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# Development of a brief clinician-reported outcome measure of multiple sclerosis signs and symptoms: The Clinician Rating of Multiple Sclerosis (CRoMS)

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ABSTRACT

*Objective:* No available assessment tool offers a brief and psychometrically sound way for clinicians to quantify assessment of MS in a typical office visit. The objective of this study was to develop a brief clinician-reported outcome measure of MS signs and symptoms to standardize and quantify assessments that occur during a typical neurology office visit.

*Methods:* A questionnaire, called the Clinician Rating of Multiple Sclerosis (CRoMS), was developed in the following steps: literature review; concept elicitation interviews (to generate questionnaire themes and content) with patients with MS ($n$ = 14); concept elicitation interviews with neurologists ($n$ = 9); online qualitative survey with neurologists in the US, UK, Germany, and Sweden ($n$ = 72); online survey with neurologists to evaluate the first draft of the clinician-reported outcome measure (ClinRO) ($n$ = 26); an in-person meeting with neurologists to discuss and revise the draft ClinRO ($n$ = 9); and interviews with neurologists and MS nurses to further refine and finalize the ClinRO ($n$ = 16).

*Results:* Across all steps of this research, several signs and symptoms consistently emerged as important for assessment in a typical office visit: walking, balance, upper limb function, coordination, weakness, fatigue, pain, sensory symptoms, bladder function, visual function, cognition, spasticity, spasms, and mood. The importance of these signs and symptoms was supported by neurologists during the online surveys and the in-person meeting. Neurologists were generally able to complete the draft ClinRO measure without difficulty, although minor revisions were suggested to refine the ClinRO for future use.

*Conclusion:* The CRoMS may be a useful tool for efficiently assessing the severity of MS symptoms. This brief clinician-reported measure could help standardize and quantify assessments in clinical studies and clinical settings.

## 1. Introduction

A wide range of tools are used to assess patients with multiple sclerosis (MS) (Multiple Sclerosis Trust 2011), including patient-reported measures (Doward et al., 2009; Fischer et al., 1999b,a; Hobart et al., 2001; Hohol et al., 1995), performance-based instruments (Fischer et al., 1999a), and tests of walking capacity (Gijbels et al., 2012). The clinician perspective is particularly important because a clinician's assessment has an immediate impact on treatment decisions, and the most frequently used outcome measures in clinical trials rely on clinician ratings. However, commonly used clinician-rated measures for MS have limitations. For example the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983; Kurtzke, 2008) and the UK Neurological Disability Scale (formerly known as the Guy's Neurological Disability Scale) (Sharrack and Hughes, 1999) are often time consuming to complete properly, which makes them impractical for use in clinical settings (Baldassari et al., 2018).

The content of the EDSS and other currently available clinician-rated measures also raises questions. These instruments were developed before the introduction of current instrument development standards,

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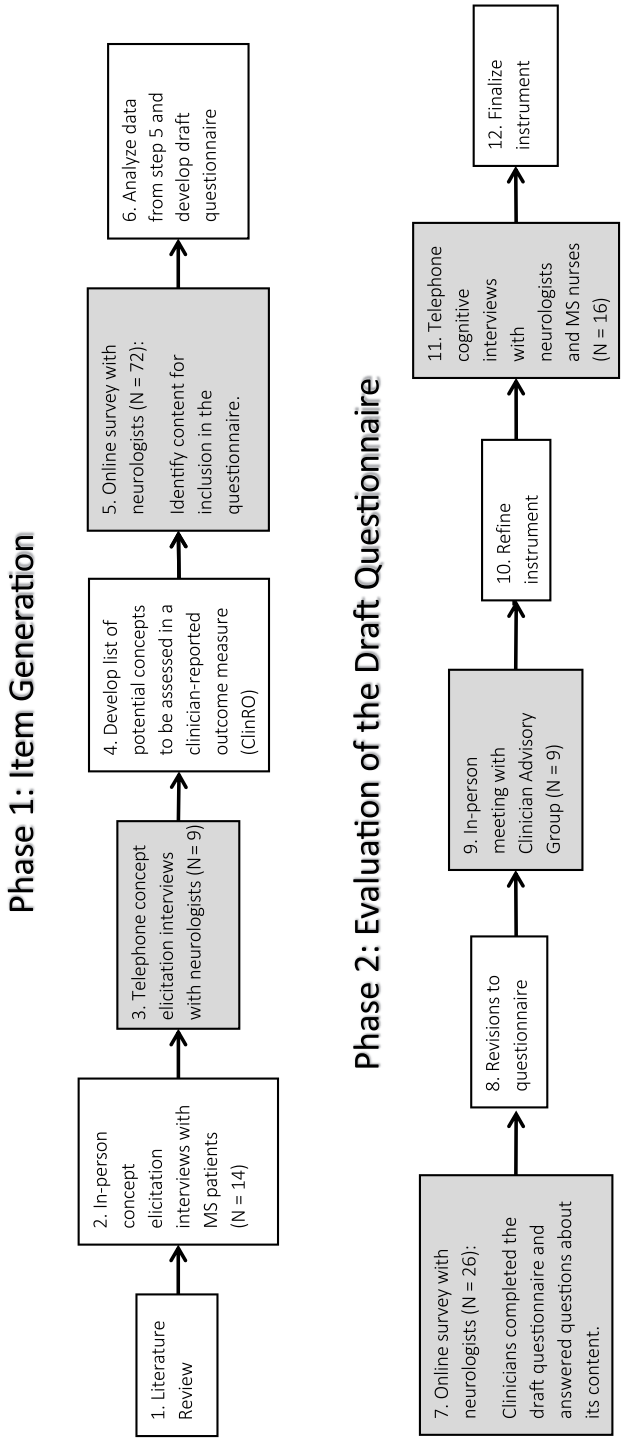


