks et al. 2020).

In this paper, we report the preliminary results of the second MSCRG global priority-setting project.

Study aim

In 2020, we started an international priority-setting project with the aim of identifying the most relevant topics in MS healthcare evaluating research questions that should be addressed in the next 5 Cochrane SRs. We concentrated efforts to identify and prioritise interventions that could potentially reduce disparities in the care of people with MS worldwide. Therefore, we made targeted determination to recruit people from different geographic areas, health care systems, income levels and from diverse cultural backgrounds (Nasser et al. 2013, The Lancet Neurology 2021, Wijeratne et al. 2021).

2. Methods

The methods were informed by guidance from the Cochrane Priority Setting Methods Group. As recommended in the JLA process (The James Lind alliance guidebook 2016, Priority Setting Guidance Note for Cochrane Groups. September 2019), topics were identified and ranked through an anonymous, web-based questionnaire.

The project began in May 2020 with the formation of a Priority Setting Exercise Working Group (WG) including members of the MSCRG, the Cochrane Neurological Sciences Field (CNSF) and the Affiliate of Cochrane Italy Geographic Group. The WG nominated an international multi-stakeholder Steering Group (SG) including clinicians and researchers with expertise in MS, one methodologist, an information specialist, a representative of the MS International Federation (MSIF) and one PwMS. The SG defined the scope of the project, shortlisted and refined a provisional list of priority topics, advised on participant recruitment, planned and assisted with

dissemination of the survey. Each WG and SG member provided a disclosure of interest. The list of members of the WG and SG is available in **Supplementary data 1**.

2.1 Priority topics

Our aim while identifying priority topics to be included in the questionnaire was to develop a comprehensive list of relevant questions to be proposed to as wide a target audience as possible. As such, we decided to create a multidisciplinary working group representative of different perspectives.

As a first step, the WG [2 clinicians (EB and MGC), one researcher (FN), one statistician (RDA) and the director of MSGRG (GF)] identified gaps in the evidence base across different MS care pathways by assessing the “MS Diagnostic and Therapeutic Care Pathways (DTCPs)” developed by multi-stakeholder groups and implemented within the Italian National Health System (Bezzini et al., 2020) and in the UK guidance developed by the National Institute for Health and Care Excellence (<https://www.nice.org.uk/guidance/cg186>). -We also considered the recommendations on MS care by the American Academy of Neurology (Rae-Grant et al., 2018), the European Committee for Treatment and Research in Multiple Sclerosis/European Academy of Neurology (ECTRIMS/EAN) (Montalban et al., 2018), the Brazilian Consensus (Marques et al., 2018) and by the Middle-East North Africa Committee for Treatment and Research in Multiple Sclerosis (MENACTRIMS) Consensus (Yamout et al., 2020).

After appraising the existing MSCRG portfolio of SRs, 24 preliminary research questions of potential uncertainty in five core areas (diagnosis, pharmacological treatments, health communication and participation, rehabilitation and social support interventions) were identified. Each member of the WG independently ranked the priority and the relevance of each question choosing both one of three categories, “high priority”, “important but lower priority”, “not a priority”, and one of the following three areas “potentially relevant to PwMS”, “important for clinicians” and “answerable using the existing evidence by means of a SR”. After discussion, the WG agreed on a list of 12 topics.

The list was proposed for discussion to the SG and an iterative process produced 4 further structured topics. The representative of PwMS suggested two additional topics on the psychological burden of MS. All topics were transformed into questions to be included in the questionnaire, formulated according to a “Population, Intervention, Comparison and Outcome” (PICO) format. The WG and the SG reached consensus on 16 research priority questions, numbered from Q1 to Q16 (Table 1).

Table 1 – List of questions included in the questionnaire

| N° | Question Text |
|----|---|
| Q1 | Does magnetic resonance imaging (MRI) help predict disease progression in people with multiple sclerosis? |
| Q2 | Do cerebrospinal fluid (spinal tap/lumbar puncture) findings help predict disease progression in people with multiple sclerosis? |

| | |
|-----|---|
| Q3 | Does multidisciplinary care by teams of different social and health professionals improve health outcomes and experiences for people with multiple sclerosis? |
| Q4 | Is treatment with intravenous steroids more beneficial than oral steroids in people with multiple sclerosis who have relapses? |
| Q5 | What are the benefits and harms of treating people with multiple sclerosis with one disease-modifying drug* compared to another? |
| Q6 | What are the benefits and harms of medications for reducing spasticity ** in people with multiple sclerosis? |
| Q7 | What are the benefits and harms of further treatment options for people with multiple sclerosis who stop taking a highly efficacious drug? |
| Q8 | What should the therapeutic approach be for people with multiple sclerosis, being treated with disease-modifying therapies*, who are planning a pregnancy or are pregnant? |
| Q9 | What should the treatment approach be for people with multiple sclerosis being treated with disease-modifying therapies*, who test positive for the COVID-19 virus? |
| Q10 | What are the benefits and harms of exercise for people with multiple sclerosis? |
| Q11 | How can people with multiple sclerosis be supported in work and social participation? |
| Q12 | What kind of support can increase participation in treatment decision making by people with multiple sclerosis? |
| Q13 | What kind of activities can help with self-management and coping by people with multiple sclerosis? |
| Q14 | What are the benefits and harms of palliative care § for people with advanced multiple sclerosis? |
| Q15 | What are the benefits and harms of psychological care for people with multiple sclerosis? |
| Q16 | Does psychological health affect disease progression in people with multiple sclerosis? |

* Alemtuzumab, Azathioprine, Cladribine, Cyclophosphamide, Daclizumab, Dimethyl fumarate, Fingolimod, Glatiramer acetate, Immunoglobulins, Interferon beta-1a (Avonex, Rebif), Interferon beta-1b, Laquinimod, Methotrexate, Mitoxantrone, Natalizumab, Ocrelizumab, Pegylated interferon beta-1a, Rituximab, Teriflunomide.

** Aminopyridines, Baclofen, Benzodiazepines, Botulinum toxin, Cannabinoids, Gabapentin, Tizanidine

§ World Health Organisation Definition of Palliative Care: Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.

