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RESEARCH REPORT

Rasch-Built Overall Disability Scale for IgM-Associated Polyneuropathy With and Without Anti-MAG Antibodies: IgM-RODS

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ABSTRACT

Background and Aim: IgM monoclonal gammopathy-associated polyneuropathy with(out) anti-myelin associated glycoprotein (±anti-MAG) is a rare immune-mediated disease that may cause severe limitations in daily activities and quality of life. The absence of a systematic comparison between patients with/without anti-MAG IgM polyneuropathy, no disease-specific functional metric, and lack of international consensus regarding assessment and treatment of these patients are factors obstructing future clinical trials. Therefore, it was decided to develop an interval Rasch-built activity/participation scale specifically for IgM polyneuropathy ±anti-MAG (IgM-RODS) and examine its clinimetric properties.

Methods: A pre-phase IgM-RODS questionnaire containing 146 activity/participation items, based on the WHO International Classification of Functioning, Disability and Health, was completed by participants (≥18 years) of the IMAGiNe observational registry that fulfilled international criteria for IgM-polyneuropathy ±anti-MAG. Data was subjected to Rasch analyses, and reliability/validity studies were performed as well.

Results: The pre-RODS data of 259 subjects (originating from 8 different countries) underwent quality assessment, and 244 remaining records were submitted to the Rasch model, evidencing the model's expectations. Based on requirements like exceeding fit residuals, misfit statistics, item bias, local dependency, and less face validity, we systematically removed items until the final 36-item IgM-RODS fulfilled all Rasch requirements and showed acceptable test–retest reliability, cross-cultural, construct and discriminant validity, and unidimensionality. Compared to the Inflammatory-RODS, the IgM-RODS showed lower standard errors across the metric, indicating greater sensitivity.

Interpretation: The 36-item IgM-RODS is a disease-specific interval measure suitable for detecting functional deficits in patients with IgM-polyneuropathy ±anti-MAG. Future studies are needed to determine its responsiveness.

Tatiana Hamadeh and Johannes P. M. van de Mortel contributed equally to this study.

The members of IMAGiNe Consortium are listed in Appendix A.

1 | Introduction

IgM monoclonal gammopathy-associated polyneuropathy (hereon referred to as IgM-associated polyneuropathy) is a rare, heterogeneous, and generally indolent disease that, despite a slow clinical course, causes limitations in daily activities and quality of life [1–3]. Approximately 30%–60% of peripheral neuropathies associated with gammopathies are IgM-related [4–6]. Anti-MAG (myelin-associated glycoprotein) antibody titers have been documented in about half of patients with IgM-associated polyneuropathy, and this coexistence has been suggested to contribute to the pathophysiological mechanism in typical clinical cases [7–10]. Although the disability rate and functional consequences could be similar between IgM-associated polyneuropathy patients with (+) anti-MAG versus those without (−), a systematic functional comparison in a large cohort of subgroups is lacking.

Assessing the natural disease progression and the effect of treatment has proven to be difficult, and previous ENMC workshops on outcome measures in immune-mediated neuropathies have largely failed to create an agreed upon core set of scientifically valid metrics tailored for patients with IgM-associated polyneuropathy [11–14]. Therefore, it is not surprising that the limited trials conducted for this debilitating illness have yielded negative results, leaving no proven treatment for the condition and raising more questions that need to be resolved before pursuing new treatment attempts [15]. The repeated use of suboptimal outcome measures, the slow disease course needing a longer follow-up period to capture relevant changes, and/or the possibility that the administered treatments were not aggressive enough have all been suggested as potential factors contributing to the negative results in clinical trials [14]. Moreover, international consensus on how to assess and treat patients with IgM-associated polyneuropathy is lacking. This highlights the critical need for the development of a new disease-specific functional metric at the interval level. It is imperative that forthcoming clinical trials for new upcoming drugs conscientiously select transformed and valid interval-level metrics to safeguard any subsequent parametric analyses from false positive/negative outcomes [1, 16].

The IgM ± anti-MAG peripheral neuropathy (IMAGiNe) consortium is an international collaborative effort of neurologists, patient representatives, and hematologists/oncologists dedicated to continuing the observational prospective registry established since 2017. The primary objectives are to establish new methods to improve diagnosis, disease classification, investigate the role of anti-MAG, identify potential biomarkers, and optimize treatment regimes [17]. The IMAGiNe study strives to lay the foundation for future clinical trials through the development of novel, functional, and more sensitive disease-specific patient-reported outcome measures.

The primary objective of the current paper is to present the development of a Rasch-built overall disability scale (RODS) specifically designed for patients with IgM-associated polyneuropathy with and without anti-MAG (±anti-MAG) antibodies, and to examine its validity and reliability [18, 19]. Using Rasch analyses on the IMAGiNe data will determine whether the subgroups of patients with versus without anti-MAG antibodies exhibit systematic differences in behaviors when completing the questionnaire. These findings would suggest differing rates of functional decline or variations in the severity of functional impairments between the subgroups [20].

2 | Materials and Methods

2.1 | Patients' Eligibility and Ethical Approval

The IMAGiNe consortium comprises researchers in the field of neuromuscular disorders from 21 hospitals in 10 countries (the Netherlands, Belgium, France, Spain, Italy, United Kingdom, United States, Brazil, Denmark, Serbia). A total of 259 unrelated patients with IgM-associated polyneuropathy ± anti-MAG were recruited between December 2015 and April 2023 to participate in the IMAGiNe observational study. Eligibility was based on the following criteria: age 18 years and older, fulfilling the published international criteria for IgM monoclonal gammopathy associated polyneuropathy, with or without anti-MAG antibodies [21–23]. Participants were newly or previously diagnosed patients, with and without treatment. Exclusion was primarily based on concomitant diseases or medication possibly interfering with assessments. Participants with an active malignancy or undergoing treatment aside from IgM-associated polyneuropathy were excluded. For reliability studies, we examined a total of $n = 60$ random patients that completed a T1 assessment after 2–4 weeks of inclusion, fulfilling the minimum requirements for reliability studies as previously documented [24]. The Medical Ethical Committee of all participating centers approved the study protocol. All patients provided written informed consent [17].

2.2 | Questionnaire Development

As previously reported, published standardized requirements for scale development were applied to create the IgM-RODS disease-specific activity and participation scale [19, 25]. In brief, eligible patients were requested to complete a list of previously selected and reported pre-phase (pre-RODS) 146 activity and participation items [25], scoring each item as (0) unable to perform, (1) able to perform, but with difficulty, or (2) easily performed, without difficulty. An item was scored (3) if it was not applicable to the patient. The 146 items were previously translated by each participating site according to the international standards [19]. For the United States, distances were converted into miles, and weight references were converted into pounds.

