



Original article



Research priorities in multiple sclerosis in Latin America: A multi-stakeholder call to action to improve patients care Research priorities in MS in LATAM

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ABSTRACTS

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As human and economic resources are limited, especially in Latin America (LATAM), it is important to identify research priorities to improve multiple sclerosis (MS) patients care in the region. The objective was to generate a multidisciplinary consensus on research priorities in MS for patients care in LATAM by involving healthcare professionals and MS patient associations.

Methods: consensus was reached through a four-step modified Delphi method designed to identify and rate research priorities in MS in LATAM. The process consisted of two qualitative assessments, a general ranking phase and a consensus meeting followed by a more detailed ranking phase

Results: a total of 62 participants (35 neurologists, 4 nurses, 12 kinesiologists, 7 neuropsychologists and 4 patient association members) developed the process. At the final ranking stage following the consensus meeting, each participant provided their final rankings, and the top priority research questions were outlined. 11 research priorities were identified focusing on healthcare access, costs of the disease, physical and cognitive evaluation and rehabilitation, quality of life, symptoms management, prognostic factors, the need of MS care units and patient's management in emergencies like COVID-19.

Conclusion: this work establishes MS research priorities in LATAM from multiple perspectives. To pursue the actions suggested could launch the drive to obtain information that will help us to better understand the disease in our region and, especially, to better care for affected patients.

1. Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS), pathologically featured by the presence of demyelination and neurodegeneration that progress in time and that lead to significant disability in most affected patients 20 or 30 years after disease onset (Comi et al., 2017; Cristiano and Rojas, 2017).

The frequency and distribution of the disease varies geographically, as has been demonstrated in several epidemiological reports (Cristiano et al., 2013; Rivera and Macias, 2017). In Latin America (LATAM), the reported annual incidence rate ranged from 0.15 to 1.9 cases per 100,000 person-years, and prevalence ranged from 0.75 to 38.5 cases per 100,000 inhabitants. Frequency was significantly lower when compared with North American and European regions (Cristiano et al., 2013; Cristiano and Rojas, 2017; Rivera and Macias, 2017).

Despite the lower frequency of the disease in LATAM, many countries of the region face several difficulties in providing the recommended healthcare due to multiple factors, including delays in access to healthcare, segmented health care systems, and scarce human and economic resources (Carnero Contentti et al., 2020, 2019; Rivera and Macias, 2017).

Clinical research for MS in LATAM is derived primarily from investigator-initiated studies mostly based on research and needs developed in the northern hemisphere. It is not focused on local needs and priorities, creating a gap in the information in our region that would otherwise help to better care for MS patients (Carnero Contentti et al., 2020, 2019). As human and economic resources are limited, especially in LATAM, it is important to identify research priorities to improve MS patients care in the region to better distribute those resources and to optimize the diagnosis, treatment and overall healthcare based on local evidence.

Taking this into consideration, our objective was to generate a multidisciplinary consensus on research priorities in MS for patients care in LATAM by involving healthcare professionals and MS patient associations.

2. Methods

2.1. Design

Our consensus was reached through a four-step modified Delphi method (Dalkey, 1969; Ota et al., 2008; Schneider et al., 2016) designed to identify and rate research priorities in MS in LATAM. The process consisted of two qualitative assessments, a general ranking phase and a consensus meeting followed by a more detailed ranking phase. The Delphi method is a consensus-based technique that provides a systematic method of collecting and aggregating informed judgments from a group of experts via multiple iterations (Dalkey, 1969). Controlled

feedback from sequential rounds encourages participants to reassess, alter and/or develop opinions (Dalkey, 1969). The Delphi method maximizes the benefits of using an expert panel while minimizing potential disadvantages by implementing anonymity. The method has been extensively used in determining research priorities in other healthcare areas (Efstathiou et al., 2007; Lynch et al., 2001; Ota et al., 2008; Soelberg Sorensen et al., 2019).

To carry out the process, we developed a project manager team composed of two MS specialists and a health research methodology expert to oversee the design, execution, and analysis of all phases of the project. Research methods were pre-established in face-to-face meetings, and email correspondence was later implemented. Agreement was reached regarding participant selection, consensus thresholds, survey format and question structure, and analysis processes.

2.2. Participants

Neurologists, nurses, physical therapists, neuropsychologists, psychiatrists, psychologists, and directors and members of patient associations in LATAM linked to the care of patients with MS were invited. All potential participants were identified through the Latin American Committee and Treatment of MS (LACTRIMS) database as well as MS centers and observational cohort studies databases. Only those who agreed to participate in the process were included in the final working group.