2.2 Development of the questionnaire

The questionnaire, initially developed in English, was translated into eleven languages (Albanian, Arabic, Chinese, French, German, Italian, Norwegian, Portuguese, Russian, Serbian, and Spanish) by volunteer native speakers.

The online questionnaire (**Figure 1**) was divided into four sections. **The first section** included the 16 research questions. Responders were asked to indicate their top three choices and to rank their first, second and third priority. **In the second section** participants were prompted to explain, in a free-text box, the reasons why the questions they selected were important. **In the third section**, respondents were asked if, in their opinion, there was an additional topic that they felt should be considered which was not already included among the 16 original questions listed in section 1. They were asked to rank their suggestion among their top three choices as appropriate. Finally, **in the fourth section** participants were asked to describe in a free-text form their experience of living with MS in the country where they live.

With the help of the Cochrane Informatics & Technology (IT) Services the questionnaire was published on the MSCRG website using Cochrane's Drupal platform (a free and open-source web content management framework). The homepage of the website included a presentation of Cochrane, systematic reviews, the Cochrane Library and the aim of the survey. Before accessing the questionnaire, participants had to fill-out a consent form confirming that they understood the information and consented to the use of their anonymous responses in the study. Participation to the survey was considered permission to use their data.

Comprehensiveness and technical accessibility of the online questionnaire were evaluated by the members of the SG.

2.3 Participants and recruitment

There was no quantitatively defined target population in our recruitment strategy; the WG produced an electronic leaflet with the key messages of the survey, a link to access the questionnaire and an invitation to disseminate it further. Members of the WG, SG and the MSIF promoted the survey by means of the digital leaflet and a predefined e-mail sent to international MS advocacy organisations and clinical and research community websites. PwMS disseminated the survey through their contacts using invitation emails and announcements posted on their advocacy websites and social media accounts. The invitation to participate in the survey through the electronic leaflet was also circulated to Cochrane networks.

2.4 Data analysis

Analysis was performed on the respondents' characteristics, the top ranked questions and potential determinants of the ranking.

a. Respondents' characteristics

Each participant was classified according to:

a1. "Experience of MS":

Responses to the "About You" section of the questionnaire (Figure 1), were collapsed into the following: 1. PwMS, 2. Carer and family member, 3. Care professional (in any health or social care role) and academic researcher or private sector employee or consultant researcher; 4.

Other/unspecified ("member of a support or interest group" and "other").

Responses "PwMS" and "carer and family member" were also grouped in further analysis as "lay people".

a2. “Country where participant usually lives”:

Descriptive analyses were reported by geographic area according to the six World Bank Regions, (Africa, East Asia and Pacific, Europe and Central Asia, Latin America and Caribbean, Middle East and North Africa, South Asia) (worldbank.org/en/about/annual-report/region-perspectives).

Given that the characteristics of a country’s national health service may be an important determinant of access to care, the respondents’ countries were classified by type of healthcare system: 1. Universal supported by public taxation; 2. Universal, supported by compulsory social insurance; 3. Non universal, supported by private voluntary insurance; 4. Non universal, supported by direct payment (www.europarl.europa.eu/workingpapers/saco/pdf/101_en.pdf, www.ssa.gov/policy/docs/progdesc/ssptw/, www.ssa.gov/policy/docs/progdesc/ssptw/, 16b).

Finally, the respondents’ countries of origin were stratified by income level as reported by the World Bank according to the scale of high, upper-middle, lower-middle, low income (datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groupsand, datahelpdesk.worldbank.org/knowledgebase/articles/378834-how-does-the-world-bank-classify-countries).

The distributions by the two characteristics of respondents, “Experience of MS” and “Country where participant usually lives”, were summarized by reporting the number and proportion of each possible value. The denominator for the percentage calculation was based upon the total number of respondents in the study population. The 95% Confidence Interval (CI) of proportions are reported where appropriate.

b. Identification of the top ranked questions:

The following three analyses were employed to evaluate the relevance of research questions in terms of their apparent weighting in the eyes of respondents

First we assessed the “**relevance**” of the proposed research question: the greater the number of respondents who considered the question worth ranking among the top three, the larger the audience that identifies the question as a priority.

Second, we assessed the “**size and dispersion**” of interest: the ranking respondents’ top three choices was converted from first, second and third into scores 3, 2, 1 respectively with a “zero” score associated with unchosen ranks. Scores can then be summarised as a *mean* that indicates the average interest expressed for that specific question by respondents and a *standard deviation* that indicates the dispersion of the agreement between respondents (i.e. a small standard deviation indicates that the respondents expressed approximately the same interest, whereas a large standard deviation indicates a disagreement among respondents as to the level of interest).

Finally, we assessed the “**ranking of interest**”: being the proportion of respondents that ranked the question as most relevant (i.e. the research question that should be answered first).

Given the structure of the database we considered the proportion of top ranks expressed per question based on number of expressed ranks and on total respondents.

c. Determining the respondents’ characteristics and the ranking of questions

Multivariable logistic regression analysis was used to determine whether the main respondents’ characteristics affect the ranking of the questions. World Bank geographic area, healthcare system, income level and respondents’ experience of MS were considered as potentially influencing the choice of the top significant questions at univariate analysis as a priority. Given the distribution by level, we further combined poorly represented geographic areas with their neighbouring countries

as follows South Asia with East Asia and the Pacific; Sub-Saharan Africa with Middle East and North Africa.

3. Results

The survey was accessible from October 20, 2020 to February 6, 2021.

Records were collected in an excel database. There were 1.372 web contacts, of these 1.190 (86.73%) questionnaires were correctly completed. Participants did not complete the questionnaire in twelve cases, in four cases they were mistakenly duplicated and in 166 cases were not considered valid as all the 16 questions had the same preference without any priority chosen by respondents.

3.1 Respondents' characteristics

Participants classified by the country where they usually live.

Responses came from 55 countries worldwide and were geographically dispersed (**supplementary data Table I**), with 24% from Norway alone and 22% from Brazil. Seven countries provided >75% of respondents and twelve countries provided >90% of respondents. Eight countries were represented by only two responders each, while nineteen countries were represented by one respondent each (Table 2). More than 80% of respondents live in "Europe and Central Asia" and "Latin America and the Caribbean". More than half of respondents live in high income countries and 95% in high or upper-middle income countries. Ninety percent declared having access to a universal healthcare system supported either by public taxation or compulsory social insurance (Table 3).