2.3 | Additional Outcome Measure for Validity Purposes

From the data collected, the previously 24-item Inflammatory-RODS (I-RODS) was extracted for construct validity and sensitivity studies of the IgM-RODS [25]. The Rasch-built I-RODS was developed to assess activity and participation in patients having Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and IgM-associated polyneuropathy [13]. However, it has been suggested that the IgM-RODS is not sensitive enough to capture the slow disease course in patients

with IgM-associated polyneuropathy, since its responsiveness scores were low in these patients (only 20% over 12 months follow-up) [13].

Two additional discriminant validity studies were performed: (i) It was hypothesized that the IgM-RODS scores would be substantially higher (=functionally better) in patients with no tremor versus those having tremor, and (ii) since IgM-associated polyneuropathy presents itself mainly with sensory impairments, we decided to examine various sensory qualities (pin prick, light touch, vibration sense using the Rydel-Seiffer tuning fork, and 2-point discrimination test at the index fingers) as part of the INCAT sensory sumscore (ISS) using reported normative values on the tuning fork and two-point discrimination tests [26–28]. The hypothesis was that subjects with more sensory deficit would have lower IgM-RODS scores (Note: The higher sensory deficit, the higher the score on the ISS). Finally, to improve the discriminant validity assessment, we decided to transform the ISS through Rasch technique into a linear metric.

2.4 | Assessment Procedure

Standardized instructions were given verbally and in writing to patients before completion of the pre-phase IgM-RODS questionnaire. In case of any doubt completing an item/task, the patient was requested to choose the answer as close as possible to their ability to complete such a task. Patients were instructed to choose "not applicable" only in cases when the patient had serious difficulty determining any of the other options related to the item of interest. Not applicable scores were transformed to "missing" values for modeling.

2.5 | Rasch Analyses and Statistical Aspects

2.5.1 | Rasch Description

The pre-phase IgM-RODS was subjected to the Rasch Unidimensional Measurement Model (RUMM2030). We examined whether model expectations would be met [29, 30]. There are various educational papers explaining in a simplistic way the Rasch methodology [20, 31]. In brief, the model allows us to evaluate the clinimetric properties of outcome measures (e.g., questionnaires, tests, etc.) by assessing whether the tool in question fulfills the model's requirements. The Rasch requirements include (1) proper fit of the statistical parameters within the reported values, (2) absence of differential item functioning (DIF) to exclude possible confounding factors, (3) evidence of ordered thresholds indicating that the item responses function equally, (4) lack of evidence of local dependency between items [32], and (5) unidimensionality. The latter is the statistical proof that the tool assessed is not measuring other confounding variables instead of the one intended. Meeting the Rasch model requirements transforms the outcome measure into an interval-level tool, enabling a precise assessment of individuals in clinical and trial settings, and generating scores that can be reliably used in parametric analyses [20].

In this paper, we describe the Rasch analysis conducted to construct a disease-specific and interval-level scale for IgM-associated polyneuropathy with or without anti-MAG (IgM-RODS) that meets all Rasch model requirements [31, 33]. The following person factors were introduced for the purposes of the current study: sex (male vs. female), age categories (≤ 70 vs. 71 to ≤ 79 vs. 80+ years), anti-MAG presence (positive vs. negative vs. unknown), country categories (USA/UK vs. the Netherlands vs. miscellaneous [remaining countries]). To ensure model stability, age and country categories were chosen and subdivided to guarantee a minimum of 50 records in each subgroup. Due to the wide variation in the number of patients per center, ranging from 8 to 103, countries were grouped accordingly to maintain subgroups of approximately equal or acceptable sizes.

2.5.2 | Reliability, Validity Studies, and Sensitivity Analyses of IgM-RODS

Reliability of the final IgM-RODS was examined by determining the Person Separation Index (PSI) that should be ≥ 0.7, but preferably > 0.9 for clinically proper discriminatory ability [33]. Test–retest studies for items' and patients' locations on the final IgM-RODS were also determined using quantile regression studies between the T0 (entry) and T1 (2–4 weeks later) recruited data. Construct convergent validity of the final IgM-RODS scale was determined through correlation studies with the extracted I-RODS (quantile regression studies). The corresponding standard errors (SEs) across the locations of the patients on the IgM-RODS versus I-RODS were compared to determine which of the two metrics was more sensitive. Lower SEs would indicate a higher sensitivity thereby permitting a smaller sample size for a trial design [34, 35]. We aimed to obtain cross-cultural validity for the IgM-RODS by examining item bias on the person factor "country categories" (an absence of item bias on "country categories" would demonstrate cross-cultural validity) [36, 37]. Finally, to assess discriminant validity of the IgM-RODS, we investigated whether lower scores on the IgM-RODS correlated with the presence of tremor or with high sensory deficit on the ISS (Student's *t* test). Analyses were undertaken using Stata for Windows XP (Version 13.0; StataCorp, College Station, TX).

3 | Results

3.1 | Study Population and Data Quality Control

A total of 259 patients (Denmark: 31, France: 21, Italy: 19, the Netherlands: 103, Serbia: 8, Spain: 24, United Kingdom: 24, and United States: 29) who were initially recruited through the IMAGiNe registry were eligible for this analysis. However, the records of 15 patients were omitted through data quality control (based on $> 10\%$ missing of scores on the pre-RODS items), thus leaving 244 records for Rasch analyses. No items had to be omitted. The basic characteristics of the 244 selected patients with IgM-associated polyneuropathy with/without anti-MAG are presented in Table 1. Tremor was present in 52.1% of the patients, of which 31% were anti-MAG positive, 60% were anti-MAG negative, and 9% were unknown. In the tremor-negative subgroup, 26% of the patients were anti-MAG positive. Detailed clinical descriptions of the cohort are outside the scope of this paper and will be described in a clinical paper separately.

TABLE 1 | General characteristics of eligible patients with IgM polyneuropathy.

Number of patients	*n* = 244
Age (years), mean (SD), range	73 (8.9), 45–93
Gender, *n* (%)	
Female	65 (26.6)
Male	179 (73.4)
Anti-MAG present, *n* (%)	
Yes	138 (56.6)
No	60 (24.6)
Unknown	46 (18.9)
Country, *n* (%)	
Netherlands	96 (39.3)
Denmark	30 (12.3)
United States	26 (10.7)
United Kingdom	24 (9.8)
Spain	23 (9.4)
France	20 (8.2)
Italy	17 (7.0)
Serbia	8 (3.3)
Person factor age category (years) for Rasch analyses, *n* (%)	
≤ 70	77 (31.6)
71–79	112 (45.9)
80 years plus	55 (22.5)
Person factor country category for Rasch analyses, *n* (%)	
English-Americans (United States/ United Kingdom)	50 (20.5)
Netherlands	96 (39.3)
Miscellaneous (Serbia, Spain, Italy, Denmark, France)	98 (40.2)

3.2 | Initial Rasch Analyses on the Pre-Phase IGM-RODS

The pre-phase 146 items IgM-RODS scale did not meet Rasch model requirements. The item's fit residual statistics (mean: −0.456, SD: 1.308), person's fit residual (mean: −0.349, SD: 1.556) and item-trait interaction ($\chi 2$ probability [$p < 0.00001$]; degrees of freedom [DF] 438) showed deviation from model expectations, thus demonstrating no invariance of item difficulty across the scale. In addition, a proportion of 0.197 (95% CI: 0.169–0.224) of the *t* tests fell outside the ±1.96 range, indicating multidimensionality.

