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## 00MDS-NMS

### **Title: Expanded and Independent Spanish validation of the MDS- Non Motor Rating Scale**

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the [Version of Record](https://doi.org/10.1002/mdc3.13658). Please cite this article as doi: [10.1002/mdc3.13658](https://doi.org/10.1002/mdc3.13658)

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**Abstract**

Background: The Movement Disorder Society-sponsored Non-motor Rating Scale (MDS-NMS) assess the severity and disability caused by non-motor symptoms (NMS) in Parkinson's disease (PD).

Objective: This article encapsulates the formal process for completing this program and the data on the first officially approved non-English version of the MDS-NMS (Spanish).

Methods: The MDS-NMS translation program involves four steps: translation and back-translation; cognitive pre-testing to ensure that raters and patients understand the scale and are comfortable with its content; field testing of the finalized version; analysis of the factor structure of the tested version against the original English language version for the 9 domains that could be analyzed in a confirmatory factor analysis. To be designated an 'Official MDS translation', the confirmatory factor analysis Comparative Fit Index had to be  $\geq 0.90$ .

Results: The Spanish MDS-NMS was tested in 364 native-Spanish-speaking patients with PD from 7 countries. For all subjects with fully computable data with all domains of the MDS-NMS ( $n=349$ ), the Comparative Fit Index was  $\geq 0.90$  for the 9 eligible domains. Missing data were negligible and moderate floor effect (42.90%) was found for the Non-Motor Fluctuations subscale. Item homogeneity coefficient was adequate, and the correlation of the MDS-NMS domains with other measures for related constructs was acceptable ( $\geq 0.50$ ).

Conclusions: The Spanish version of the MDS-NMS followed the IPMDS Translation Program protocol, reached the criterion to be designated as an Official Translation, and is now available on the MDS website.

**Word count:** title: 78 characters; abstract (239); text (3228), 5 tables, 1 figure, 5 supplemental tables, 31 references.

**Running title:** MDS-NMS.

**Key Words:** non-motor symptoms, rating scale, Parkinson's disease

## MDS-NMS

Non-motor symptoms (NMS) are an important factor of the deterioration of the health-related quality of life (QoL) of patients with Parkinson's disease (PD).<sup>1,2</sup> NMS burden increases in their severity over time, impacting on patients' disability, caregivers' burden, and societal costs.<sup>3</sup> Assessment of NMS in PD are now crucial to value-based health care and recommended by patient-led organizations and the International Parkinson and Movement Disorder Society (IPMDS).<sup>4</sup> The IPMDS non-Motor PD Study Group recently developed and validated the International Parkinson and Movement Disorder Society-Non Motor Rating Scale (MDS-NMS) in English, an updated version of the Non-Motor Symptom Scale (NMSS).<sup>5,6</sup> The MDS-NMS was validated for use in PD using a sample of 402 English-speaking PD patients from America and England.

Given the importance of NMS burden in PD, having a scale that is validated in multiple non-English languages is pivotal to international efforts to treat NMS. To obtain equivalent and locally validated non-English versions of the MDS-NMS, a Translation Program Protocol has been established by the IPMDS ([www.movementdisorders.org](http://www.movementdisorders.org)).<sup>7</sup> The objective of this study was to organize and perform an independent validation of the MDS-NMS Spanish version following the IPMDS methodology for the translation and validation process.<sup>8</sup>

### **Methods**

**Study Design and Patients:** This was an international, multicenter, observational, cross-sectional study. We invited for participation, Spanish-speaking patients from 14 Movement Disorders Units from Spain, and 8 centers from North, Central, and South America (Mexico, Argentina, Colombia,

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Ecuador) and United States (Miami Florida and Boca Raton, Florida) at any age and disease stage, diagnosed with idiopathic PD as per the MDS-PD criteria,<sup>9</sup> and without significant cognitive impairment according to the judgment of the evaluating neurologist and a Montreal Cognitive Assessment (MOCA) score > 21.<sup>10</sup>

Ethical aspects: Each site contributing to the study received approval of its respective ethics committee/IRB for participation, and the study was conducted according to Good Clinical Practice.<sup>11</sup> Patients provided signed informed consent before participating in this study.