2.3. Delphi procedure

2.3.1. Phase I

The first phase used a web-based, open-ended questionnaire (see Online Supplementary 1) asking participants to identify up to three research questions of relevance to the field of MS but focusing on unmet needs in the LATAM region. Participants were asked to complete the questionnaire via email. The project manager team did not provide bibliography; rather, participants were required to provide bibliography supporting their answers if they considered it necessary, as well as personal demographic information, and to declare any potential financial or intellectual conflicts of interest. The process lasted 4 weeks, and reminder emails were sent to obtain all participant responses. Once all questionnaires were received, the project manager team compiled the responses and reviewed the proposals to generate a list of candidate research questions that progressed to Phase II. Only participants that responded to Phase I were included in Phase II.

2.3.2. Phase II

Participants were sent a compiled list of questions obtained in Phase I and asked to assess if each question was relevant regarding MS research in LATAM. For every research question they were asked: "Is this question

a research priority for MS in LATAM?" and a YES or NO answer was required. A 75% agreement threshold was set; therefore, all questions with over 75% agreement on their relevance assessment were put through to the next phase (Table 1)

2.3.3. Phase III

During the third phase, participants received a questionnaire (Supplementary 2) that asked them to rank each candidate research question obtained from Phase II, individually, on a 5-point Likert scale (Table 2) for five criteria: scientific merit, significance, innovation, relevance, and feasibility (Table 3). Participants were also asked to comment or add new research questions if considered appropriate. Once all questionnaires were received, the answers were analyzed. We used a predetermined consensus threshold (Table 1) to consider priorities for research questions that progressed to Phase IV. Research questions that did not meet the consensus threshold were not brought forward for review.

2.3.4. Phase IV

Phase IV of the project was planned to be implemented in person in November 2020. However, due to the COVID-19 pandemic the Phase IV was conducted through a virtual format during October 2020. We invited all participants from Phases I to III to discuss the analysis obtained from Phase III. During the meeting, the highest ranked research questions, listed in a descending order by percentage of agreement, were discussed by the participants. After the meeting, participants were asked to reassess the ranking order of the research questions and propose a different ranking order, if needed. The final research questions agreed by participants were included in the research priorities identified.

2.4. Research ethical approval

The study was approved by the Research Protocol Ethics Committee from the Hospital Universitario de CEMIC, Argentina.

2.5. Statistical analysis

Continuous data were expressed with their means and ±SD. The categorical data were expressed in percentages.

3. Results

A total of 74 potential participants received the project protocol and the implementation process to analyze and decide whether they agreed to participate. If further details were required, these were provided by the project manager team to participants who decided whether to participate or not. The final group that accepted to participate was composed of 62 respondents (35 neurologists, 4 nurses, 12 kinesiologists, 7 neuropsychologists and 4 patient association members). The whole process from phase I to phase IV last 9 months (Fig. 1). Participants came from Argentina, Brazil, Colombia, Costa Rica, Chile, Ecuador, El Salvador, Guatemala, Mexico, Paraguay, Panama, Peru, Dominican Republic, Uruguay and Venezuela. Participant demographics are shown in Table 4. After the confirmation of the group, the phase I was implemented.

Table 1
Phase II consensus thresholds.

Consensus threshold	
Inclusion	>75% of respondents provide positive result (four of five) on the Likert scale for all criteria
Exclusion	>75% of respondents provide negative result (one or two) on the Likert scale for all criteria
Non-consensus	When the proposed priority research questions have met neither the inclusion nor exclusion consensus threshold

Table 2
Phase III, 5-point Likert scale.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Table 3
Phase III criteria definition.

Criteria	Criteria definitions
Scientific merit	Clear, concise research question with a strong rationale (e.g., clinical equipoise) and approach
Clinical significance	Potential impact on clinical practice
Innovation	Explores new scientific avenues, has a novel hypothesis, and will create new knowledge
Relevance	Importance to patient populations and key strategic research priorities
Feasibility	Potential to recruit participants in a timely manner, obtain funding, and expand internationally

3.1. Phase I: qualitative assessment–soliciting research questions of interest

The invitation to complete a web-based, open-ended questionnaire (with unrestricted answers) was distributed in May 2020 and remained open to answers for 4 weeks.

Identical questions were removed. This process was performed by the project manager team. In Phase I, 103 research questions were received; after removal of identical questions, 85 passed to Phase II.

3.2. Phase II: qualitative assessment–assessment of relevance

Sixty-two responded to the rating evaluation questionnaire. In this phase, of 85 questions included, 54 reached inclusion thresholds, 31 did not reach consensus thresholds, and 2 additional research questions were included.