3.3 | Data Handling of the Pre-Phase IgM-RODS to Fit Rasch Modeling

Throughout the analyses, we continuously monitored the class intervals to ensure their stability.

Step 1: Two items demonstrated disordered thresholds (able to drive a car, able to search for a job) and were removed ($n = 144$ items remaining).

Step 2: A total of 12 items demonstrated misfit statistics and/or fit residuals exceeding ±2.5 and were removed one by one (132 items remaining).

Step 3: Seven items demonstrated DIF and were evaluated and removed stepwise (125 items remaining). Four items demonstrated uniform DIF on sex and three on country category (examples in Figure 1). No DIF was seen on person factor "anti-MAG" indicating no difference in functional behavior between the subgroups (anti-MAG positive, negative, and unknown subgroups behaving similarly). Eventually, the final IgM-RODS achieved cross-cultural validity by demonstrating no item bias on the person factor "country category". No items had nonuniform DIF.

Step 4: Local dependency between items was examined by identifying correlations amongst their residuals. A large number of items demonstrated local response dependency. All item sets with residual correlations above 0.20 were evaluated starting with the highest correlations (> 0.7, > 0.6, ... up to > 0.20). Of

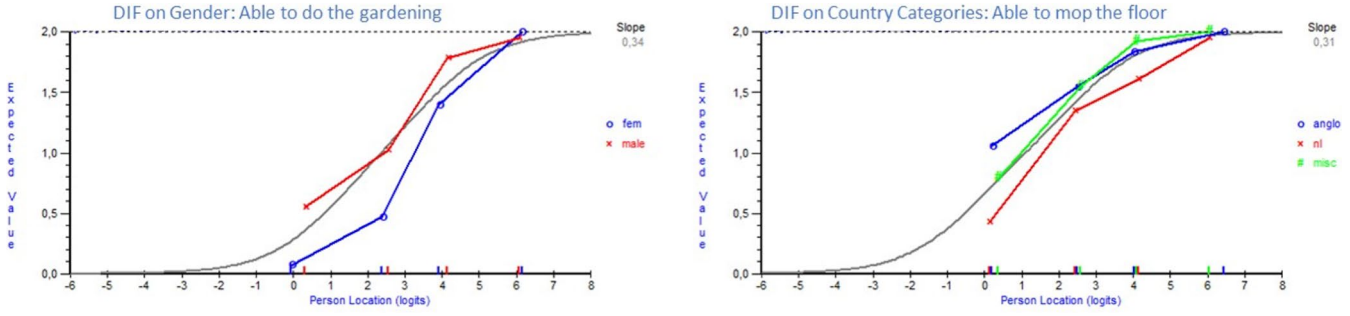

FIGURE 1 | Examples of items showing uniform item bias. ICC = item characteristic curve (gray S-shaped line). The left picture shows how differential item functioning (DIF) puts the female group (blue line) to the right (more difficult to perform) side of the ICC curve, and the male group (red line) to the left (more easily performed) side regarding gardening. The right graph demonstrated Dutch patients having more difficulty to mop the floor compared to the other two country categories.

TABLE 2 | Summary of Rasch analyses statistics for IgM-RODS construction.

	Item fit residuals		Person fit residuals		Item-trait chi-square interaction			Unidimensionality, independent *t* test (95% CI)
Analyses	**Mean**	**SD**	**Mean**	**SD**	**DF**	***p***	**PSI**	
1st	−0.456	1.308	−0.349	1.556	438	< 0.00001	0.98	0.197 (0.169–0.224)
28th	−0.380	0.893	−0.314	1.005	165	0.003	0.97	0.176 (0.149–0.204)
Final	−0.328	0.857	−0.244	0.809	108	0.535	0.96	0.066 (0.038–0.093)

Note: In the final analysis, item and person fit residuals are acceptable, whereas χ^2 is nonsignificant, indicating invariance across the trait. A PSI of 0.96 indicates a reliable internal consistency.
Abbreviations: DF = degrees of freedom, PSI = Person Separation Index, SD = standard deviation.

each item set, the item showing less clinical relevance (less face validity based on opinion of experts [ISJM/CGF]) and/or with the most over- or under-discrimination on its category probability curve and/or with the worst contribution to the continuum on the person-item threshold distribution map was removed. Eventually, a total of 85 items were removed one by one (40 items remaining).

Step 5: There was a gradual improvement in fit statistics for the items and persons, but the chi-square item-trait remained significant (Table 2). For further model improvement and final fit, two additional steps were taken: (i) Three items were deleted based on insufficient face validity (e.g., change a light bulb; 37 items remaining), and (ii) the *p* value for the fit statistics was lowered to $p = 0.01$, enabling the removal of 1 additional item (36 items remaining). The final 36 items met all Rasch model expectations (item fit residuals: mean −0.328, SD 0.857; person fit residuals: mean −0.244, SD 0.809; item-trait $\chi 2$: $p = 0.53$, DF: 108) (Table 2; Figures 2 and S1), ultimately resulting in the successful construction of the IgM-associated polyneuropathy with/without anti-MAG specific RODS (final IgM-RODS). There was only one local dependency between items "walk 3 or more flights of stairs" and "walk a flight of stairs carrying a bag" (correlation: 0.209) that were left untouched due to their location on the person-item threshold distribution graph, hence maintaining a more acceptable continuum. Acceptable unidimensionality was acquired; independent *t* tests between the two groups of items (five positively vs. five negatively loaded): 0.066 [95% CI: 0.038–0.093]). The item "able to brush your teeth" was the easiest item to perform, while "able to run" was the most difficult to accomplish (Figure 2). The item difficulty ranged from −6.110 to 5.076 (total range: 11.186) logits and patient's location ranged from −5.213 to 7.865 (total range: 13.078) logits. There was no floor effect seen; 14 patients (5.7%) had ceiling effect (maximum score). To obtain access to the scoring algorithm, as well as the associated logits and SEs of the final items, please contact the corresponding author for licensing.