**Fig. 1.** Summary of project steps
*Note:* Shaded boxes indicate clinician involvement.

which emphasize qualitative research with the target population to identify content and generate items (Patrick et al., 2011a,b; Powers et al., 2017). Thus, existing measures may be missing important content. For example, the EDSS does not clearly assess several MS symptoms that are important to patients, including cognitive function, depression, and fatigue. Furthermore, above a certain level of disability, the EDSS classification is primarily influenced by the patient's ambulatory ability (Amato and Ponziani, 1999; van Munster and Uitdehaag, 2017). Thus, it may be insensitive to some impairments in areas other than walking. These issues with content could contribute to some of the psychometric weaknesses that have been reported for the EDSS, such as limited ability to distinguish between individuals with different levels of disability, poor responsiveness, and high inter-rater variability (van Munster and Uitdehaag, 2017; Amato et al., 1988; Goodkin et al., 1992; Hobart et al., 2000).

To address missing content in MS measures, researchers have developed instruments focusing on specific symptoms like fatigue (Mills et al., 2010) and spasticity (Hobart et al., 2006), but symptom-specific approaches do not provide an overall assessment of a patient's condition. In sum, no available measure offers a brief and psychometrically sound way for clinicians to quantify signs and symptoms assessed in a typical office visit. Such an instrument would facilitate assessment of outcomes in clinical trials and tracking of patients' progress in clinical practice. Therefore, the purpose of this study was to develop a brief clinician-reported outcome measure (ClinRO) of MS signs and symptoms to standardize and quantify assessments that occur during a typical neurology office visit.

## 2. Methods

### 2.1. Overview

A ClinRO was developed in a series of qualitative research steps (summarized in Fig. 1) to identify relevant concepts, refine the draft instrument, and assess its content validity. These steps were designed to be consistent with good measurement practices for ClinRO development described by the ISPOR Clinical Outcome Assessment Emerging Good Practices Task Force (Powers et al., 2017), while considering guidelines for developing patient-reported outcome measures (Patrick et al., 2011a,b; Food and Drug Administration [FDA] 2009).

### 2.2. Procedures for item generation (Phase 1: steps 1–6)

Phase 1 focused on identifying instrument content and drafting the questionnaire. This phase began with a literature review (step 1) to inform development of discussion guides for subsequent interviews (Patrick et al., 2011b). The literature review focused on identifying the most common symptoms and impact of MS, as well as previously developed instruments for MS assessment.

Then, concept elicitation interviews (Patrick et al., 2011a) with patients (step 2) and clinicians (step 3) were conducted to identify signs and symptoms for inclusion in the questionnaire. These were conducted using semi-structured discussion guides, developed based on literature review and input from neurologists (authors RTN and PD). The patient interview guide (step 2) was designed to elicit the patients' insights into the symptoms and impact of MS. Patients were also asked what their clinicians assess in a typical office visit. The clinician interview guide (step 3) included topics, questions, and probes designed to understand MS symptoms and impact assessed by neurologists during office visits. Qualitative analysis of data from steps 2 and 3 was conducted with a thematic analysis approach using ATLAS.ti software. Coding dictionaries of themes, concepts, and terms were developed.

A list of potential concepts for inclusion in the ClinRO was developed (step 4), and an online concept elicitation survey with clinicians (step 5) was conducted to gather input from a broader range of clinicians. This survey asked about the MS signs, symptoms, and impact

routinely assessed during office visits. The information gathered from patients and clinicians in steps 2, 3, and 5 was used to develop the first draft of the ClinRO (step 6).

### 2.3. Procedures for evaluating and refining the questionnaire (Phase 2: steps 7–12)

Phase 2 was conducted to refine the draft ClinRO and assess its content validity, which is the extent to which an instrument contains the relevant and important aspects of the concept it was designed to measure (Patrick et al., 2011a,b; FDA 2009; Rothman et al., 2009). Content validity is established through qualitative research with the target population (i.e., neurologists and neurology nurses who treat patients with MS).