Table 2 - Distribution of valid respondents. Individually labelled countries represent >90% of respondents

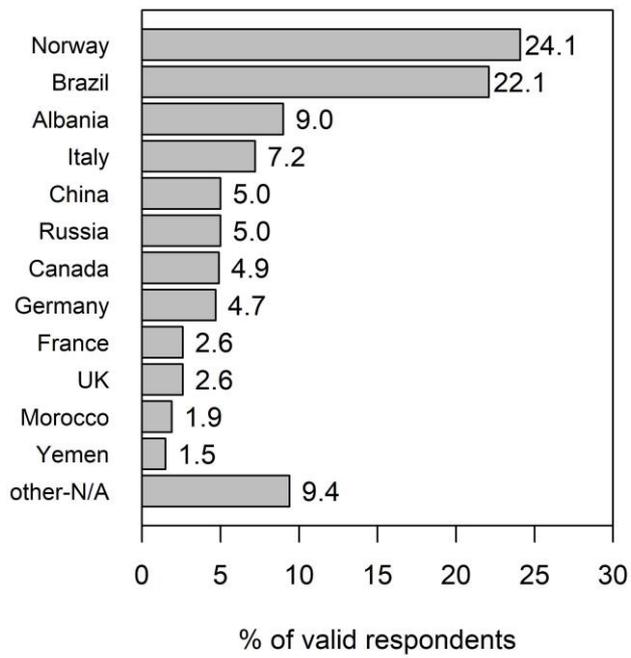
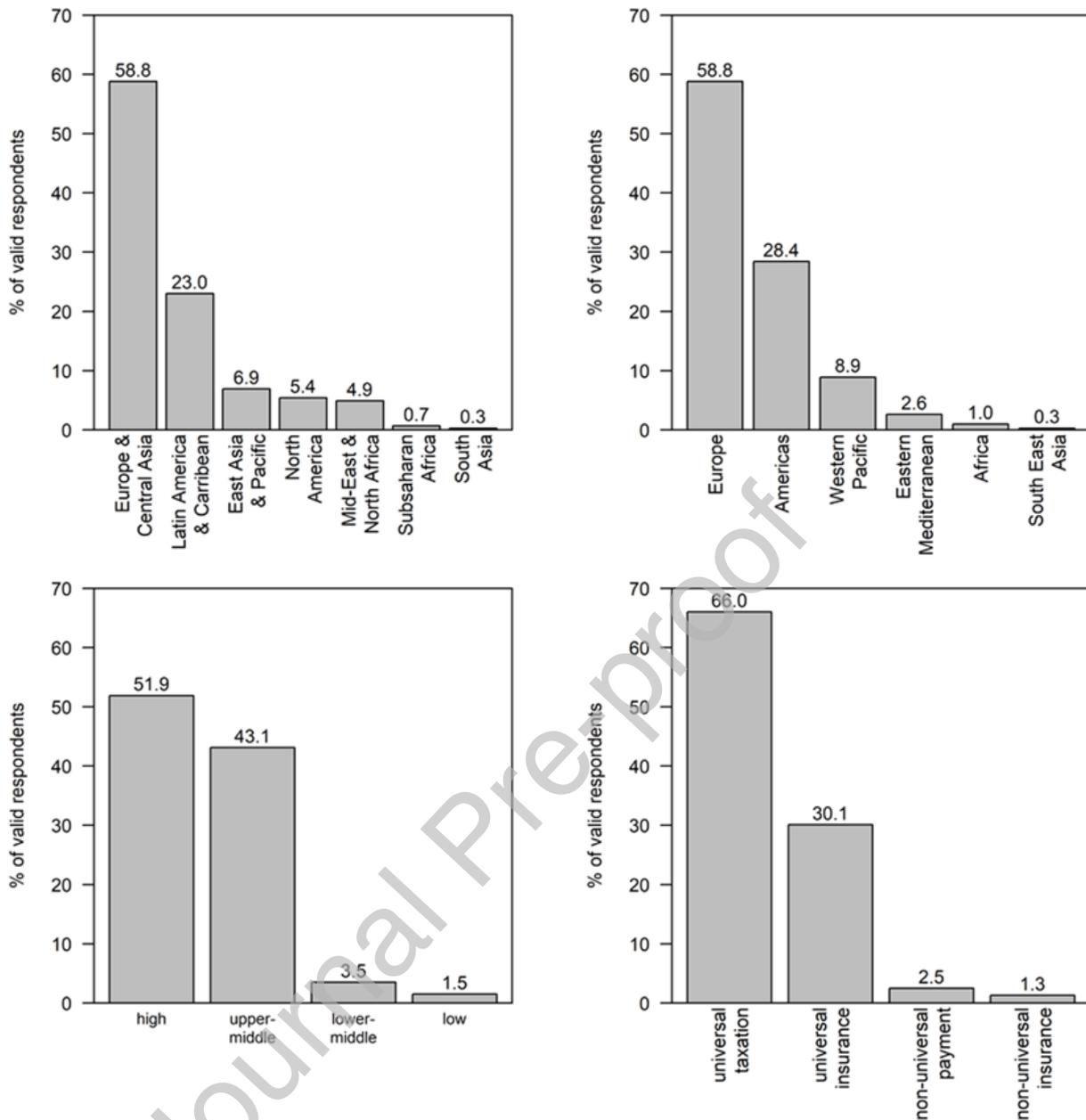


Table 3 - Distribution of valid respondents by geographic area (according to the World Bank; upper left; according to the WHO: upper right), by income (lower left) and by healthcare system lower right



Participants classified by their experience of Multiple Sclerosis

“PwMS” represented almost three-quarters of the respondents, 27 valid responses could not be classified in the pooled classification, because they were completed by both PwMS and family members/carers. One-thousand-fourteen respondents, including the 27 valid responses mentioned above, were “Lay people” and 158 were “Healthcare professionals” (Table 4).