3.4 | Reliability, Validity, Sensitivity Studies IgM-RODS

The IgM-RODS scale demonstrated a robust reliability score of PSI = 0.96, proving the IgM-RODS is able to discriminate between at least seven groups of patients with various degrees of ability (=degrees of disease severity) [33]. Figure 3 shows acceptable and significant test–retest reliability findings for the final IgM-RODS.

The IgM-RODS demonstrated a high correlation with the extracted I-RODS data, indicating that participants with a high IgM-RODS score consistently matched high scores in the I-RODS (construct validity studies: R^2: 0.95; Figure 4A). The SEs of the IgM-RODS were consistently lower compared with the SEs across the I-RODS measurements (Figure 4B; $p < 0.0001$). The graph shows that for any point on the disability continuum, the IgM-RODS is more sensitive than the I-RODS and assesses a broader "location" or range of abilities as well (range IgM-RODS: 13.078 logits; range I-RODS: −2.464 to 7.983 = 10.447 logits). Figure 5A shows that the IgM-RODS scores were substantially higher if tremor was absent ($p = 0.001$). Additionally, the IgM-RODS scores were higher if patients had lower ISS scores (the latter indicating having less sensory deficit, Figure 5B; *t* test: lowest vs. middle ISS tertile: $p = 0.002$; lowest vs. highest ISS tertile: $p < 0.0001$; middle vs. highest ISS tertile: $p = 0.0004$).

4 | Discussion

The current paper presents a Rasch-built activity and participation interval scale specifically designed for patients with IgM-associated polyneuropathy with or without anti-MAG antibodies (IgM-RODS) according to the objectives of the IMAGiNe study [17]. The IgM-RODS fulfilled all Rasch model expectations and demonstrated good discriminatory validity and reliability scores (Figures 3–5) with no item bias on anti-MAG presence, sex, or age groups. The anti-MAG positive vs. negative vs. unknown subgroups in our cohort did not show differences in functional behavior (DIF) since no item was consistently easier or more difficult for any of the subgroups. This suggests that anti-MAG presence most probably did not have a significant influence on item responses. However, this should be stated with some caution, since anti-MAG was unknown in nearly 20% of the patients and should be seen as a limitation of this paper.

This study demonstrates that having a sensory deficit or tremor influences functionality in a negative manner, showing lower scores on IgM-RODS (Figure 5) as has been previously reported in various neuropathies [38, 39]. The Rasch-built IgM-RODS also showed a higher level of measurement precision, bypassing known shortcomings of ordinal-based scales generally used in previous trials in IgM-associated polyneuropathy [13, 40, 41]. A

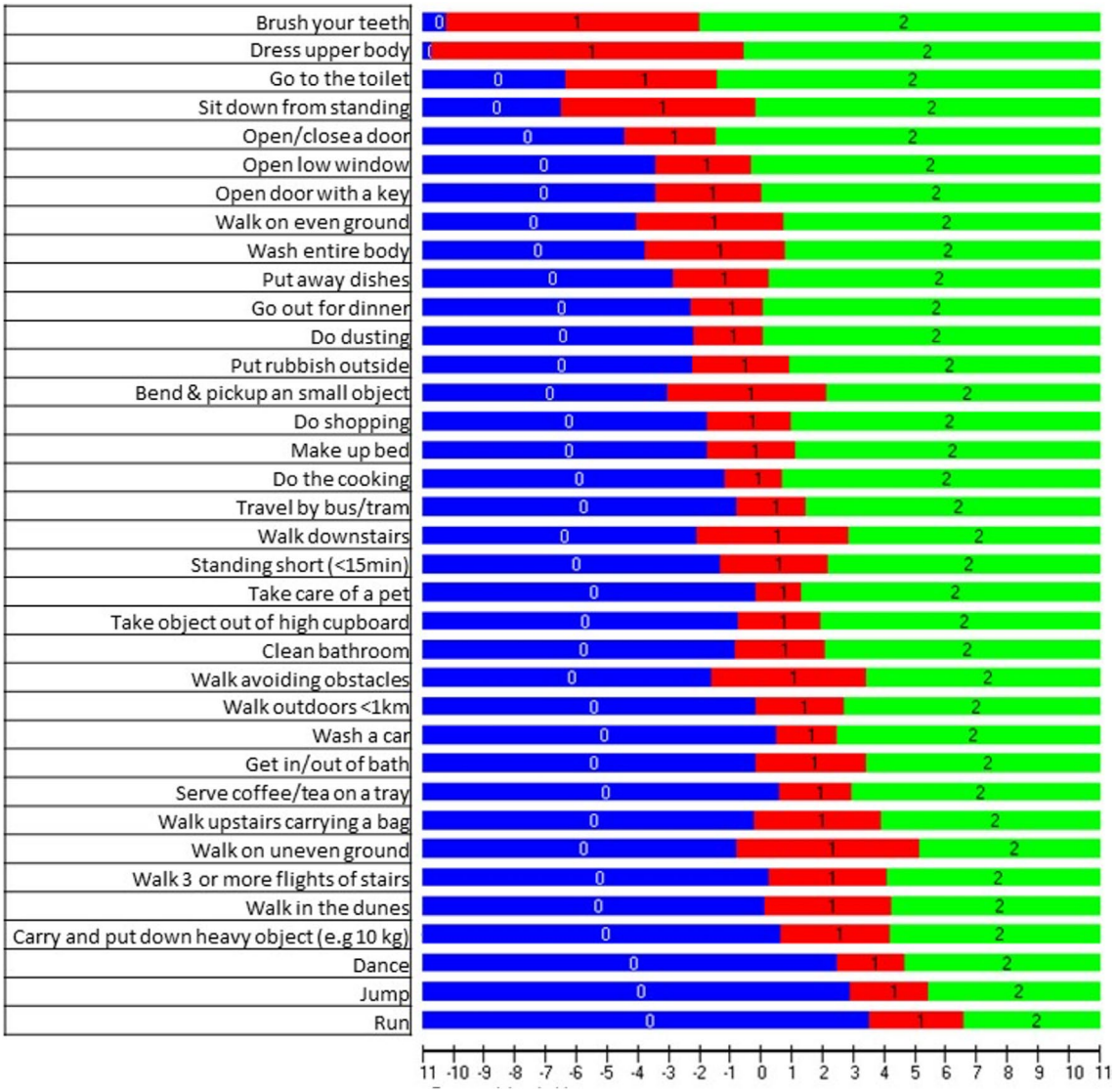

FIGURE 2 | Final threshold map of the IgM-associated polyneuropathy with/without anti-MAG specific Rasch-built overall disability $n = 36$ items scale (IgM-RODS). Threshold map of the final 36 items as part of the IgM-RODS. The map shows the expected response for each ability-related item (=degree of illness) of the patients using IgM-RODS. The blue parts correspond with a score of 0 (=unable to perform), the red parts indicate "able to perform, but with difficulty" (Score 1), and the green bars correspond with "able to perform, without difficulty" (Score 2). Zero logit (location = 0) is set as the average of item difficulty and patient's ability. This means that a patient with a mean score would be able to complete item able to cook (this item requires −0.214 logits) and would also be able to perform the easier tasks (those having a lower logit location score); conversely, this patient will have great difficulty with the more difficult tasks and will most probably fail on these. RODS: Rasch-built overall disability scale. *Note:* Standing short (< 15 min) means: Standing a short period of time, maximum 15 min. See also Figure S1.

higher level of precision (having lower SEs) also means that a smaller sample size for trials would suffice [34, 35]. In addition, the final interval measure enables a quantitative comparison of any changes throughout the scale [20].