An online clinician survey was conducted to evaluate the draft ClinRO (step 7). Respondents rated one recent patient with the draft questionnaire, which included 16 items assessing MS signs and symptoms, followed by nine items assessing MS impact. Then, respondents were asked about the comprehensiveness and clarity of the questionnaire.

The ClinRO was revised (step 8) based on feedback in the online survey and then evaluated by neurologists and nurses specializing in MS during the in-person meeting (step 9). Participants in this in-person meeting completed the draft ClinRO and spent several hours discussing the instructions, response options, and content of the ClinRO, with the goal of coming to a consensus on content and wording. The ClinRO was refined based on this discussion (step 10).

The questionnaire was then evaluated by clinicians in cognitive interviews (step 11). The term “cognitive interviews” refers to interviews designed to assess and refine a questionnaire based on input from the target population (Patrick et al., 2011a). Respondents completed the draft ClinRO and provided feedback on its relevance, clarity, ease of use, and comprehensiveness, as well as the feasibility of using the ClinRO in clinical practice. For qualitative analysis, a coding dictionary was developed, and transcripts were coded using ATLAS.ti. The questionnaire was reviewed and revised throughout this process (step 12).

### 2.4. Participants

#### 2.4.1. Patients

Patients in concept elicitation interviews (step 2) were required 1) to be at least 18 years of age; 2) have a diagnosis of MS from a neurologist; and 3) have had at least one relapse in the last 12 months if diagnosed with relapsing remitting MS. Participants were recruited from two clinical sites in the US.

#### 2.4.2. Clinicians

All clinicians in steps 3, 5, 7, and 11 were required to have direct experience treating patients with MS. Specific inclusion criteria varied slightly across the steps. Clinicians participating in the concept elicitation (step 3), online concept elicitation survey (step 5), in-person meeting (step 9), and cognitive interviews (step 11) were required to see at least five adult patients diagnosed with MS per month. Clinicians in the online ClinRO evaluation survey (step 7) were required to see at least 10 patients per month. The concept elicitation interviews (step 3) and the online concept elicitation survey (step 5) were conducted with neurologists. The online ClinRO evaluation survey (step 7), the in-person meeting (step 9), and cognitive interviews (step 11) included both neurologists and nurses specializing in MS. The online concept elicitation survey (step 5) included neurologists from the US, UK, Sweden, and Germany. Clinicians participating in the other phases of instrument development were based in the US.

**Table 1**
Clinicians participating in qualitative research.

| Step number | Step description | *N* | Type of clinicians | Country | Average number of years working with patients with MS (Mean [Range]) | Average number of patients with MS seen per month (Mean [Range]) |
|---|---|---|---|---|---|---|
| 3 | Telephone concept elicitation interviews | 9 | Neurologists | US | 14.8 (5–30) | 105.6 (30–300) |
| 5 | Online survey | 72 | Neurologists | US (26), UK (25), Germany (11), Sweden (10) | 14.6 (2–40) | 50.6 (5–300) |
| 7 | Online survey | 26 | Neurologists | US | 16.2 (3–45) | 97.2 (10–250) |
| 9 | In-person meeting | 9 | Neurologists and nurses specializing in MS | US | 15.3 (8–30) | 95.0 (10–180) |
| 11 | Telephone cognitive interviews | 16 | Neurologists and nurses specializing in MS | US | 16.0 (5.5–30) | 98.9 (20–165) |

## 3. Results

### 3.1. Sample description

Concept elicitation interviews were conducted with 14 patients with MS (step 2). The sample was 78.6% female ($n$ = 11; mean age = 51.1 years; 71.4% white). Mean duration of MS diagnosis was 17.3 years. The sample included participants with relapsing-remitting ($n$ = 6; 42.9%), secondary progressive ($n$ = 6; 42.9%); primary progressive ($n$ = 1; 7.1%), and chronic progressive MS ($n$ = 1; 7.1%).

A total of 113 clinicians participated in development on the ClinRO across all phases of this study (Table 1). Some of these 113 clinicians participated in more than one step of development: one participated in four steps, five participated in three steps, six participated in two steps, and 101 participated in one step. All clinicians had extensive experience treating patients with MS.

Concept elicitation interviews (step 3) were conducted with nine neurologists with MD degrees. Two were general neurologists, six specialized in MS in an MS focused clinic, and one clinician specialized in MS but did not practice in an MS focused clinic. The online concept elicitation survey (step 5) was completed by 72 neurologists (19 general neurologists and 53 neurologists specializing in MS). The online ClinRO evaluation survey (step 7) was completed by 26 clinicians (general neurologists, $n$ = 4; neurologists specializing in MS, $n$ = 21; nurse practitioner specializing in MS, $n$ = 1). The in-person meeting (step 9) included four neurologists specializing in MS, two general neurologists, and three nurses specializing in MS. Cognitive interviews were completed by telephone with a total of 16 clinicians (step 11), including 14 neurologists holding MD degrees. Three were general neurologists, and 11 specialized in MS. The other two clinicians in this step were nurses specializing in MS.