Table 4 - Distribution of valid respondents by experience of MS

| Experience of MS* | N° | % |
|--------------------------|-----------|----------|
| people with MS | 889 | 74.7% |
| carers | 43 | 3.6% |
| family members | 129 | 10.8% |
| care professionals | 168 | 13.9% |
| academic researchers | 71 | 6.0% |
| private researchers | 19 | 1.6% |
| other/unspecified | 18 | 1.5% |
| Further Pooling** | | |
| lay people | 1014 | 86.5% |
| healthcare professionals | 158 | 13.5% |

* respondents could indicate more than one status.

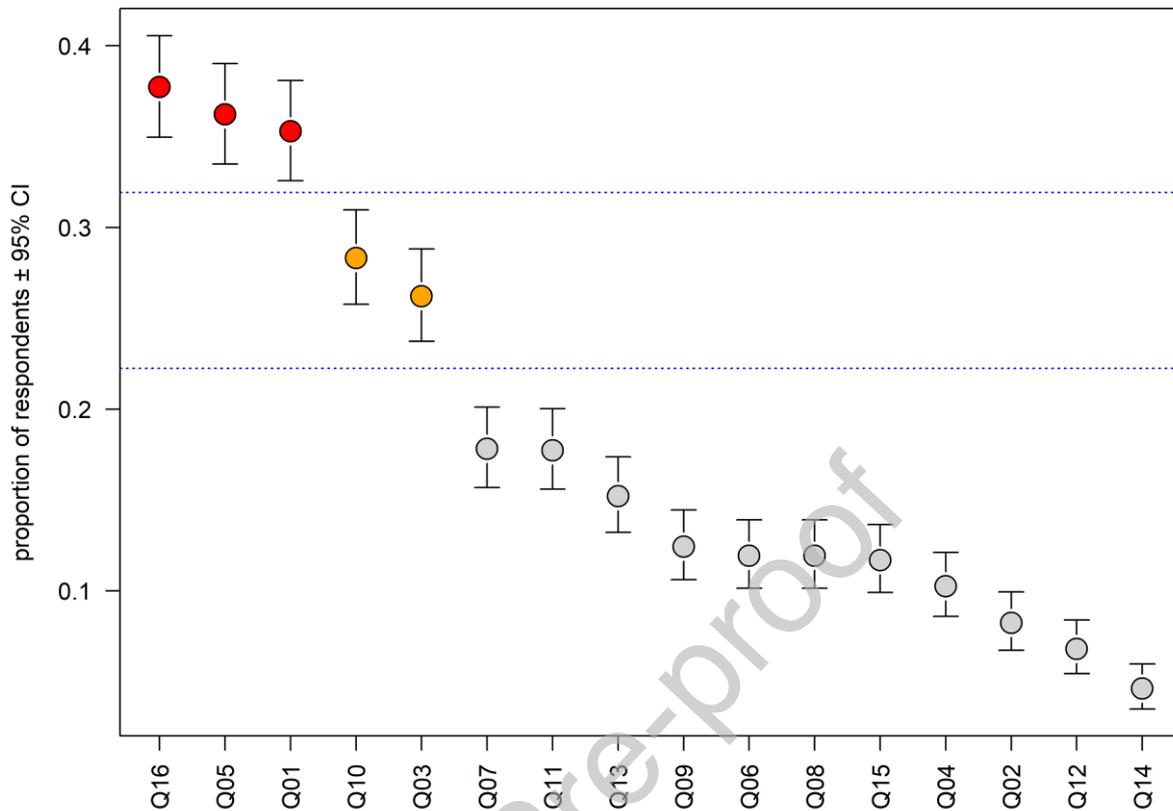
** the 27 respondents who indicated both PwMS and carer were included among lay people, while the 18 respondents identified as “other/unspecified” were excluded.

3.2 Priority answers among the proposed 16 questions

Relevance

The percentage of respondents who identified a research question as being among their top three priorities, was distributed as follows: Q16 “Does psychological health affect disease progression in PwMS?” (37.7%; 95% CI 35-40.6), Q5 “What are the benefits and harms of treating PwMS with one disease-modifying drug compared to another?” (36.2%; 95% CI 33.5%-39.0) and Q1 “Does MRI help predict disability worsening of PwMS?” (35.3%; 95% CI 32.6%–38.1%). Roughly one third of the valid preferences were for these three proposed research questions. Twenty-five percent of responders gave a preference to Q10 “What are the benefits and harms of exercise for people with multiple sclerosis?” (28.3%; 95% CI 25.8%–31.0%) and Q3 “Does multidisciplinary care by teams of different social and health professionals improve health outcomes and experiences for people with multiple sclerosis?” (26.2%; 95% CI 23.7%–28.8%) and less than 20% to the remaining questions (Table 5).

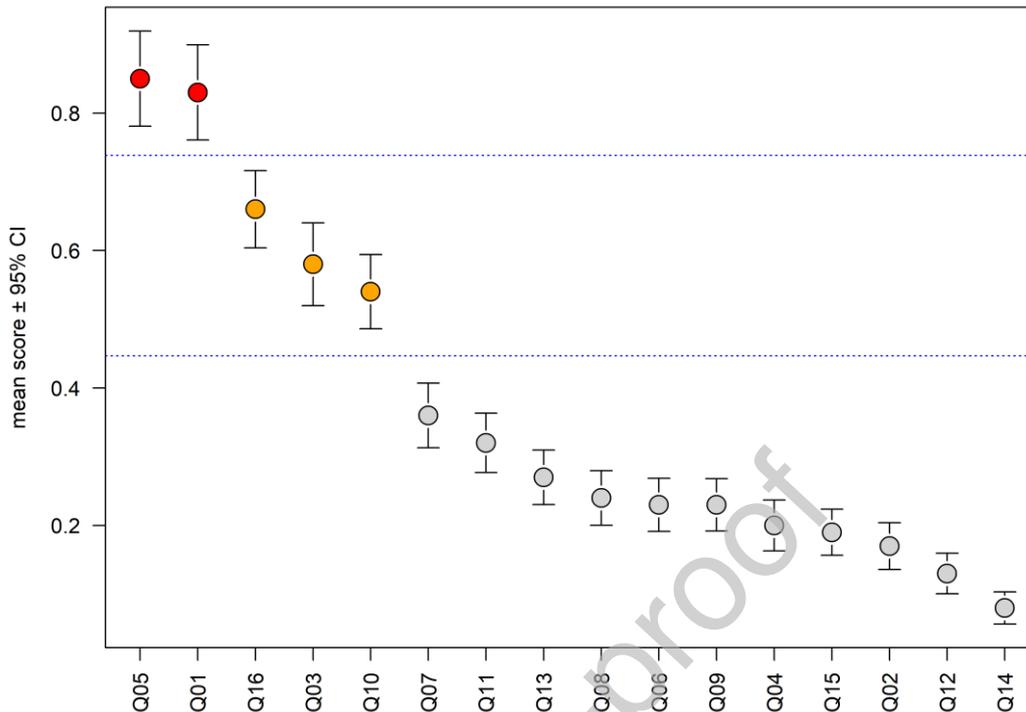
Table 5. Proportion of respondent's interest with 95%CI. The dotted lines indicate the two cut-off values of the interest level. (see Table in supplementary data a).