Alongside construct validity, the final model demonstrated cross-cultural validity by showing no item bias related to the country categories. However, we acknowledge that including additional patients per country is necessary to establish a comprehensive and complete country-based cross-cultural validity [36, 37]. This, plus the evaluation of changes and behavioral patterns over time of patients with IgM-associated polyneuropathy with/without anti-MAG, is one of the main reasons that the consortium will continue recruitment until reaching at least 500 patients worldwide, each with a follow-up period of at least 3 years. The longitudinal data of this large cohort will serve future clinical trials by helping us determine the slope of deterioration in patients with a natural course as well as those showing potential clinical dynamics (improvement, deterioration, or stability) during treatment.

For future trial designs, experts in the field of IgM-associated polyneuropathy should strive to predefine how responsiveness should be assessed using the IgM-RODS [42]. Although various papers have reported an increment in disability during follow-up, a real slope calculation of deterioration in functionality as well as the determinants leading to it using an interval/ratio outcome measure is lacking [39, 43, 44]. In our view,

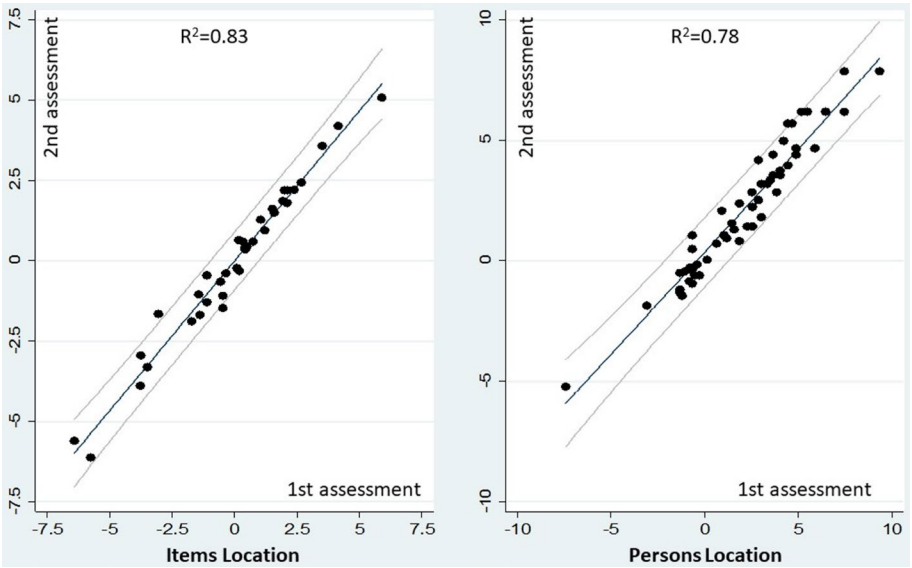

FIGURE 3 | Test–retest IgM-RODS reliability findings in $n = 60$ patients with IgM peripheral polyneuropathy. Significant test–retest ($p < 0.00001$) were seen for the items' location and persons' location through quantile regression studies (plus 95% CI).

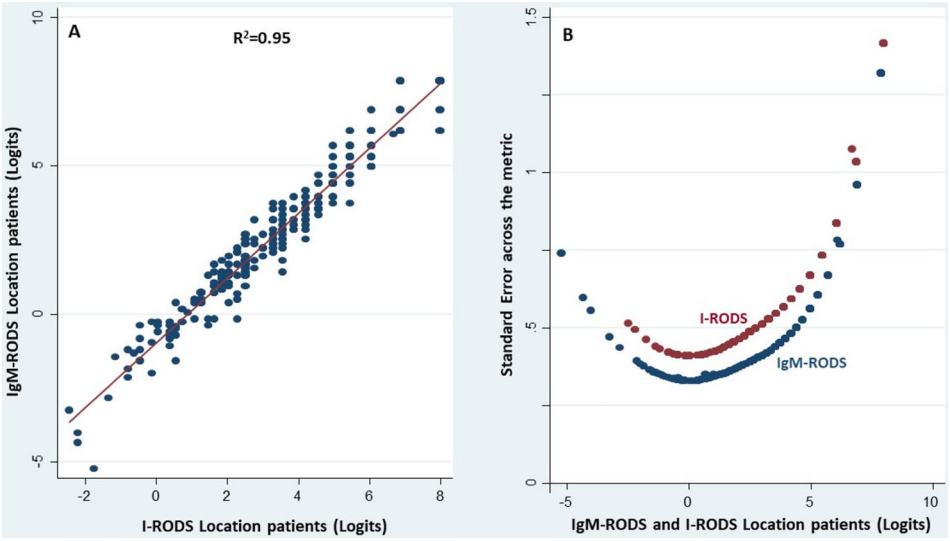

FIGURE 4 | Association between IgM-RODS and I-RODS (A) and Standard errors (SEs) comparison across the IgM-RODS and the I-RODS location (B). (A) Construct validity of the IgM-RODS demonstrated through a strong association with the I-RODS. (B) The graph shows that for any point on the disability continuum the SEs obtained with the IgM-RODS measures were consistently lower than that generated with the I-RODS (*t* test: $p < 0.0001$). In addition, the location on the IgM-RODS covers a wider than the I-RODS (range IgM-RODS: 13.078 logits; range I-RODS: 10.447 logits). RODS: Rasch-built overall disability scale.

being a responder should shift from statistical significance to clinical relevance when it comes to designing and interpreting results from clinical trials. A concept that is increasingly being used as a surrogate for clinical relevance and effect size calculation is the minimum clinically important difference (MCID) [45]. The MCID is defined as "the smallest difference in score in the domain of interest, which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive costs, a positive change in the patient's managements" [46]. Nowadays, the MCID concept is categorized into two main streams: anchor-based methods often related to patient's own judgement of their clinical state, and the distribution-based methods that are more statistically driven [47–50]. Consensus meetings involving experts and patient representatives should help refine the MCID concept to better suit the typically indolent population of patients with IgM-associated polyneuropathy. In any case, as long as no consensus is reached on which method to use, the combination of an anchor-based and a distribution-based method has been recommended, and preferably using a method that takes the SEs across a metric into account (Figure 4B) [34, 45]. The anchor-based method helps physicians to share the decision making with patients on their own health, validating whether it improved, deteriorated or remained unchanged from patients' perspective [51, 52].