**Table 2**
Step 2: Signs and symptoms of MS reported by patients during concept elicitation interviews[a] ($N$ = 14).

| Signs and symptom of MS that patients reported experiencing during open ended concept elicitation discussion | $N$ (%) |
|---|---|
| Walking | 14 (100.0%) |
| Coordination/Balance | 13 (92.9%) |
| Weakness | 13 (92.9%) |
| Muscle impairment | 12 (85.7%) |
| Sensory | 12 (85.7%) |
| Mood/Emotional functioning | 12 (85.7%) |
| Fatigue/Exhaustion/Tiredness | 11 (78.6%) |
| Vision | 11 (78.6%) |
| Bladder | 8 (57.1%) |
| Cognitive | 7 (50.0%) |
| Difficulty standing | 6 (42.9%) |
| Heaviness in legs | 5 (35.7%) |
| Bowel | 4 (28.6%) |
| Pain | 4 (28.6%) |
| Heat sensitivity | 4 (28.6%) |
| Sleep | 3 (21.4%) |
| Sexual function | 3 (21.4%) |
| Swelling of feet | 2 (14.3%) |
| Other[b] | 11 (78.6%) |

[a] Signs and symptoms were reported in response to open ended questions such as: What is MS like for you? What do you experience? What MS symptoms do you currently experience? Are there symptoms you experienced in the past that you are not currently experiencing?

[b] Other signs and symptoms reported by one participant included: swelling of fingers, poor trunk control, difficulty swallowing, changes in voice, issues with blood circulation in legs, vomiting/sick to stomach, choking, hearing, nostril shrunk, ear collapsed, reflexes, taste of aluminum foil, and hallucinations.

### 3.2. Identifying concepts and generating items (Phase 1: steps 1–6)

Fourteen MS outcome measures were identified in the literature review (Doward et al., 2009; Fischer et al., 1999b,a; Hobart et al., 2001; Hohol et al., 1995; Gijbels et al., 2012; Kurtzke, 1983; Sharrack and Hughes, 1999; Allali et al., 2012; Baroin et al., 2013; Confavreux et al., 1992; Cutter et al., 1999; Podsiadlo and Richardson, 1991; Schwartz et al., 1999; Sipe et al., 1984). These previously developed instruments were reviewed when preparing discussion guides for steps 2 and 3.

Patients in concept elicitation interviews (step 2) reported a wide range of MS signs and symptoms (Table 2), most commonly walking, coordination/balance, and weakness. Patients also reported MS-related impairments in daily activities, mood/emotions, work performance, driving, and self-care. Patients were asked about interactions with clinicians during regular office visits. All patients saw neurologists, and they reported that neurologists typically ask at least one general question about their MS in addition to performing the neurological exam. Six patients (42.9%) reported that their doctors also ask more targeted questions about specific symptoms. The majority ($n$ = 10; 71.4%) reported that they are not asked about the impact of MS.

In concept elicitation interviews (step 3), neurologists reported assessing a wide range of MS signs, symptoms, and impacts during regular follow-up visits with patients. Neurologists reported relying primarily on patient history (i.e., direct questions to the patient), the neurological exam, performance-based measures (e.g., EDSS, timed-walk tests, cognitive tests), and observation of the patient (Table 3). Unstandardized questioning about patient history was the most common assessment method.

In the online concept elicitation survey, clinicians were asked to provide the five most important signs or symptoms assessed during office visits (Table 4). The most commonly assessed symptoms were bladder function (44.4%), visual symptoms (44.4%), walking/gait (37.5%), sensory symptoms (36.1%), cognition (31.9%), fatigue (27.8%), weakness (22.2%), and mood/psychological symptoms (20.8%). The most common assessment approaches were asking the patient a direct question, the neurological exam, and informal observation of the patient (Table 5). Performance-based measures were used less frequently, most commonly to assess walking (by 23.6% of the sample).

The results of the first five steps of instrument development were used to generate items for the draft ClinRO, which instructed clinicians to rate the current status of a patient with MS while considering all information gathered during the most recent office visit. The first draft had 25 items, including 16 assessing signs and symptoms and nine assessing the impact of MS (e.g., mobility, activities of daily living, social functioning, leisure activities, work performance). Response options were “none,” “mild,” “moderate,” “severe,” and “insufficient information.”