Raters: Neurologists, members of the IPMDS, were invited by email to participate in this project.

Sample size: The sample size for the translation study was based on the need for 5 subjects per item of the questionnaire to perform the statistical analysis.<sup>12</sup> Because there are 60 items (52 MDS-NMS items and 8 nonmotor fluctuations items) on the MDS-NMS, a sample of at least 300 was required.

Assessments: Socio-demographic, predominant hemi-body affected by PD, current use of antiparkinsonian drugs including the levodopa-equivalent daily dose (LEDD),<sup>13</sup> and other treatments, and PD historical data were obtained through an ad hoc questionnaire. In addition, the following rating scales were administered:

1. *MDS-NMS* (see Appendix): After the pilot study,<sup>5</sup> the final version of the MDS-NMS has 52 items, grouped according to clinical content into 13 domains: (A) Depression (5 items), (B) Anxiety (4 items), (C) Apathy (3 items), (D) Psychosis (4 items), (E) Impulse Control and Related Disorders (4 items), (F) Cognition (6 items), (G) Orthostatic Hypotension (2 items), (H) Urinary (3 items), (I) Sexual

(2 items), (J) Gastrointestinal (4 items), (K) Sleep and Wakefulness (6 items), (L) Pain (4 items), and (M) Other (5 items; unintentional weight loss, decreased smell, physical fatigue, mental fatigue, and excessive sweating). Items are scored for frequency (from 0 [never] to 4 [majority of time]) and severity (from 0 [not present] to 4 [severe]), which are multiplied to generate the item total score. Scores for each domain and the total rating scale (maximum, 832 points) are calculated by summing the corresponding items.

The Non-Motor Fluctuations (NMF) subscale has 8 items: depression, anxiety, thinking or cognitive abilities, bladder symptoms, restlessness, pain, fatigue, and excessive sweating. Each item is scored for typical degree of change from "on" to "off" periods, from 0 (no change) to 4 (large). The sum of degree of change for the 8 items is multiplied by the amount of time spent in the "off" state with NMS, which ranges from 1 (rarely) to 4 (majority of time). Maximum possible score is 128.

2. *MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS)*: The MDS-UPDRS includes 4 parts: part I, Non-motor Aspects of Experiences of Daily Living (nM-EDL); part II, Motor Aspects of Experiences of Daily Living (M-EDL); part III, Motor Examination (ME); and part IV, Motor Complications (MComp). In addition, it contains the Hoehn and Yahr scale (HY), a tool for staging the severity of PD.<sup>14</sup>

3. *Wearing Off Questionnaire-19 (WOQ-19)*: This questionnaire includes 9 items assessing motor fluctuations including tremor, difficulty in speech, weakness, problems with balance, slowness, reduced dexterity, general stiffness, muscle cramps, difficulty getting out of the chair (WOQ-19 Motor score); and 10 items evaluating non-motor fluctuations including anxiety,

sweating, mood changes, numbness, panic attacks, cloudiness of mind, abdominal discomfort, feeling hot and cold, aches and pain (WOQ-19 Non-motor score).<sup>15</sup> For each item, patients were asked to check whether symptoms were present and whether they improved after the following dose of dopaminergic treatment: a cut off of 2 for the WOQ-19 Total score indicated a diagnosis of generic wearing off,<sup>15</sup> while a cut off of 1 for either the WOQ-19 Motor or Non-motor score specifically disclosed a diagnosis of motor or non-motor fluctuations, respectively.

Procedure: Assessments were performed during the "on" state when possible, and patient assessments between all centers were harmonized.

Phases in the development of the Spanish version of the MDS-NMS followed the prescribed protocol established by the IPMDS for official translations of the MDS-NMS:

- 1) *Translation, back-translation, comparison with the original, and amendments of the scale text.* A forward translation was developed by a third-party translation company experienced in the translation of rating scales and reviewed by the Spanish Translation Committee created for this project. All wording was selected to meet the criterion of being at the 7<sup>th</sup> grade reading level. Documents were reviewed by the administrative team and reviewers independent of the Spanish organizers, and a draft translated scale was developed based on feedback. The back-translation obtained from a third-party translation company was reviewed by the MDS Translation Steering Committee, and the translation was then provisionally approved for Cognitive Pre-testing.
- 2) *Cognitive pre-testing:* This is a qualitative approach for assessing instrument completion regarding task difficulty for examiner and respondent, and

respondent interest, attention span, discomfort, and comprehension.<sup>16</sup> The provisionally approved translation was administered to 20 PD patients and 4 raters for cognitive pre-testing. This phase identifies potentially culturally sensitive or complex items.<sup>17</sup> Based on the results of the initial cognitive pretesting, other round(s) of translation, back translation and cognitive pretesting could be required. Once cognitive pretesting was completed and no further problems were noted, the final translation could be approved as "Official Working Document".

3) *Field testing*: It was conducted on a large sample of an international sample of native Spanish speakers.

4) *Statistical analyses*, including validity testing, factor and clinimetric analyses.

Data analysis: We conducted the following analyses

#### *Primary Analyses*

*Data quality* which was established after checking for missing data (acceptable, <5%).<sup>18</sup>

*Cognitive Pretesting*: Data from the respondents (raters and patients) were analyzed using a framework approach.<sup>19</sup> Areas of expressed difficulty were examined and changes to the scale were made if necessary.

*Factor Analysis*: R (Version 4.2.0) packages *lavaan* and *psych* were used to do the primary confirmatory and secondary exploratory factor analyses, respectively. We used an adjusted weighted least square (WLSMV) approach to factor estimation that minimizes the weighted sum of squared differences between observed and estimated correlation matrices not counting diagonal elements. To assist in interpretation of the factors we used an orthogonal VARIMAX rotation that constrains the factors to be uncorrelated. Any participants with missing

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values were deleted from analysis of that domain only. Thus, the sample size from domain to domain could vary. The investigators obtained participants' approval to collect the data. Data without patient names or medical record numbers were transferred to the analytic team via a secure website.

*Confirmatory factor analysis (CFA):* CFA was used to determine if the factor structure for the English language MDS-NMS<sup>20</sup> could be confirmed in data collected using the Spanish translation. We evaluated the CFA results based on the Comparative Fit Index (CFI) for only 9 of the subscales with more than 3 items.<sup>21</sup> Because two items (as in Orthostatic Hypotension and Sexual subscales) and three items (as in Apathy and Urinary subscales) lead to under-identified and saturated models, respectively, we could not obtain valid model fit results. Therefore, CFAs were conducted for each of the 10 subscales (9 domains of the MDS-NMS plus the NMF subscale) that met this requirement. According to the protocol, to establish a successful translation and to designate that translation as an Official MDS translation of the MDS-NMS, we required that the CFI for each eligible subscale of the translated MDS- NMS be 0.90 or greater relative to the English language version. Mean and variance adjusted weighted least square (WLSMV) estimator was used to confirm model fit.

### Secondary Analysis

*Exploratory Factor Analysis (EFA):* We conducted EFA for each of the subscales (13 domains of the MDS-NMS plus the NMF subscale) to explore the underlying factor structure without the constraint of a pre-specified factor structure, and once the factors were chosen, an item was retained in a factor if the factor loading for that item was 0.40 or greater. We used the orthogonal VARIMAX rotation to assist the interpretation of the factors, which sets the factors to be uncorrelated.

### Tertiary Analysis

We used the IBM-SPSS v.28 for these statistical analyses. The primary variables in the study had non-normal distribution (Shapiro-Wilk Test, all  $p < 0.001$ ). To establish the homogeneity of the included PD sample, we compared the main sociodemographic and clinical characteristics using the Fisher's exact and chi-squared test for categorical variables and T-Student, ANOVA, Mann-Whitney U, and Kruskal-Wallis tests, based on the normal and non-normal distribution of the numerical variables, respectively.

Prevalence of NMS was based on scores  $\geq 1$  in each MDS-NMS item, domain, and total scale, denoting the presence of a symptom (0 = no symptom present). For comparison, the prevalence of NMS assessed with the MDS-UPDRS and WOQ-19 NMS was obtained using the same method.