Size and dispersion of interest

The distribution of the mean rank score among a respondents' top three choices did not substantially differ from the distribution of the proportion of respondents' relevance. Q5 (0.85 ± 1.22 , 95%CI 0.78–0.92) and Q1 (0.83 ± 1.22 , 95%CI 0.76–0.90) had the highest score followed by the cluster of questions Q16, Q3 and Q10. The standard deviation was consistently small, indicating a generally good agreement in ranking among respondents (Table 6).

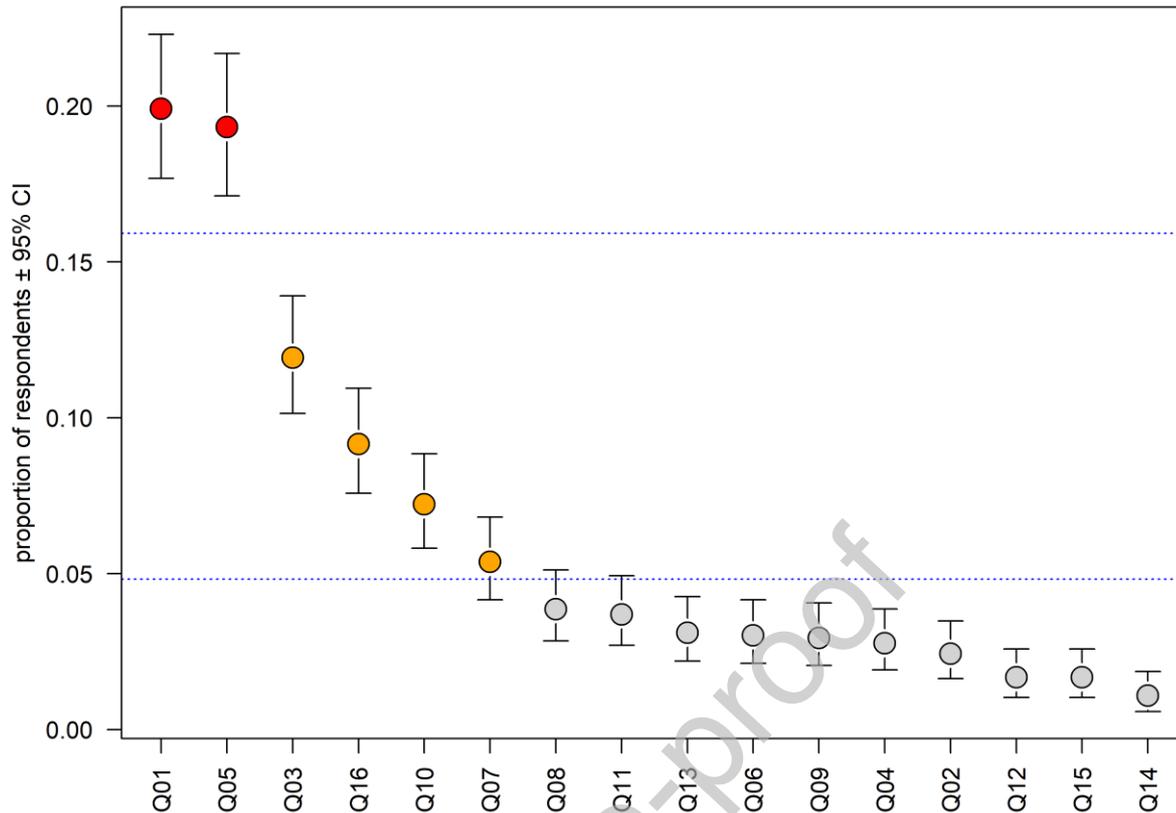
Table 6. Mean scoring interest expressed for a specific question by respondents and standard deviations with 95% CI (see **Table in supplementary data b**).



Ranking of interest

The proposed research questions, considered the top priority for development into a SR by at least 5% of the valid respondents were: Q1, which was selected as most important 237 times by 19.9% of responders, Q5 selected 230 times by 19.3% of responders, Q3 142 times by 11.9% of responders, Q16 109 times by 9.2% of responders and Q10 86 times by 7.2% of responders. There is also Q7 “What are the benefits and harms of further treatment options for people with multiple sclerosis who stop taking a highly efficacious drug?”, selected by 5.4% of responders. (Table 7)

Table 7. Proportion of respondents with 95% CI top that rank question as most relevant (see Table supplementary data c).



The ranking of questions did not differ significantly between 1014 lay people and 158 healthcare professionals, except for Q16 where 103 lay people (10.2%) compared with only 5 professionals (3.2%) ranked it as their first priority ($P=0.005$).

3.3 Influence of respondent's characteristics on ranking.

The multivariable logistic regression analysis was performed on the six questions selected by the respondents as a priority in the univariate analysis (Q1, Q5, Q16, Q3, Q10 and Q7). The analysis indicated a significant influence of geographic area, income level and experience of MS, after accounting for the effect of the other predictors.

Geographic area (i.e. the difference between Europe plus Central Asia vs. Latin America plus the Caribbean) and income group (i.e. the difference between high and upper-middle income) significantly influenced the classification as top priorities of Q1 (respectively OR: 4.27; 95%CI: 2.06 / 8.87, and OR. 3.24; 95%CI: 1.75 / 6.00), and Q5 (respectively OR 5.19; 95%CI: 2.61/10.35 and OR 3.11; 95%CI 1.71/ 5.65), while Q16 was significantly influenced by geographic area (OR 3.48; 95%CI: 1.43/8.47) and not income level.