### 3.3. Evaluating and refining the questionnaire (Phase 2: steps 7–12)

In step 7, 26 neurologists completed the first draft of the ClinRO, rating a patient with MS they had seen recently. Most of the signs/symptoms included on the draft instrument were present for the majority of patients, and all response options were used, although “severe” was used less frequently than “none,” “mild,” and “moderate.” The signs/symptoms most commonly rated as “moderate” or “severe” were fatigue (69.2%), balance (53.9%), walking/standing (46.2%), and weakness (34.6%). The “insufficient information” response option was rarely used, except for sexual function (46.2%). The great majority of clinicians reported that the response options and instructions were clear, although several suggested that definitions of the response options (none, mild, moderate, severe, insufficient information) should be added.

Comments from 26 neurologists in step 7 were presented to the Clinician Advisory Group during the in-person meeting (step 9). There

**Table 3**
Step 3: Methods used to assess MS signs and symptoms during offices visits as reported by neurologists during concept elicitation interviews[a] ($N = 9$).

| Signs/Symptoms | Total | Direct question | Neurological exam | Observation of patient | Standardized/ Performance measure | Name of standardized measure | Method unclear |
|---|---|---|---|---|---|---|---|
| Bladder | 9 | 9 | | | 1 | Unknown | |
| Cognitive | 9 | 8 | 2 | 2 | 5 | MMSE<br>MoCA<br>SDMT<br>EDSS<br>SLUMS | |
| Depression | 9 | 9 | | | 2 | BDI-FS | |
| Fatigue/Exhaustion/ Tiredness | 9 | 9 | | | | | |
| Mood/Emotions | 9 | 9 | | 1 | | | 1 |
| Pain | 9 | 9 | | | | | 1 |
| Vision | 9 | 6 | 7 | | 2 | Ishihara color<br>Sloan contrast | 1 |
| Walking/Gait issues | 9 | 8 | 7 | 7 | 8 | 25-foot timed walk 500-meter walk | 1 |
| Balance | 8 | 6 | 4 | 5 | | | 1 |
| Bowel | 8 | 8 | | | 1 | Unknown | |
| Weakness | 8 | 6 | 7 | | | | |
| Sensory | 7 | 7 | 4 | 1 | | | |
| Coordination | 6 | 2 | 4 | | | | |
| Muscle impairment | 6 | 4 | 5 | 1 | | | 1 |
| Reflexes | 4 | | 4 | | | | |
| Sexual function | 4 | 3 | | | 1 | Unknown | |

Abbreviations: BDI-FS = Beck Depression Inventory-Fast Screen; EDSS = Expanded Disability Status Scale; MMSE = Mini-Mental Status Examination; MoCA = Montreal Cognitive Assessment; SDMT = Symbol Digit Modalities Test; SLUMS = Saint Louis University Mental Status Exam.

[a] Assessment methods were reported in response to open ended questions such as: When a patient comes in to your office, how do you assess his or her current condition? What types of questions do you ask? Do you use any standardized measure(s) in your practice with MS patient? Are there signs and symptoms you assess in ways other than directly asking the patient or administering standardized measures?

was a consensus that the instructions should say ratings should be based on "clinical judgment" derived from all available sources of information. The advisors agreed with results of the step 7 survey recommending definitions of the five response options. During the meeting, the advisors worked together to draft these definitions.

The advisors unanimously recommended dropping the second part of the questionnaire focusing on impact of MS. They believed these concepts should be assessed by a patient-reported questionnaire rather than a clinician-completed measure because clinicians tend to focus on signs and symptoms rather than impact. This deletion resulted in a shorter questionnaire focusing only on the signs and symptoms of MS. The advisors also emphasized that the questionnaire must be brief to be useful in clinical studies and clinical practice. Thus, the questionnaire was shortened and edited prior to the subsequent cognitive interview phase.

The version of the questionnaire used in the first set of cognitive interviews contained 15 items assessing MS signs and symptoms (step 11). Revisions were made throughout the interview process based on feedback gathered from respondents. In total, there were seven rounds of interviews, each with a slightly updated version of the questionnaire. All 16 clinicians agreed that the questionnaire was easy to complete, relevant to patients with MS, and a potentially valuable tool in clinical practice, research, or both settings. Clinicians were asked to read the instructions and complete the draft ClinRO thinking about the most recent patient they saw with MS. On average, clinicians spent one minute and 17 s (range = 26 s to 2 min and 23 s) completing the ClinRO. This included time for reviewing instructions.

The instructions for the questionnaire include the recall period and definitions of the response options. Several recall periods were explored during the cognitive interviews, including the past month, since the last office visit, since the last study visit, and since the last time you saw the patient. The clinicians advised that the recall period could vary depending on the needs of the clinic or study. The questionnaire includes five response options: none, mild, moderate, severe, and insufficient information. None of the clinicians had difficulty using these response options.

Across the cognitive interviews, there was some disagreement regarding whether spasticity and spasms should be included as separate items. While some clinicians recommended dropping one of these items, the majority agreed they were separate concepts. For example, one clinician said: "They are not the same thing. Spasms are painful cramps, and spasticity is a global description of stiffness and tension in muscles. If one has a lot of spasticity one may have an increased tendency to have spasms, but they are not equivalent." Because most of the clinicians differentiated between these concepts, separate items assessing spasms and spasticity were retained.