Following the original English validation procedure,<sup>6</sup> we assessed the following clinimetric properties: *Acceptability*: Floor and ceiling effect (satisfactory threshold,  $\leq 15\%$ );<sup>22</sup> skewness (criterion values, from  $-1$  to  $+1$ );<sup>23</sup> and range of observed versus theoretical values; *Internal consistency*: For each domain (1) interitem correlation (standard values,  $0.20-0.75$ );<sup>24</sup> (2) item homogeneity coefficient calculated as the average corrected item-total interitem correlation by domain (standard,  $0.15$  for broad domains);<sup>25</sup> (3) corrected item-total correlation (standard,  $\geq 0.40$ );<sup>18</sup> and (4) Cronbach's  $\alpha$  (standard,  $\geq 0.70$ );<sup>22</sup> *Hypotheses testing*: For convergent validity, we hypothesized that MDS-NMS domains would be highly associated (Spearman rank correlation coefficient value,  $r_s > 0.50$ ),<sup>26</sup> with corresponding components of the MDS-UPDRS part 1, and NMF subscale with the WOQ-19NMS, and moderate or weak correlation ( $r_s = 0.20-0.50$ ) with other PD severity measures. The known-groups validity of the

MDS-NMS and NMF was tested by determining the difference in total scores for subgroups based on sex, age, PD duration, HY, predominant hemibody affected, and LEDD. To provide similar descriptive results compared with the original validation,<sup>6</sup> we stratified the population in similar tertiles.

## Results

### Sample characteristics:

We included 364 PD patients, 160 (44%) from Spain and 204 from North, Central, and South America (56%). Centers provided between 5 and 45 cases to the study cohort. When the PD sample from Spain was compared to the American PD sample, no significant differences were found in terms of age ( $p=0.39$ ), PD duration ( $p=0.11$ ), education ( $p=0.84$ ), and gender ( $p=0.52$ ), except for higher HY stage in the American PD sample ( $p<0.001$ ).

Sociodemographic and clinical characteristics are detailed in Table 1.

### Cognitive Pretesting

The responses from the 20 patients and 4 raters (samples of 5 patients and 1 rater each from Argentina, Mexico, Spain, and the United States) were collated and subjected to framework analyses identifying common themes and concerns. No major concerns or problems were identified, and the final translation was designated an Official Working Document and approved for use in the validation phase.

### Primary Analyses

*Data quality:* Fully computable data were available in 349 subjects (96%) for all domains of the MDS-NMS, one subject (0.3%) had missing data in the depression domain, one subject (0.3%) had missing data in the impulsive control and related disorders, cognition, and orthostatic hypotension domains, three subjects (0.8%)

in the urinary and sexual dysfunction domains, and three subjects (0.8%) in the sleep and wakefulness, pain and other domains, respectively.

*Factor analysis:* Supplemental Table 1 displays the CFA results for each of the 10 eligible subscales (9 domains of the MDS-NMS plus the NMF subscale). All 10 subscales of the Spanish MDS-NMS satisfied our pre-specified criterion of Comparative Fit Index  $\geq 0.90$  in comparison with the English-language factor structure.

### Secondary Analyses

*Exploratory Factor Analysis:* The results of the EFA displaying the factor structures for results for all domains of the MDS-NMS and the NMF subscale are included in the Supplemental Table 2 and Figure 1.

### Tertiary Analyses:

*Data Acceptability:* The MDS-NMS total scores showed no significant floor and ceiling effects (0.50%, 0.30%, respectively), but the NMF showed a floor effect (42.90%) and adequate ceiling effect (0.30%) (Table 2). There were no ceiling effects for individual domains, but floor effects ranged from a low of 8.00% (sleep and wakefulness) to a high of 78.10% (impulse control disorders and related disorders), in line with results from the validation sample. As a whole, there was a positive skewness that was higher than the standard, mirroring the floor effect.

*Internal consistency:* These results are shown in Table 3. Some items of the MDS-NMS and in the NMF subscale had an interitem (within domain) and corrected item-total correlation coefficient less than the 0.20 standard value, but the item homogeneity coefficient was more than the 0.15 threshold value for all domains.