3.3. Phase III: rating evaluation–rating of research questions

Participants were invited to complete this questionnaire by email in July 2020. The questionnaire remained online for 3 weeks. The project manager team compiled the ratings for each research question as well as any additional research questions. The results of the questionnaire were reviewed to determine whether each candidate research question met the predetermined consensus thresholds (Table 3). Research questions that met either the inclusion or consensus thresholds progressed to Phase IV for review by the consensus panel. Candidate research questions that met the exclusion consensus threshold were not brought forward for review. In total, 62 individuals participated in the rating evaluation. A total of 56 questions were included for review, and 11 top research priority questions were defined for the final phase for consideration and assessment at the consensus meeting.

3.4. Phase IV: consensus meeting–vetoing and ranking of research priorities

The consensus online meeting was held in October 2020. There was an online process and 7 days offline to complete the discussion and agreement process. At this meeting, the members of the consensus panel were given the opportunity to discuss the eligible candidate research questions as a group. The consensus meeting was recorded, and all consensus panel members were informed that it was being recorded before the start of the meeting.

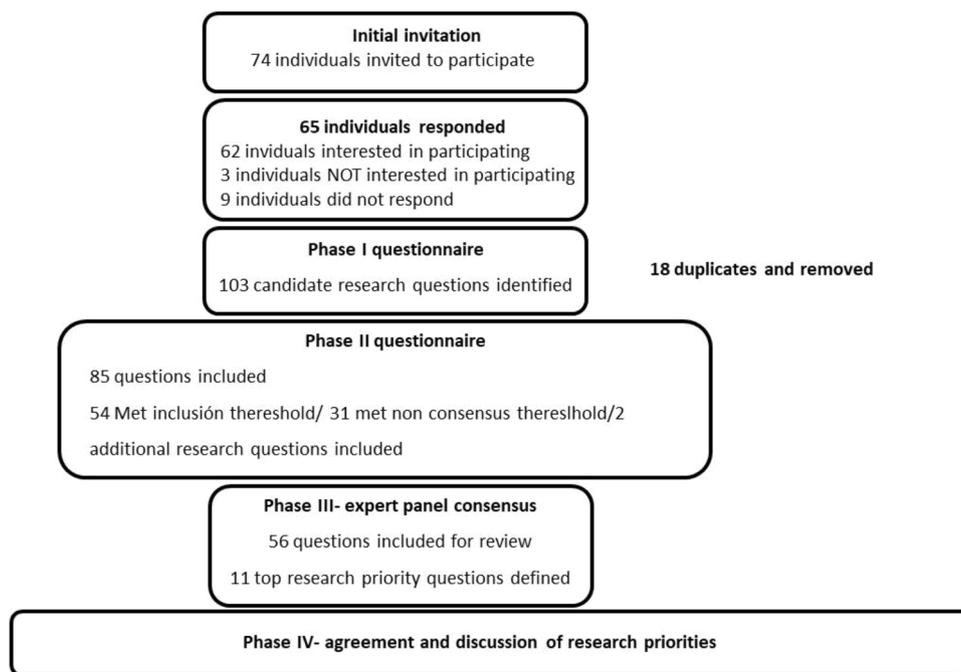


Fig. 1. Flow diagram of research priorities in the MS process.

Table 4
Participant demographics.

N (%)	
Number of invited	74
Number of participants	62
Female gender	26 (35)
Mean age, years (±SD)	45 ± 12
Occupation Neurologist Nurses Kinesiologist Neuropsychologist	35 5 12 10
Patient association directors	5

3.5. Final research priorities

The final stage identified 11 research priorities. At the final ranking stage following the consensus meeting, each participant provided their final rankings, and the top priority research questions are outlined in Table 5.

4. Discussion

Many advances in the field of diagnosis, biomarkers and therapeutics

Table 5
Priority research questions for MS in LATAM.

Will describing how MS patients access disease-modifying treatments allow physicians to design strategies to improve the care of MS patients in LATAM?
What are the main factors of non-adherence to treatment in MS patients in LATAM?
Do MS care units, compared to usual care, improve a patient's care in LATAM?
Do the identification and management of symptoms improve the care and quality of life of MS patients?
During health emergencies like COVID-19, which tools do we have and use to maintain an adequate control of patients?
How is the quality of life affected in MS patients and what are the main factors related to its decline in LATAM?
Can the identification of costs associated with MS improve MS health policies in LATAM?
Is MS treated early in LATAM?
How does physical rehabilitation proceed in patients with MS in LATAM?
What is the effectiveness of neuropsychological rehabilitation programs in patients with MS in LATAM?
What are the prognostic factors for MS disease progression in LATAM?

in MS have been achieved over recent years (Comi et al., 2017; Fox and Chataway, 2017; Gass et al., 2015; Moccia et al., 2017; Reich et al., 2018; Soelberg Sorensen et al., 2019; Thompson et al., 2018). Most of these, currently applied to MS patients in research and innovation, originate in North America and Europe where there are many differences in terms of needs and human and economic resources when compared with LATAM. Consequently, LATAM should determine its priorities in patient-centered research as based on local, unmet needs.