None of the above considered predictors significantly influenced the ranking of Q3, Q10 and Q7. Healthcare professionals indicated Q5 as their top priority (OR: 1.75; 95%CI: 1.13/ 2.72) significantly more frequently than lay people; the opposite was true for Q16 (OR: 3.03; 95% CI: 1.17/7.86) (Table 8 and supplemental data d).

Table 8 Multivariable Logistic Regression analysis

| Question | Predictor | | | |
|--|---|--|---|--|
| | Geographic area (World Bank)** | HealthCare system | Income level (World Bank) | Experience of MS (Lay or Professional) |
| Q1 | | | | |
| Does MRI help predict disability worsening of PwMS | P=0.003 Europe and Central Asia vs. Latin America and Caribbean: OR 4.27 [2.06; 8.87] | P= 0.686, <i>Not relevant to the overall predictor effect</i> <i>pairwise comparison by predictor level not relevant</i> | P<0.001 Upper-Middle Income vs. High Income: OR 3.24 [1.75; 6.00] | P= 0.167, <i>Not relevant to the overall predictor effect</i> <i>pairwise comparison by predictor level not relevant</i> |
| Q5 | | | | |
| What are the benefits and harms of treating PwMS with one disease-modifying drug compared to another? | P<0.001 Latin America and Caribbean vs. Europe and Central Asia OR 5.19 [2.61; 10.35] | P= 0.241, <i>Not relevant to the overall predictor effect</i> <i>pairwise comparison by predictor level not relevant</i> | P<0.001 high income vs. upper-middle income: OR 3.11 [1.71; 5.65] | P=0.012 professionals vs. lay people OR 1.75 [1.13; 2.72] |
| Q16 | | | | |
| Does psychological health affect disease progression in PwMS | P=0.047*** Latin America and Caribbean vs. Europe and Central Asia: OR 3.48 [1.43; 8.47] | P= 0.218, <i>Not relevant to the overall predictor effect</i> <i>pairwise comparison by predictor level not relevant</i> | P= 0.539 <i>Not relevant to the overall predictor effect</i> <i>pairwise comparison by predictor level not relevant</i> | P=0.022 lay people vs. professionals: OR 3.03 [1.17; 7.86] |
| Q3 Q10 Q7 | <i>Not relevant to the overall predictor effect</i> <i>pairwise comparison by predictor level not relevant</i> | <i>Not relevant to the overall predictor effect</i> <i>pairwise comparison by predictor level not relevant</i> | <i>Not relevant to the overall predictor effect</i> <i>pairwise comparison by predictor level not relevant</i> | <i>Not relevant to the overall predictor effect</i> <i>pairwise comparison by predictor level not relevant</i> |

OR: Odds ratio

* P-value is relevant to the overall predictor effect after accounting for all the other predictors; pairwise comparison by predictor level is reported only when relevant (95% CI did not include 1.00).

** After adding South Asia with East Asia and the Pacific; Sub-Saharan Africa with the Middle East and North Africa.

*** This positive result may represent an artifact due to an unbalanced distribution of cases.

Free text question

An additional free-text research question proposal (Figure 1) was provided by 50.4% of respondents. Of these, 477 out of 583 people (81.8%) indicated that their question was so important as to be ranked among the top three. The textual analysis of the proposed questions will be the aim of a further manuscript.

4. Discussion

As part of our priority setting exercise, we developed an online survey regarding proposed research questions to be evaluated as candidates for development into SRs. Research question proposals were developed with both input from information on gaps in the evidence base for interventions and the personal experience of clinicians, researchers, PwMS and advocates. In our international survey a systematic dissemination strategy was not applied, so the success in reaching potential respondents was largely based on the commitment of those who promoted the survey. People with experience of MS were asked to choose and prioritize sixteen proposed research questions, opportunity for respondents to propose their own priorities was provided.

In our study, all forms of data analysis applied lead to the following five questions being prioritized: **Q1. Does MRI help predict disability worsening of PwMS?** MRI is essential in clinical practice throughout the diagnostic pathway and in the assessment of treatment efficacy (McDonald 2017, MAGNIMS 2021). Indeed, neuroimaging represents one of the recommended efficacy end points in registered trials for new drugs. (www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-multiple-sclerosis_en-0.pdf). However, health systems differ in their ability to sustain the considerable costs associated with performing and interpreting CNS neuroimaging. In addition, not all neuro diagnostic centres have access to the necessary expertise and technology to perform and interpret all the MRI sequences recommended by international guidelines, or to express reports in a meaningful way to be effectively translated into clinical feedback to people affected by the condition. Given that for many PwMS MRI can be a source of great anxiety, provoking substantial out-of-pocket costs as well. With the uncertain but crucial role of neuroimaging there is an ongoing need to assess the prognostic value in different phases of the disease, through a rigorous, systematic approach to the available evidence. It is not surprising therefore that our survey identified this research area as a priority, with a significant influence of country related predictors; Q1 was rated three times more in high compared to upper or medium income countries (OR 3.24) or four times more important in Europe than Latin America (OR 4.27).

Q5. What are the benefits and harms of treating PwMS with one disease-modifying drug compared to another? This question ranked second, indicating the urgent need for direct comparisons among DMTs, an aspect often emphasized by researchers and evaluated in network meta-analyses. Despite the abundance of clinical trials on MS, head-to-head comparisons with appropriately long follow-up to evaluate effectiveness and safety of DMTs are lacking, often because pivotal trials are mainly aimed at obtaining approval by regulatory authorities in order to make new promising treatments promptly available for PwMS. In clinical practice, results from direct comparisons between DMTs over a long follow-up would inform decisions on which treatment approach is best for a specific person, while balancing benefit and harms in an evidence-based, personalized perspective of precision medicine. Ideally this could offer the possibility of using the right drug for the right PwMS following local cost of living parameters. Our multivariate

analysis suggests that there is an important influence of predictors in this urgent issue, as respondents from Latin America and the Caribbean (5.19 times) vs. Europe and Central Asia and from high income countries compared with respondents from upper-middle income countries (3 times), that demonstrate different requirements when choosing between several expensive new drugs. Clinicians who must choose which drug to prescribe are more interested in this question than are the patients (OR 1.75) who feel safe in any case because they put their trust in their health care professionals

Q 16. Does psychological health affect disease progression in PwMS? Seventy-five percent of respondents to this question were PwMS. Providing a response to this area of ‘grey evidence’ could include evaluating the effect of psychological health on prognosis but also on how important psychological support can be for both psychiatric disorders and "invisible symptoms" like fatigue, pain, bowel/bladder dysfunction, sexual dysfunction and vision changes (Silveira et al., 2019, Lakin et al., 2021). This particular question is of great importance to PwMS, and they commonly cited it as a priority topic three times more often than professionals. Disease modifying treatments may be efficacious in slowing disability but not effective in enabling PwMS to participate in life (cf. WHO ICF model of disability) and we must acknowledge that this aspect was raised by the PwMS in the SG. From the perspective of a person living with a chronic disease, psychological health may be of greater value in day-to-day life.