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*Hypothesis testing: Convergent Validity:* MDS-NMS domains correlated 0.34-0.77 with the corresponding MDS-UPDRS items, and NMF subscales 0.32-0.50 with the corresponding WOQ-19 NMS items (Table 4). The correlation between the MDS-NMS and NMF total scores with the MDS-part 1-4 ranged from 0.26 to 0.80, and 0.21 to 0.59, respectively. With the WOQ-19 NMS and MS, correlations with MDS-NMS were 0.42, and 0.33, and with the NMF: 0.54 and 0.18, respectively (Table 5); *Know-Groups Validity:* Using the MDS-NMS, 99.5% of the sample showed at least one NMS, compared to the 90.9% with the MDS-UPDRS part I. The MDS-NMF identified 57.1% of the sample with NMF, and 59.1% with the WOQ-19.

The total MDS-NMS and NMF subscale scores showed no significant differences between subgroups defined by age, predominantly affected PD hemibody, and gender for NMF scores. However, MDS-NMS and NMF scores increased significantly in females, with increasing HY stage, PD duration, and LEDD (Supplemental Table 3). Likewise, in terms of severity, after adjusting for multiple comparisons, depression and anxiety domains, and total NMS, MDS-UPDRS part 1 and WOQ-19 NMS total scores were higher in females than males (Supplemental Table 4). Comparisons of prevalence for NMS domains and MDS-UPDRS items are shown in Supplemental Table 5. All NMS symptoms were captured more frequently in the MDS-NMS and NMF compared to MDS-UPDRS and WOQ-19 NMS, respectively.

### Discussion

The IPMDS has organized a worldwide program to provide official and clinimetrically validated versions of several MDS-owned rating scales. Several official non-English versions are currently in progress for the MDS-NMS, but the

Spanish MDS-NMS is the first completed program for this scale. Of note, we have addressed the various cultural differences that may be present in an international language such as Spanish. To achieve this international validation, we have achieved harmonization across the major Spanish-speaking cultures in Spain and the Americas. Based on the results of this study, the Spanish version of the MDS-NMS fulfills the clinimetric criteria to be designated as an MDS-approved Official Translation

([http://www.movementdisorders.org/publications/rating\\_scales](http://www.movementdisorders.org/publications/rating_scales)). The overall factor structure of the Spanish version was consistent with that of the English version based on the high CFIs for the 10 eligible subscales of the MDS-NMS in the confirmatory factor analysis ( $CFI \geq 0.90$ ).

We included a representative sample of patients with mild-moderate PD severity according to the HY stage. Interestingly, considering the high prevalence (99.5%) and burden of NMS (mean:  $88.07 \pm 73.47$ , range: 1-489), in addition to levodopa and other dopaminergic drugs, very few patients were receiving specific treatment for NMS, mostly antidepressants (26.90%) and anxiolytics (21.40%).

Concerning the validation aspects, the data quality was very satisfactory for all sections of the MDS-NMS and NMF, considering the existence of 52 and 8-item questionnaires, respectively, indicating the scale's excellent feasibility. In the present study, only 208 (57%) patients experienced NMF, which might explain the high floor effect on the NMF total score. Compared to the original English version of the MDS-NMS,<sup>6</sup> similar item homogeneity coefficients and Cronbach's alpha values were found, indicating a good internal consistency.

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As hypothesized, convergent validity between the MDS-NMS domains and other scales measuring similar constructs was satisfactory. The MDS-NMS identified a high prevalence of NMS and NMF in the included sample, similar to the MDS-UPDRS and WOQ-19 NMS. Due to differences between the rating scales, their components are not equivalent, showing slight differences in prevalence rates. MDS-NMS and NMF scores correlated moderately with individual MDS-UPDRS parts I, II, IV, and WOQ-19 NMS. The correlation between motor fluctuations severity observed in the MDS-UPDRS part IV with MDS-NMS and NMF, supported recent studies reporting the association of motor fluctuations with a greater increase in the NMS burden.<sup>27</sup>