In conclusion, the Rasch-built IgM-RODS presented fulfilled all Rasch model requirements, validity and reliability, thereby

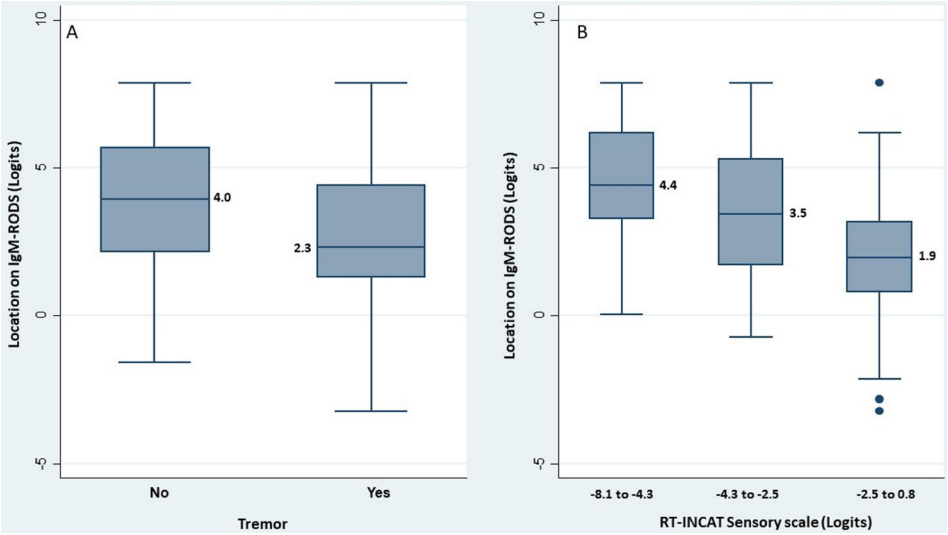

FIGURE 5 | Discriminant validity studies on IgM-RODS. (A) IgM-RODS demonstrating higher values (better functionality) in patients with no tremor versus those having tremor ($p = 0.001$). (B) IgM-RODS demonstrating higher values in patients with less sensory deficit (lowest tertile on the INCAT sensory sumscore [ISS]) [26] compared to patients with more sensory deficit (middle to highest tertiles) (*t* test: lowest vs. middle tertile: $p = 0.002$; lowest vs. highest ISS tertile: $p < 0.0001$; middle vs. highest ISS tertile: $p = 0.0004$); a low ISS score indicates less sensory deficit. *Note 1:* The ordinal ISS was transformed to a linear metric through Rasch technique before being subjected to the discriminant validity studies. *Note 2:* We intend to publish a specific more detailed clinical paper on the sensory findings in this cohort of patients IgM polyneuropathy with/without anti-MAG antibodies and therefore we suggest not to include further detailed description of the RT-ISS findings in this manuscript.

becoming the recommended tool capable of capturing activity and participation restrictions. Future studies with a larger cohort of patients are needed to strengthen cross-cultural validation. A follow-up over a longer period of time is essential to determine the responsiveness of the IgM-RODS. Experts in IgM-associated polyneuropathy, with or without anti-MAG, along with patient representatives, should convene to discuss and standardize the criteria for defining a responder in anticipation of future clinical trials evaluating new therapeutic options. The IgM-RODS is the only interval-based metric specifically designed for patients with IgM-associated polyneuropathy with/without anti-MAG. Its use is recommended in future clinical trials aiming to strengthen its clinimetric soundness.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. A. J. Steck, "Anti-MAG Neuropathy: From Biology to Clinical Management," *Journal of Neuroimmunology* 361 (2021): 577725, https://doi.org/10.1016/j.jneuroim.2021.577725.

2. B. Bardel, V. Molinier-Frenkel, F. Le Bras, et al., "Revisiting the Spectrum of IgM-Related Neuropathies in a Large Cohort of IgM Monoclonal Gammopathy," *Journal of Neurology* 269, no. 9 (2022): 4955–4960, https://doi.org/10.1007/s00415-022-11139-2.

3. M. Campagnolo, M. Ruiz, Y. M. Falzone, et al., "Limitations in Daily Activities and General Perception of Quality of Life: Long Term Follow-Up in Patients With Anti-Myelin-Glycoprotein Antibody Polyneuropathy," *Journal of the Peripheral Nervous System* 24, no. 3 (2019): 276–282, https://doi.org/10.1111/jns.12342.

4. R. A. Kyle and P. J. Dyck, "Neuropathy Associated With the Monoclonal Gammopathies," in *Peripheral Neuropathy*, ed. P. J. Dyck and P. K. Thomas (Elsevier Saunders, 2005), 2255–2276.

5. K. B. Yeung, P. K. Thomas, R. H. King, et al., "The Clinical Spectrum of Peripheral Neuropathies Associated With Benign Monoclonal IgM, IgG and IgA Paraproteinaemia. Comparative Clinical, Immunological and Nerve Biopsy Findings," *Journal of Neurology* 238, no. 7 (1991): 383–391, https://doi.org/10.1007/bf00319857.

6. R. A. Rison and S. R. Beydoun, "Paraproteinemic Neuropathy: A Practical Review," *BMC Neurology* 16 (2016): 13, https://doi.org/10.1186/s12883-016-0532-4.

7. A. J. Steck, A. K. Stalder, and S. Renaud, "Anti-Myelin-Associated Glycoprotein Neuropathy," *Current Opinion in Neurology* 19, no. 5 (2006): 458–463, https://doi.org/10.1097/01.wco.0000245368.36576.0d.

8. E. Nobile-Orazio, "Update on Neuropathies Associated With Monoclonal Gammopathy of Undetermined Significance (2008-2010),"

Journal of the Peripheral Nervous System 15, no. 4 (2010): 302–306, https://doi.org/10.1111/j.1529-8027.2010.00283.x.

9. J. S. Katz, D. S. Saperstein, G. Gronseth, A. A. Amato, and R. J. Barohn, "Distal Acquired Demyelinating Symmetric Neuropathy," *Neurology* 54, no. 3 (2000): 615–620, https://doi.org/10.1212/wnl.54.3.615.

10. J. P. M. van de Mortel, S. D'Sa, A. F. J. E. Vrancken, N. C. Notermans, J. M. I. Vos, and M. C. Minnema, "Polyneuropathy Associated With IgM Monoclonal Gammopathy; Advances in Genetics and Treatment, Focusing on Anti-MAG Antibodies," *Hema* 3, no. 4 (2022): 663–688.