Q 3. Does multidisciplinary care by teams of different social and health professionals improve health outcomes and experiences for PwMS? A small randomized controlled trial (Papeix et al., 2015) with a disabled MS population suggested that an integrated multidisciplinary and multi professional approach was not superior to usual care in promoting quality of life. Since its first version in 2014, NICE has recommended that care for people with MS should comprise coordinated multidisciplinary long term delivery (www.nice.org.uk/sharedlearning/separating-diagnostic-neurology-from-management-of-long-term-neurological-conditions-a-new-concept-of-service-delivery). While there is recent agreement among guideline developers on the need for multidisciplinary approaches for PwMS, including psychological support (Ghezzi, 2018) and information delivery (Köpke et al, 2018), there is debate about which outcomes are most relevant for the people affected. Mattarozzi speculates, based on a large Italian case series, that the organisation of care (inclusive of multidisciplinary care), tailored information and service characteristics (hospital size) provided by MS centres, influence the variation in PwMS’ satisfaction and their relationships with health professionals (Mattarozzi et al, 2017). Given the heterogeneity of organisational healthcare models in different countries, the concept of “multidisciplinary care” may have different levels of feasibility in different settings.

Q 10. What are the benefits and harms of exercise for PwMS? For years there has been a controversial approach concerning exercise in PwMS as it was thought to exacerbate symptoms. In the past decade there has been an acceleration of research in this area and there is evidence that supervised and individualized exercise programs or home-based exercise training can improve physical fitness, functional capacity, fatigue and quality of life (Sá, 2014, Halabchi et al., 2017, Ghahfarrokhi et al., 2021), Even for PwMS with severe functional impairment, exercise could be considered, in some circumstances, as an alternative valid approach to drug intervention (Edwards et al., 2017). Moreover, exercise can decrease neural apoptosis and neurodegeneration, and may be effective at stimulating neuroplasticity, speculating a disease modifying effect (Learmonth et al., 2021). There is the need however to move forward, with all stakeholders, in advancing standardized and shared outcome measures (Dalgas et al., 2021).

We acknowledge that there are some limitations to our survey, i.e. 75% of participants were PwMS and a low number of clinicians or researchers participated. This was not unexpected given that the survey was predominantly promoted and disseminated to PwMS and by international MS organisations and clinicians. A second limitation relates to the absence of data on participants’ age,

gender and disease status, which are well known as important determinants of people's care needs, at least for people with MS and their carers (Golden 2017, Coyle PK 2021, Gil-González et al., 2020). We wanted to propose a very direct and easy to answer questionnaire, and decided to asking only essential participant characteristics,

A third limitation relates to the online survey method. The questionnaire was disseminated via web and participation to the survey was on a voluntary basis. This may have created a selection bias by favouring respondents with better digital knowledge and availability of a web connection. Though unavoidable, given practical contrasts, this may impact the generalizability of our results, given that more than 95% of participants live in High and UMI-countries, while 66% live in countries with universal taxation (Table 3). Consequently, this imbalance – in terms of healthcare characteristics and average income- is likely to have enhanced the health needs of higher income countries, which may have privileged some specific questions.

Moreover, from a statistical point of view, the factors identified as having significant influences on prioritization should be considered with care, as the distribution of the sample across the different predictors was largely unbalanced, and collinearities between them cannot be excluded.

Acknowledged influences of income status aside, our survey results are drawn from a globally diverse population, and the majority of responses have come from PwMS, making this survey highly representative of their views. Furthermore, a below 20% failure rate, and just 10% of questionnaires completed with the help of a carer, indicate a strong motivation of PwMS to express their preferences. The additional free-text research questions proposed by responders represent an opportunity to provide additional insight into the needs and requirements of the respondents.

Given the high number of participants, these results should be considered a substantial contribution to the understanding of the expectations of PwMS and their carers, and an important source of suggestions for future research in the field.

This priority setting exercise was a valuable opportunity to engage stakeholders on key evidence-based pre-determined questions, involving motivated people to disseminate the survey globally and allowing people with different experience with MS to actively prioritize new Cochrane review titles. Such participant perspective could be a way to potentially reduce research waste and produce reviews on relevant topics (Chalmers et al., 2014) better informing health decision makers in countries with different economic and organizational settings.

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CRedit authorship contribution statement

Maria Grazia Celani: Conceptualization, drafting of the protocol, formal analysis, resources, data curation, writing – original draft, writing – review & editing, project administration.

Francesco Nonino: Conceptualization, drafting of the protocol, writing – review & editing, project administration.

Elisa Baldin: Conceptualization, drafting of the protocol, review & editing.

Graziella Filippini: Conceptualization, drafting of the protocol, writing, review & editing, project administration.

Teresa Anna Cantisani: Resources, supervision and editing.

Roberto D'Amico: Conceptualization, review & editing,

Ben Ridley and Kathryn Mahan: resources, writing – review & editing, project administration.

Angelo Alberto Bignamini and Massimiliano Orso: Data curation, formal analysis, writing – review & editing.

Steering Group: Resources and supervision.

Paolo Rosati: online software design.

Ethics approval: Approval by the local Ethics Committee of the MSCRG (Comitato Etico AVEC di Bologna) was not deemed as necessary by the Committee itself, since data were anonymously collected.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Journal Pre-proof

Figure 1



Welcome to our short survey

In this survey, you will be asked to share your views on which questions should be prioritized for research using [systematic reviews](#).