The MDS-NMS domains also showed a satisfactory discriminative ability to differentiate between patients grouped according to the PD and HY staging at a point in time. In agreement with other authors, we found a higher burden of NMS in females,<sup>28, 29</sup> also with the MDS-UPDRS part I, II, and WOQ-19 NMS, indicating similar capabilities to detect gender NMS burden differences. The most affected NMS domains in females were depression and anxiety using the MDS-NMS. Of note, although not statistically significant in terms of PD motor asymmetry, we found that patients with predominant left extremities affected by PD (right brain hemisphere) had a higher NMS burden than the right one. This finding was consistent with brain asymmetry, and its association with NMS severity found in another PD cohort, suggesting increased susceptibility or awareness in the right hemisphere for NMS.<sup>30</sup>

Limitations of the study are related to potential sample selection bias as data come from specialized clinical units. However, the multicenter, international collaboration and wide sample are circumstances buffering that

bias. As per exclusion criteria excluding patients with significant cognitive impairment, the sample distribution showed a predominance of patients with mild/moderate PD according to the HY stage. Finally, data about longitudinal validity and interpretability were not available.

On the other hand, the benefits of translating and validating the MDS-UPDRS into Spanish will include the possibility of reaching millions of individuals worldwide, including healthcare professionals and PD patients. Approximately 21 countries worldwide speak Spanish as their official language, and Spanish is spoken by more than 492 million individuals worldwide.<sup>31</sup> This validation will also unify PD clinical assessments, eventually improving patient outcomes. Its availability now allows for large clinical trials that use the MDS-NMS as a pivotal outcome to include study sites, investigators, and patients from these countries when new treatment protocols emerge.

In conclusion, the cross-cultural adaptation of the scale and the confirmation that the MDS-NMS Spanish version is structurally equivalent to the original English measure is relevant for future transnational studies enrolling patients from Spanish-speaking countries.

### **Acknowledgments**

The authors acknowledge grant support from the International Parkinson and Movement Disorder Society to plan, develop, and validate the Spanish version of the MDS-NMS in an international study.

**Conflict of Interest:** Nothing to report.

**Study Funding:** Grant support from the International Parkinson and Movement Disorder Society.

### **Financial Disclosures for the previous 12 months**

E. Cubo: has received honoraria for educational presentations and advice service by Abbvie, Italfarmaco and grants from the Spanish Ministry of Economy and Competitiveness [PI19/0964], the Fundación "la Caixa" and Fundación "Caja de Burgos" (Course 2019/2020), Horizon 2020: Multi-Domain Lifestyle Targets for Improving ProgNOsis in Huntington's Disease. DOMINO-HD. Horizon 2020.

S.L.: Consulting and Advisory Board Membership with honoraria: National Institutes of Health, CHDI Management, Inc. Grants and Research: National Institutes of Health, CHDI, International Parkinson and Movement Disorder Society, Parkinson's Foundation. Honoraria: St. Jude Children's Hospital. Intellectual Property Rights: None. Ownership Interests: None. Royalties: None. Expert Testimony: None. Salary: Duke University.

P.Martinez-Martin: has received honoraria from the International Parkinson and Movement Disorder Society (MDS) for management of the Clinical Outcome Assessments Program.

G.T.Stebbins. received honoraria for consulting and advisory board membership with Acadia Pharmaceuticals, Adamas Pharmaceuticals Inc., Biogen Inc., Ceregene Inc., CHDI Management Inc., Cleveland Clinic Foundation, Ingenix Pharmaceutical Services (i3 Research), MedGenesis Therapeutix Inc., Neurocrine Biosciences Inc., Pfizer Inc., Tools-4-Patients, Ultragenyx Inc., and Sunshine Care Foundation. He also received honoraria from the International Parkinson and Movement Disorder Society, American Academy of Neurology, Michael J. Fox Foundation for Parkinson's Research, Food and Drug Administration, National Institutes of Health, Alzheimer's Association. He also received grants and research from National Institutes of Health, Department of Defense, Michael J. Fox Foundation for Parkinson's Research, Dystonia Coalition, CHDI, Cleveland Clinic Foundation, International Parkinson and Movement Disorder Society, CBD Solution

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P. Mir: has received support for attending meetings and/or travel or honorarium for lecturing from Abbott, Allergan, Abbvie. Bial, Britannia, Italfarmaco, Merz, UCB, Teva and Zambon and has received grants from Spanish Ministry of Science and Innovation [RTC2019-007150- 1], the Instituto de Salud Carlos III-Fondo Europeo de Desarrollo Regional (ISCIII-FEDER) [PI19/01576], the Consejería de Salud y Bienestar Social de la Junta de Andalucía [PE-0210-2018] and the Consejería de Transformación Económica, Industria, Conocimiento y Universidades de la Junta de Andalucía [PY20\_00903].