11. I. S. Merkies and G. Lauria, "131st ENMC International Workshop: Selection of Outcome Measures for Peripheral Neuropathy Clinical Trials 10-12 December 2004, Naarden, the Netherlands," *Neuromuscular Disorders* 16, no. 2 (2006): 149–156, https://doi.org/10.1016/j.nmd.2005.12.003.

12. M. P. Lunn, J. M. Leger, I. S. Merkies, et al., "151st ENMC International Workshop: Inflammatory Neuropathy Consortium 13th-15th April 2007, Schiphol, the Netherlands," *Neuromuscular Disorders* 18, no. 1 (2008): 85–89, https://doi.org/10.1016/j.nmd.2007.08.004.

13. E. K. Vanhoutte, C. G. Faber, I. S. Merkies, and PeriNom Ssg, "196th ENMC International Workshop: Outcome Measures in Inflammatory Peripheral Neuropathies 8-10 February 2013, Naarden, the Netherlands," *Neuromuscular Disorders* 23, no. 11 (2013): 924–933, https://doi.org/10.1016/j.nmd.2013.06.006.

14. M. H. J. Pruppers, I. S. J. Merkies, M. P. T. Lunn, N. C. Notermans, and Group IMS, "230th ENMC International Workshop," *Neuromuscular Disorders* 27, no. 11 (2017): 1065–1072, https://doi.org/10.1016/j.nmd.2017.08.001.

15. M. H. Pruppers, I. S. Merkies, and N. C. Notermans, "Recent Advances in Outcome Measures in IgM-Anti-MAG+ Neuropathies," *Current Opinion in Neurology* 28, no. 5 (2015): 486–493, https://doi.org/10.1097/wco.0000000000000236.

16. B. Aliu, D. Demeestere, E. Seydoux, et al., "Selective Inhibition of Anti-MAG IgM Autoantibody Binding to Myelin by an Antigen-Specific Glycopolymer," *Journal of Neurochemistry* 154, no. 5 (2020): 486–501, https://doi.org/10.1111/jnc.15021.

17. T. Hamadeh, P. T. C. van Doormaal, M. H. J. Pruppers, et al., "IgM Anti-MAG(+/−) Peripheral Neuropathy (IMAGiNe) Study Protocol: An International, Observational, Prospective Registry of Patients With IgM M-Protein Peripheral Neuropathies," *Journal of the Peripheral Nervous System* 28, no. 2 (2023): 269–275, https://doi.org/10.1111/jns.12547.

18. I. S. Merkies, G. Lauria, and C. G. Faber, "Outcome Measures in Peripheral Neuropathies: Requirements Through Statements," *Current Opinion in Neurology* 25, no. 5 (2012): 556–563, https://doi.org/10.1097/WCO.0b013e328357f30f.

19. D. L. Streiner and G. L. Norman, *Health Measurement Scales. A Practical Guide to Their Development and Use*, 2nd ed. (Oxford Medical Publications. Oxford University Press, 1998).

20. E. K. Vanhoutte, M. C. E. Hermans, C. G. Faber, et al., "Rasch-Ionale for Neurologists," *Journal of the Peripheral Nervous System* 20, no. 3 (2015): 260–268, https://doi.org/10.1111/jns.12122.

21. Joint Task Force of the EFNS and the PNS, "European Federation of Neurological Societies/Peripheral Nerve Society Guideline on Management of Paraproteinemic Demyelinating Neuropathies. Report of a Joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society—First Revision," *Journal of the Peripheral Nervous System* 15, no. 3 (2010): 185–195, https://doi.org/10.1111/j.1529-8027.2010.00278.x.

22. N. Latov, "Pathogenesis and Therapy of Neuropathies Associated With Monoclonal Gammopathies," *Annals of Neurology* 37, no. 1 (1995): S32–S42, https://doi.org/10.1002/ana.410370705.

23. N. C. Notermans, H. Franssen, M. Eurelings, Y. Van der Graaf, and J. H. Wokke, "Diagnostic Criteria for Demyelinating Polyneuropathy Associated With Monoclonal Gammopathy," *Muscle & Nerve* 23, no. 1 (2000): 73–79, https://doi.org/10.1002/(sici)1097-4598(200001)23:1%3C73::aid-mus9%3E3.0.co;2-5.

24. J. C. Hobart, S. J. Cano, T. T. Warner, and A. J. Thompson, "What Sample Sizes for Reliability and Validity Studies in Neurology?," *Journal of Neurology* 259, no. 12 (2012): 2681–2694, https://doi.org/10.1007/s00415-012-6570-y.

25. S. I. van Nes, E. K. Vanhoutte, P. A. van Doorn, et al., "Rasch-Built Overall Disability Scale (R-ODS) for Immune-Mediated Peripheral Neuropathies," *Neurology* 76, no. 4 (2011): 337–345, https://doi.org/10.1212/WNL.0b013e318208824b.

26. I. S. Merkies, P. I. Schmitz, F. G. van der Meche, and P. A. van Doorn, "Psychometric Evaluation of a New Sensory Scale in Immune-Mediated Polyneuropathies. Inflammatory Neuropathy Cause and Treatment (INCAT) Group," *Neurology* 54, no. 4 (2000): 943–949, https://doi.org/10.1212/wnl.54.4.943.

27. I. S. Martina, R. van Koningsveld, P. I. Schmitz, F. G. van der Meche, and P. A. van Doorn, "Measuring Vibration Threshold With a Graduated Tuning Fork in Normal Aging and in Patients With Polyneuropathy. European Inflammatory Neuropathy Cause and Treatment (INCAT) Group," *Journal of Neurology, Neurosurgery, and Psychiatry* 65, no. 5 (1998): 743–747, https://doi.org/10.1136/jnnp.65.5.743.

28. S. I. van Nes, C. G. Faber, R. M. Hamers, et al., "Revising Two-Point Discrimination Assessment in Normal Aging and in Patients With Polyneuropathies," *Journal of Neurology, Neurosurgery, and Psychiatry* 79, no. 7 (2008): 832–834, https://doi.org/10.1136/jnnp.2007.139220.

29. D. Andrich, B. Sheridan, and G. Luo, *Rasch Models for Measurement: RUMM2030* (RUMM Laboratory Pty Ltd., 2010).

30. G. Rasch and Probabilistic Models for Some Intelligence and Attainment Tests, *Copenhagen* (Danish Institute for Educational Research, 1960).

31. J. F. Pallant and A. Tennant, "An Introduction to the Rasch Measurement Model: An Example Using the Hospital Anxiety and Depression Scale (HADS)," *British Journal of Clinical Psychology* 46, no. 1 (2007): 1–18, https://doi.org/10.1348/014466506x96931.