**Table 4**
Step 5: Most important MS symptoms or clinical signs to consider when assessing a patient diagnosed with MS as reported by neurologists in online concept elicitation survey ($N = 72$).

| Most important symptoms or clinical signs to consider when assessing a patient diagnosed with MS (n,%)[a] | Group 1: General neurologists ($N = 19$) | Group 2: Neurologists specializing in MS ($N = 53$) | Total sample ($N = 72$) |
|---|---|---|---|
| Bladder function | 5 (26.3%) | 27 (50.9%) | 32 (44.4%) |
| Visual symptoms | 9 (47.4%) | 23 (43.4%) | 32 (44.4%) |
| Walking/Gait | 7 (36.8%) | 20 (37.7%) | 27 (37.5%) |
| Sensory | 6 (31.6%) | 20 (37.7%) | 26 (36.1%) |
| Cognition | 6 (31.6%) | 17 (32.1%) | 23 (31.9%) |
| Fatigue | 8 (42.1%) | 12 (22.6%) | 20 (27.8%) |
| Weakness | 4 (21.1%) | 12 (22.6%) | 16 (22.2%) |
| Mood/Psychological | 4 (21.1%) | 11 (20.8%) | 15 (20.8%) |
| Coordination/Ataxia | 3 (15.8%) | 11 (20.8%) | 14 (19.4%) |
| Pain | 3 (15.8%) | 11 (20.8%) | 14 (19.4%) |
| Bowel function | 2 (10.5%) | 11 (20.8%) | 13 (18.1%) |
| Spasticity | 1 (5.3%) | 12 (22.6%) | 13 (18.1%) |
| Mobility | 4 (21.1%) | 6 (11.3%) | 10 (13.9%) |
| Balance | 1 (5.3%) | 7 (13.2%) | 8 (11.1%) |
| Motor function | 3 (15.8%) | 4 (7.5%) | 7 (9.7%) |
| Non-specific response | 2 (10.5%) | 4 (7.5%) | 6 (8.3%) |
| Paresis | 1 (5.3%) | 5 (9.4%) | 6 (8.3%) |
| Eye movement | 1 (5.3%) | 4 (7.5%) | 5 (6.9%) |
| Relapse | | 4 (7.5%) | 4 (5.6%) |
| Strength | | 4 (7.5%) | 4 (5.6%) |
| Dizziness | | 3 (5.7%) | 3 (4.2%) |
| Speech | | 3 (5.7%) | 3 (4.2%) |
| Cranial nerves | 1 (5.3%) | 1 (1.9%) | 2 (2.8%) |
| EDSS | 1 (5.3%) | 1 (1.9%) | 2 (2.8%) |
| Falls | | 2 (3.8%) | 2 (2.8%) |
| Medication tolerability | 1 (5.3%) | 1 (1.9%) | 2 (2.8%) |
| Other | | 2 (3.8%) | 2 (2.8%) |
| Quality of life | | 2 (3.8%) | 2 (2.8%) |
| Swallowing | 1 (5.3%) | 1 (1.9%) | 2 (2.8%) |
| Activities of daily living | 1 (5.3%) | | 1 (1.4%) |
| Fluctuation in symptoms | | 1 (1.9%) | 1 (1.4%) |
| Incontinence | | 1 (1.9%) | 1 (1.4%) |
| Infections | 1 (5.3%) | | 1 (1.4%) |
| Paralysis | | 1 (1.9%) | 1 (1.4%) |
| Physical function | | 1 (1.9%) | 1 (1.4%) |
| Pyramidal signs | 1 (5.3%) | | 1 (1.4%) |
| Reflexes | | 1 (1.9%) | 1 (1.4%) |
| Sexual functioning | | 1 (1.9%) | 1 (1.4%) |
| Treatment issues | 1 (5.3%) | | 1 (1.4%) |
| Tremors | | 1 (1.9%) | 1 (1.4%) |
| Upper limb/Extremity function | 1 (5.3%) | | 1 (1.4%) |

Abbreviation: EDSS = Expanded Disability Status Scale.

[a] Respondents were permitted to select up to five symptoms or clinical signs from their responses to a previous open-ended question asking them to list the signs or symptoms that should be assessed for every patient diagnosed with MS during routine follow-up office visits.

Based on clinician recommendations, three items (spasticity, weakness, and coordination) were split into separate items for upper and lower functioning. All clinicians who saw the version with separate items for upper and lower functioning agreed that this split was appropriate and consistent with typical assessment procedures. A single item assessing "mood (including depression and anxiety)" was split into separate items assessing anxiety and depression because clinicians indicated that these were two distinct constructs.