Systematic reviews are used to look at all the scientific evidence available on a particular topic, summarizing the results from all the research that exists and to answer a specific question in an objective, transparent and systematic way.

The survey includes 4 steps:

1. Select up to 3 questions you think are the most important and **rank** your 3 choices
2. **Tell us more** about your choices
3. If you don't see a question that is important to you or the people you offer care to, **add your question** and tell us more
4. Tell us about you and **submit**

Thank you for participating. Your views are important.

We are asking for your help to identify the most important questions on **Multiple Sclerosis** that should be addressed by updated and new [systematic reviews](#) over the next 3 years by the Cochrane Review Group: Multiple Sclerosis and Rare Diseases of the Central Nervous System.

Cochrane is a global independent network of researchers, professionals, patients, carers and people interested in health. Cochrane's work is internationally recognized as the benchmark for high-quality information about the effectiveness of health care. Our core team (Editorial Base), in collaboration with the Cochrane Neurological Sciences Field, has created a list of 16 questions for possible [systematic reviews](#) that we believe are important for the care of people with Multiple Sclerosis. The 16 questions have been approved by the Steering Group of this priority setting project.

We need your **help to prioritise** this list.

Please think about how important the 16 questions are to you by first selecting your top 3 (three) and then ranking them. You can choose fewer than three questions if you wish. You can suggest your own question later in the survey. Your participation in the survey is on a voluntary basis. No payments are offered to complete the questionnaire.

The survey is **anonymous**: you won't be asked to provide personal information or information that will allow you to be identified. Please indicate **your consent** for us to use your responses in this project by selecting the box below.

Time to complete the survey will vary depending on how much you want to say. We anticipate it will take around 10-20 minutes. If you prefer, you may ask someone to help you complete the survey. For more information on this survey, please see: <https://msrdcns.cochrane.org/topic-prioritisation>

I confirm that I understand the participant information and I consent for my responses to be used in this project YES

Step 1 – Select up to 3 top questions and rank your 3 choices

Please read the 16 suggested questions below. Then, **select up to 3 questions** you think are a priority for a new or updated systematic review and **rank your highest priority (1st), second priority (2nd) and third priority (3rd)**

| | |
|--|--------------------------|
| Q1. Does magnetic resonance imaging (MRI) help predict disease progression in people with multiple sclerosis? | <input type="checkbox"/> |
| Q2. Do cerebrospinal fluid (spinal tap/lumbar puncture) findings help predict disease progression in people with multiple sclerosis? | <input type="checkbox"/> |
| Q3. Does multidisciplinary care by teams of different social and health professionals improve health outcomes and experiences for people with multiple sclerosis? | <input type="checkbox"/> |
| Q4. Is treatment with intravenous steroids more beneficial than oral steroids in people with multiple sclerosis who have relapses? | <input type="checkbox"/> |
| Q5. What are the benefits and harms of treating people with multiple sclerosis with one disease-modifying drug* compared to another? * <i>List of DMT active ingredients (at the end of the question list, or- if technically possible - callout)</i> | <input type="checkbox"/> |
| Q6. What are the benefits and harms of medications for reducing spasticity in people with multiple sclerosis? | <input type="checkbox"/> |
| Q7. What are the benefits and harms of further treatment options for people with multiple sclerosis who stop taking a highly efficacious drug**? ** <i>reference toECTRIMS-EAN and AAN guidelines</i> | <input type="checkbox"/> |
| Q8. What should the therapeutic approach be for people with multiple sclerosis, being treated with disease-modifying therapies*, who are planning a pregnancy or are pregnant? * <i>List of DMT active ingredients (at the end of the question list, or- if technically possible - callout)</i> | <input type="checkbox"/> |
| Q9. What should the treatment approach be for people with multiple sclerosis being treated with disease-modifying therapies*, who test positive for the COVID-19 virus? * <i>List of DMT active ingredients (at the end of the question list, or- if technically possible - callout)</i> | <input type="checkbox"/> |
| Q10. What are the benefits and harms of exercise for people with multiple sclerosis? | <input type="checkbox"/> |
| Q11. How can people with multiple sclerosis be supported in work and social participation? | <input type="checkbox"/> |
| Q12. What kind of support can increase participation in treatment decision making by people with multiple sclerosis? | <input type="checkbox"/> |
| Q13. What kind of activities can help with self-management and coping by people with multiple sclerosis? | <input type="checkbox"/> |
| Q14. What are the benefits and harms of palliative care for people with advanced multiple sclerosis? | <input type="checkbox"/> |
| Q15. What are the benefits and harms of psychological care for people with multiple sclerosis? | <input type="checkbox"/> |
| Q16. Does psychological health affect disease progression in people with multiple sclerosis? | <input type="checkbox"/> |



Step 2 – Tell us about your top questions

Tell us why – Think about **your top questions** (you may have selected fewer than 3).

- Why are these important?
- What makes them a priority for you or the person(s) you care for?
- Why would research on these topics be useful?

Please add **your reasons** why the questions you have selected are important in the text box under the question title.

Tell us more about why these questions are a priority for more research using a systematic review

QUESTION 1st

QUESTION 2nd

QUESTION 3rd

Step 3 - Suggest another question and tell us more

Add one question – If you don't see a question that is important to you or the people you offer care to, **add one question**. Please briefly describe this additional priority area for research. Would you rank your question in an **overall top 3**?

Adding one additional question is optional. Use the 'Next' button to go to final step.

I think this question is also important (briefly describe and tell us why). Describe your important additional question in this box.

Would you rank your question in an overall top 3?

- Yes, No

Step 4 – About you

Which of the descriptions below best describes your experience of multiple sclerosis?

- Person with the condition
- Carer
- Family member
- Care professional (in any health or social care role)
- Researcher (as academic)
- Researcher (as private sector employee or consultant)
- Member of a support or interest group
- Other (please specify)

What country do you usually live in?

Optional - Do you have any other comments, questions, or concerns?

A second round of the survey will be organised soon. If you wish to participate again, please click here: <https://msrdcns.cochrane.org/topic-prioritisation>

Finally -submit your responses. Use the 'Done' button to submit - thank you!

Figure 1 caption is "English version of Priority Setting online questionnaire"