32. K. B. Christensen, G. Makransky, and M. Horton, "Critical Values for Yen's Q(3): Identification of Local Dependence in the Rasch Model Using Residual Correlations," *Applied Psychological Measurement* 41, no. 3 (2017): 178–194, https://doi.org/10.1177/0146621616677520.

33. W. P. Fisher, "Reliability Statistics," *Rasch Measurement Transactions* 6 (1992): 238.

34. J. Hobart and S. Cano, "Improving the Evaluation of Therapeutic Interventions in Multiple Sclerosis: The Role of New Psychometric Methods," *Health Technology Assessment* 13, no. 12 (2009): 1–177, https://doi.org/10.3310/hta13120.

35. J. M. Linacre, "Sample Size and Item Calibration Stability. Rasch Measurement," *Transactions* 7 (1994): 328.

36. A. A. Kucukdeveci, H. Sahin, S. Ataman, B. Griffiths, and A. Tennant, "Issues in Cross-Cultural Validity: Example From the Adaptation, Reliability, and Validity Testing of a Turkish Version of the Stanford Health Assessment Questionnaire," *Arthritis and Rheumatism* 51, no. 1 (2004): 14–19, https://doi.org/10.1002/art.20091.

37. F. Guillemin, C. Bombardier, and D. Beaton, "Cross-Cultural Adaptation of Health-Related Quality of Life Measures: Literature Review and Proposed Guidelines," *Journal of Clinical Epidemiology* 46, no. 12 (1993): 1417–1432, https://doi.org/10.1016/0895-4356(93)90142-n.

38. T. A. Saifee, P. Schwingenschuh, M. M. Reilly, et al., "Tremor in Inflammatory Neuropathies," *Journal of Neurology, Neurosurgery, and Psychiatry* 84, no. 11 (2013): 1282–1287, https://doi.org/10.1136/jnnp-2012-303013.

39. E. Nobile-Orazio, N. Meucci, L. Baldini, A. Di Troia, and G. Scarlato, "Long-Term Prognosis of Neuropathy Associated With Anti-MAG IgM

M-Proteins and Its Relationship to Immune Therapies," *Brain* 123, no. 4 (2000): 710–717, https://doi.org/10.1093/brain/123.4.710.

40. B. D. Wright and J. M. Linacre, "Observations Are Always Ordinal; Measurements, However, Must Be Interval," *Archives of Physical Medicine and Rehabilitation* 70, no. 12 (1989): 857–860.

41. C. Merbitz, J. Morris, and J. C. Grip, "Ordinal Scales and Foundations of Misinference," *Archives of Physical Medicine and Rehabilitation* 70, no. 4 (1989): 308–312.

42. M. H. Liang, "Evaluating Measurement Responsiveness," *Journal of Rheumatology* 22, no. 6 (1995): 1191–1192.

43. N. C. Notermans, J. H. Wokke, H. M. Lokhorst, H. Franssen, Y. van der Graaf, and F. G. Jennekens, "Polyneuropathy Associated With Monoclonal Gammopathy of Undetermined Significance. A Prospective Study of the Prognostic Value of Clinical and Laboratory Abnormalities," *Brain* 117, no. 6 (1994): 1385–1393, https://doi.org/10.1093/brain/117.6.1385.

44. J. M. Niermeijer, K. Fischer, M. Eurelings, H. Franssen, J. H. Wokke, and N. C. Notermans, "Prognosis of Polyneuropathy due to IgM Monoclonal Gammopathy: A Prospective Cohort Study," *Neurology* 74, no. 5 (2010): 406–412, https://doi.org/10.1212/WNL.0b013e3181ccc6b9.

45. T. H. P. Draak, B. T. A. de Greef, C. G. Faber, I. S. J. Merkies, and PeriNomS study group, "The Minimum Clinically Important Difference: Which Direction to Take," *European Journal of Neurology* 26, no. 6 (2019): 850–855, https://doi.org/10.1111/ene.13941.

46. R. Jaeschke, J. Singer, and G. H. Guyatt, "Measurement of Health Status. Ascertaining the Minimal Clinically Important Difference," *Controlled Clinical Trials* 10, no. 4 (1989): 407–415, https://doi.org/10.1016/0197-2456(89)90005-6.

47. D. A. Redelmeier, G. H. Guyatt, and R. S. Goldstein, "Assessing the Minimal Important Difference in Symptoms: A Comparison of Two Techniques," *Journal of Clinical Epidemiology* 49, no. 11 (1996): 1215–1219, https://doi.org/10.1016/s0895-4356(96)00206-5.

48. E. Lydick and R. S. Epstein, "Interpretation of Quality of Life Changes," *Quality of Life Research* 2, no. 3 (1993): 221–226, https://doi.org/10.1007/BF00435226.

49. G. Wells, D. Beaton, B. Shea, et al., "Minimal Clinically Important Differences: Review of Methods," *Journal of Rheumatology* 28, no. 2 (2001): 406–412.

50. D. Revicki, R. D. Hays, D. Cella, and J. Sloan, "Recommended Methods for Determining Responsiveness and Minimally Important Differences for Patient-Reported Outcomes," *Journal of Clinical Epidemiology* 61, no. 2 (2008): 102–109, https://doi.org/10.1016/j.jclinepi.2007.03.012.

51. M. de Wit, T. Abma, M. Koelewijn-van Loon, S. Collins, and J. Kirwan, "Involving Patient Research Partners Has a Significant Impact on Outcomes Research: A Responsive Evaluation of the International OMERACT Conferences," *BMJ Open* 3, no. 5 (2013): e002241, https://doi.org/10.1136/bmjopen-2012-002241.

52. S. P. Collins, P. D. Levy, J. L. Holl, et al., "Incorporating Patient and Caregiver Experiences Into Cardiovascular Clinical Trial Design," *JAMA Cardiology* 2, no. 11 (2017): 1263–1269, https://doi.org/10.1001/jamacardio.2017.3606.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:**. Persons-Items thresholds distribution map. Map showing location of patients with IgM associated polyneuropathy with/without anti-MAG antibodies using the final IgM-RODS (pink bars) and location of the 72 thresholds of the final IgM-RODS (blue bars; 36 items, three response options, meaning two thresholds per item). There was no floor effect; 14 patients (5.7%) had ceiling effect. Zero logit is set as the average of item difficulty and patient ability. This means that a patient with a mean score would be able to cook (location: −0.214 logits) or travel by bus/tram (location: 0.361) easily and would have a higher probability of executing the easier activities (having a lower logits location score); contrariwise, this patient will have a higher chance of experiencing difficulty fulfilling more difficult tasks (having a higher logits location score) and will most probably fail on these. All item weights available on request.

Appendix A

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