Clinicians often discussed the compromise between comprehensiveness and brevity, emphasizing that brevity is important. Items on sexual function, balance, pain, and sensory symptoms were all retained based on majority decision by clinicians. In contrast, the concepts of bowel functioning and bulbar symptoms were not included because most clinicians said they were less common.

### 3.4. Description of final questionnaire

The final version of the ClinRO, called the Clinician Rating of Multiple Sclerosis (CRoMS), has 19 items assessing MS signs and symptoms. Weakness, spasticity, and coordination are rated separately for upper and lower extremities. All signs/symptoms are rated on a scale of none, mild, moderate, and severe, with an "insufficient information" response option that may be used if clinicians believe they do not have enough information to accurately respond. The first page includes the instructions and definitions of the five response options, while the 19 items appear on a single page that follows (in cognitive interviews, several clinicians said it was important that all items fit on one page). Respondents are instructed to complete the items considering only signs and symptoms that have been present in the past month, but the recall period may be varied later depending on the needs of a specific study. Answers are based on clinical judgment considering all sources of information gathered during the most recent office visit including patient report, the neurological exam, neuropsychological tests, and clinicians' observations. See the Appendix for the final ClinRO.

## 4. Discussion

This research yielded a ClinRO measure with content validity (Patrick et al., 2011a) supported by qualitative data from patients and a wide range of clinicians. The CRoMS assesses the severity of MS signs and symptoms that were considered most important for assessment in a typical office visit. Neurologists and neurology nurses were able to complete the draft questionnaire quickly with limited difficulty (steps 7, 9, and 11), while using the full range of the response option scale. In addition, the draft questionnaire was refined based on extensive clinician input gathered in steps 7, 9, and 11 to ensure that the items were clear, relevant, and sufficiently comprehensive. The final questionnaire resulting from this qualitative research is likely to be an effective tool for efficiently assessing and quantifying a patient's MS severity based on the signs and symptoms most important to patients and clinicians.

The CRoMS could be useful in both clinical and research contexts. Throughout instrument development, clinicians were often asked what characteristics the questionnaire would need to have to be useful in clinical settings and adopted at their clinics. Clinicians consistently emphasized the importance of brevity, often saying that the questionnaire must fit on one page and be short enough to be completed quickly. In step 11, clinicians completed the questionnaire in about one minute, and time required for completion would likely decrease after multiple uses. Therefore, the CRoMS appears to be brief enough for use in study protocols and clinical assessments.

While the CRoMS is not intended to replace detailed rating scales such as the EDSS, a comparison between the CRoMS and the EDSS helps to highlight two strengths of the new instrument. First, unlike the EDSS, which requires an extensive assessment procedure, the CRoMS can be completed quickly based on the assessment procedures already conducted during a typical office visit. Second, because the CRoMS was developed based on extensive qualitative research, it covers the broad range of MS signs and symptoms that patients and clinicians considered to be most important, in contrast to the EDSS, which omits important symptoms such as depression, fatigue, and cognitive impairment. The brevity and comprehensiveness of the CRoMS will make it useful across a wide range of situations. In clinical settings, the CRoMS could be completed quickly after an office visit with no time required for additional assessment or performance-based testing. If completed at multiple visits, the instrument could be a useful tool for monitoring symptoms and tracking treatment effectiveness. In research, the CRoMS could be used as a study outcome measure to efficiently quantify the broad range of signs and symptoms generally considered important to patients with MS.

Limitations should also be considered. The ClinRO is a new

**Table 5**
Step 5: Methods used to assess MS signs and symptoms during offices visits as reported by neurologists during the online concept elicitation survey[a] ($N$ = 72).