D. Santos-Garcia: has received honoraria for educational presentations and advice service by Abbvie, UCB Pharma, Lundbeck, KRKA, Zambon, Bial, Italfarmaco, Teva, Archímedes, Esteve, Stada, Merz, and grants from the Spanish Ministry of Economy and Competitiveness [PI16/01575] co-founded by ISCIII (Concesión de subvenciones de Proyectos de Investigación en Salud de la convocatoria 2020 de la Acción Estratégica en Salud 2017-2020 por el proyecto "PROGRESIÓN NO MOTORA E IMPACTO EN LA CALIDAD DE VIDA EN LA ENFERMEDAD DE PARKINSON").

M.RV: has received honoraria from Boston Scientific, Ever Neuropharma, Abbot, Ferrer, Silanes and Dumont.

M. Dueñas M: no disclosures

C. Singer: has received grants from Sunovion, Revance, Pharma2B, Amneal and Adamas. He has received honoraria from the Movement Disorders Society.

### **Ethical Compliance Statement**

Each site obtained its IRB approval separately. All participants provided informed consent to the study. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines

**Appendix****Spanish & American team participants**

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### **Author roles**

1. Research project: A. Conception; B. Organization; C. Execution.
2. Analysis: A. Design; B. Execution; C. Review and Critique.
3. Manuscript Preparation: A. Writing of the first draft; B. Review and Critique.

EC: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B.

SL: 1A, 1B, 2A, 2B, 2C, 3B

PMM: 1A, 1B, 2A, 2B, 2C, 3B

GS: 1A, 1B, 2A, 2B, 2C, 3B

JL: 2B, 2C, 2C, 3B.

DC: 2B, 2C, 2C, 3B.

AGB: 1C, 3B

PM:1C, 3B

DSG: 1C, 3B

MS: 1C, 3B

MRV:1C, 3B

CS: 1B, 3C

## References

1. Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, Chaudhuri KR, Group NV. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. *Mov Disord* 2011;26:399-406.
2. Santos-Garcia D, de la Fuente-Fernandez R. Impact of non-motor symptoms on health-related and perceived quality of life in Parkinson's disease. *J Neurol Sci* 2013;332:136-140.
3. Santos Garcia D, De Deus Fonticoba T, Paz Gonzalez JM, et al. Staging Parkinson's Disease Combining Motor and Nonmotor Symptoms Correlates with Disability and Quality of Life. *Parkinsons Dis* 2021;2021:8871549.
4. Martinez-Martin P, Ray Chaudhuri K. Comprehensive grading of Parkinson's disease using motor and non-motor assessments: addressing a key unmet need. *Expert Rev Neurother* 2018;18:41-50.
5. Martinez-Martin P, Schrag A, Weintraub D, et al. Pilot Study of the International Parkinson and Movement Disorder Society-sponsored Non-motor Rating Scale (MDS-NMS). *Mov Disord Clin Pract* 2019;6:227-234.
6. Chaudhuri KR, Schrag A, Weintraub D, et al. The movement disorder society nonmotor rating scale: Initial validation study. *Mov Disord* 2020;35:116-133.
7. Goetz CG, Nutt JG, Stebbins GT. The Unified Dyskinesia Rating Scale: presentation and clinimetric profile. *Mov Disord* 2008;23:2398-2403.
8. Goetz CG, Stebbins GT, Wang L, LaPelle NR, Luo S, Tilley BC. IPMDS-Sponsored Scale Translation Program: Process, Format, and Clinimetric Testing Plan for the MDS-UPDRS and UDysRS. *Mov Disord Clin Pract* 2014;1:97-101.
9. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1988;51:745-752.
10. Dalrymple-Alford JC, MacAskill MR, Nakas CT, et al. The MoCA: well-suited screen for cognitive impairment in Parkinson disease. *Neurology* 2010;75:1717-1725.
11. Grimes DA, Hubacher D, Nanda K, Schulz KF, Moher D, Altman DG. The Good Clinical Practice guideline: a bronze standard for clinical research. *Lancet* 2005;366:172-174.
12. Gorsuch (Gorsuch, R. L. (1983). *Factor analysis* (2nd ed.). Hillsdale, NJ: Erlbaum.
13. Schade S, Mollenhauer B, Trenkwalder C. Levodopa Equivalent Dose Conversion Factors: An Updated Proposal Including Opicapone and Safinamide. *Mov Disord Clin Pract*. 2020 Mar 16;7:343-345.
14. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord* 2008;23:2129-2170.
15. Stocchi F, Antonini A, Barone P, et al. Early DEtection of wEaring off in Parkinson disease: the DEEP study. *Parkinsonism Relat Disord* 2014;20:204-211.
16. Fowler FJ. (1995). *Improving Survey Questions: Design and Evaluation*. Applied Social Research Methods Series: 38. Thousand Oaks: Sage.
17. Fowler FJ. *Improving survey questions: design and evaluation*: Thousand Oaks, CA: Sage Publications, 1995.
18. Smith SC, Lamping DL, Banerjee S, et al. Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology. *Health Technol Assess* 2005;9:1-93, iii-iv.
19. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Med Res Methodol* 2013;13:117.