In the present study, we arrived at a consensus on the research priorities for patients care in LATAM. The most relevant priorities defined was research focused on healthcare access, costs of the disease, physical and cognitive evaluation and rehabilitation, quality of life, symptoms management, prognostic factors, the need of MS care units and patient's management in emergencies like COVID-19.

Although the same methodology used in our research has not been applied in MS previously, it is possible to evaluate some priority aspects of care and research in other regions related to MS. Relevant information can be obtained from the activities performed by the MS in the 21st Century initiative (Members of the et al., 2018; Oreja-Guevara et al., 2019; Rieckmann et al., 2013; 2015; Rieckmann et al., 2018). The initiative is led by a Steering Group of MS specialists and patient advocates from 15 countries. A recent project performed by the group identified the priority aspects from the professional perspective in the care of patients with MS (Oreja-Guevara et al., 2019). The priority aspects were mainly related to symptom-free disease and ultimately a cure, continuity and quality of care, reimbursement and accessibility of treatment, neuroprotective and personalized treatments, better treatment for progressive MS and patient engagement and advocacy (Oreja-Guevara et al., 2019). Despite some priorities mentioned in our research are similar with the ones identified by MS in the 21st Century initiative focused on Europe and North America, there are others that were prominent in our region like factors related to the adherence to treatments, the role MS care units, local prognostic factors of disease progression and healthcare costs.

Regarding healthcare access and costs, it is known that there are many difficulties in our region. A significant number of patients find barriers in accessing the neurological care and specific treatment needed, with the direct consequence of disease progression and reaching disability milestones early. The development of research strategies to

identify how patients and systems could improve access to healthcare would benefit all stakeholders involved in patient care.

It is also important to evaluate whether MS care units would contribute and how they should implement and improve patient care in our region.

Other priorities determined by the group focused on the need to evaluate the quality of life in MS patients and which factors are related to its improvement.

Further priorities considered by the group focused on the role of physical and cognitive evaluation and rehabilitation, particularly on the effectiveness of programs currently used in clinical practice.

Despite the identification of research priorities, and as many perspectives are important, the most significant point would be how to translate these priorities into an effective movement that raises awareness of needs and generates a variety of research lines throughout LATAM to obtain information, fill in the gaps and improve patient care. With that purpose in mind, certain principles can be suggested to continue the process of evidence generation based on research priorities:

1. To disseminate the aforementioned priorities to all stakeholders involved in MS patient care in LATAM via the tools (web page, congresses, meetings, courses and newsletters) of the Latin American Committee for Research in Multiple Sclerosis (LACTRIMS).
2. To create working groups via LACTRIMS aimed at generating research protocols and to conduct studies following the priorities determined by the working group.
3. To provide methodological, human, technical, and economic support via LACTRIMS (and other stakeholders) to support research focused on the priorities determined.
4. To facilitate via LACTRIMS the interactions of research groups in LATAM with research groups in Europe and North American to improve the development of skills and the conduction of studies.

Many of these principles will help to move this document into action.

Our study has certain limitations that should be mentioned. Although diverse, the composition of our sample was still dominated by neurologists; results may therefore reflect such a bias. It is also important to mention that the perspective of health care payers was not considered. However, due to the diversity of the health care systems in the region, it is difficult to obtain a representative view from that sector that would allow recommendations. In our consensus, we obtained the perspective of patient associations from LATAM; nonetheless, as only data from 4 associations was obtained, information from this stakeholder may be under-considered. A possible explanation for the low number of associations involved in the project is probably given by the scarce link between health care providers and organization, a link under construction in our region. Nevertheless, there is a specific project originated from this, aimed to include many patients and perspectives not only in research as well as in their care to fully understand the situation and move forward consequently. Finally, despite our working group having a low number of members, it included a specifically selected population interested in collaborative research in the field. Considering that our objective was to determine the priority research questions in MS in LATAM, the principles derived from our study will hopefully lead to future collaborative, prospective research.

In conclusion, this work establishes MS research priorities in LATAM from multiple perspectives. To pursue the actions suggested could launch the drive to obtain information that will help us to better understand the disease in our region and, especially, to better care for affected patients.

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Edgardo Cristiano has received fees for consultations as a scientific

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Adriana Carrá has received honoraria as speaker honoraria from Biogen, Novartis, Genzyme, TEVA, Merck, Roche, Bayer and participated in advisory boards from Shire, Roche, TEVA, Merck-Serono

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5. Author declaration

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property

Declaration of Competing Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.msard.2021.103038](https://doi.org/10.1016/j.msard.2021.103038).

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