20. Martinez-Martin P, Rojo-Abuin JM, Weintraub D, et al. Factor Analysis and Clustering of the Movement Disorder Society-Non-Motor Rating Scale. *Mov Disord* 2020;35:969-975.
21. Gorsuch R. Factor analysis. Second edition. Hillsdale, NJ: Lawrence Erlbaum Associations, Inc., 1983.
22. McHorney CA, Tarlov AR. Individual-patient monitoring in clinical practice: are available health status surveys adequate? *Qual Life Res* 1995;4:293-307.
23. Hays RD, Anderson R, Revicki D. Psychometric considerations in evaluating health-related quality of life measures. *Qual Life Res* 1993;2:441-449.
24. RL P Inter-item correlations In: Michalos AC. *Encyclopedia of Quality of Life and Well-Being Research*. Dordrecht: Springer Netherlands; 2014.
25. Clark LA, Watson D. Constructing validity: Basic issues in objective scale development. *Psychol Assess* 1995;7(3):309-319.
26. Feeny D, Farris K, Cote I, Johnson JA, Tsuyuki RT, Eng K. A cohort study found the RAND-12 and Health Utilities Index Mark 3 demonstrated construct validity in high-risk primary care patients. *J Clin Epidemiol* 2005;58:138-141.
27. Santos-Garcia D, de Deus Fonticoba T, Bartolome CC, et al. Motor Fluctuations Development Is Associated with Non-Motor Symptoms Burden Progression in Parkinson's Disease Patients: A 2-Year Follow-Up Study. *Diagnostics (Basel)* 2022;12.
28. Picillo M, Palladino R, Moccia M, et al. Gender and non motor fluctuations in Parkinson's disease: A prospective study. *Parkinsonism Relat Disord* 2016;27:89-92.
29. Rodriguez-Blazquez C, Schrag A, Rizos A, Chaudhuri KR, Martinez-Martin P, Weintraub D. Prevalence of Non-Motor Symptoms and Non-Motor Fluctuations in Parkinson's Disease Using the MDS-NMS. *Mov Disord Clin Pract* 2021;8:231-239.
30. Cubo E, Martinez-Martin P, Gonzalez-Bernal J, et al. Effects of Motor Symptom Laterality on Clinical Manifestations and Quality of Life in Parkinson's Disease. *J Parkinsons Dis* 2020;10:1611-1620.
31. <https://www.epdata.es>. Accessed at October, 16th, 2022.

**Legend for Figures and Supplemental files**

**Figure 1:** Scree plots of items A to M of the MDS-NMS.

**Supplemental files:** Supplemental Table 1: Spanish Confirmatory Factor Analysis (CFA) Supplemental Table 2: Spanish Exploratory Factor structures for subscales of MDS-NMS Supplemental Table 3: Known-Groups Validity Supplemental Table 4: NMS Severity Comparison between males and females Supplemental Table 5: NMS Prevalence Comparisons