| Domain | Direct question | Neurological exam | Observation of patient | Performance-based measure | Clinician-completed measure | Patient-completed measure | Other method | Referral[b] |
|---|---|---|---|---|---|---|---|---|
| Balance | 35 (48.6%) | 46 (63.9%) | 33 (45.8%) | 12 (16.7%) | | | | 1 (1.4%) |
| Bladder | 54 (75.0%) | 10 (13.9%) | 2 (2.8%) | | 2 (2.8%) | 1 (1.4%) | 3 (4.2%) | 2 (2.8%) |
| Bowel | 39 (54.2%) | 5 (6.9%) | 2 (2.8%) | | | 1 (1.4%) | | |
| Cognitive | 40 (55.6%) | 37 (51.4%) | 20 (27.8%) | 8 (11.1%) | 7 (9.7%) | 1 (1.4%) | 1 (1.4%) | 3 (4.2%) |
| Coordination | 34 (47.2%) | 51 (70.8%) | 27 (37.5%) | 4 (5.6%) | 1 (1.4%) | | | |
| Depression | 47 (65.3%) | 18 (25.0%) | 22 (30.6%) | 1 (1.4%) | | 2 (2.8%) | 1 (1.4%) | |
| Fatigue/Exhaustion/ Tiredness | 58 (80.6%) | 8 (11.1%) | 20 (27.8%) | 2 (2.8%) | | | | |
| Mood/Emotions | 53 (73.6%) | 6 (8.3%) | 22 (30.6%) | | | 2 (2.8%) | 1 (1.4%) | |
| Spasticity | 33 (45.8%) | 50 (69.4%) | 20 (27.8%) | 1 (1.4%) | 3 (4.2%) | | | 1 (1.4%) |
| Muscle control | 31 (43.1%) | 46 (63.9%) | 20 (27.8%) | 2 (2.8%) | 2 (2.8%) | 1 (1.4%) | | |
| Pain | 56 (77.8%) | 8 (11.1%) | 16 (22.2%) | | | 3 (4.2%) | | |
| Reflexes | 10 (13.9%) | 31 (43.1%) | 6 (8.3%) | | | | | |
| Sensory | 28 (38.9%) | 40 (55.6%) | 7 (9.7%) | | | | | |
| Sexual function | 37 (51.4%) | 4 (5.6%) | 3 (4.2%) | | | | | |
| Vision | 36 (50.0%) | 51 (70.8%) | 14 (19.4%) | 3 (4.2%) | 4 (5.6%) | | | 1 (1.4%) |
| Walking/Gait issues | 44 (61.1%) | 57 (79.2%) | 33 (45.8%) | 17 (23.6%) | | | | |
| Weakness | 37 (51.4%) | 55 (76.4%) | 26 (36.1%) | 1 (1.4%) | 1 (1.4%) | | | |

[a] For each sign/symptom clinicians rated as important to assess in an office visit, they were asked "how do you assess this in your practice?"
[b] "Referral" was not listed as a response option for this series of questions. However, some clinicians indicated in free-text fields under "clinician-completed measure" or "other" that assessment of a specific MS sign, symptom, or impact involved referral to another type of clinician. These "referral" responses were removed from the rows for "clinician-completed measures" and "other" assessments because a referral indicates that the assessment is not performed at the neurologist's office during an office visit.

instrument, and further validation is necessary. Although the qualitative data provide strong evidence for content validity, quantitative data from a larger sample is not yet available. Therefore, psychometric properties such as reliability, construct validity, and responsiveness to change are unknown. A larger quantitative data set is also needed to evaluate measurement properties, identify potential subscales, and derive a scoring algorithm. For this instrument, it would be particularly important to assess inter-rater reliability to ensure that interpretation of the items and response options are reasonably consistent across clinicians. A scoring algorithm may include a specific weighting for each item based on the item's importance to patients and potential impact on overall disability. Therefore, it is recommended that the CRoMS be used as an exploratory endpoint until further psychometric work is completed.

The instrument's brevity is both a strength and limitation. During instrument development, it was necessary to consider the trade-off between brevity and comprehensiveness. Efforts were made to include the most important concepts, but it was not possible to include every MS symptom suggested by every neurologist. Some concepts were omitted to maintain brevity and ensure that the instrument would be practical for completion in busy research and clinical settings. For example, there were clinicians who suggested including assessment of bowel functioning, speech, and swallowing. However, the consensus was that these symptoms were redundant with those already included or less frequently assessed than those that were included. Still, these omitted symptoms could be important for some patients, and this should be acknowledged as a limitation of the questionnaire.

Furthermore, on a brief questionnaire like this, it is not possible to capture all details relating to signs and symptoms of MS. Most of the issues assessed by items of the CRoMS are complex, with a diverse range of possible patient experiences. For example, while item 15 of the questionnaire allows clinicians to report overall severity of sleep problems, the item does not allow for distinction among the wide range of possible sleep issues, such as insomnia and sleep apnea. To capture the details underlying the response to each item, a more thorough assessment of each symptom would be necessary.

Another limitation is the lack of standardization underlying the response to each item of the CRoMS. Because the instrument was designed to be completed after a typical office visit without requiring additional assessment, clinicians are not required to perform any specific assessment procedures for the signs and symptoms of MS. While there is likely to be substantial overlap among assessment methods used by clinicians at various sites, there will inevitably be differences. For example, a wide range of cognitive tests are used with MS patients, and clinicians are likely to have their own preferences. Therefore, two clinicians could be rating the cognition item of the CRoMS based on entirely different cognitive tests, rather than a consistent standardized assessment of cognition. Other signs and symptoms, such as walking and vision, are also assessed in a variety of ways. This could have implications for reliability of the CRoMS. Subsequent psychometric analyses examining inter-rater reliability will need to consider this limitation.

Despite limitations, this brief clinician-reported measure could help standardize and quantify assessments of patients with MS. The next steps of this research will be psychometric evaluation in a larger sample of patients with MS, including development of the scoring algorithm. Then, it is hoped that the instrument will be useful in neurology clinics and clinical trials of new treatments for patients with MS.

## Declaration of Competing Interest

Louis Matza and Katie Stewart are employees of Evidera, a company that received funding from Biogen for time spent conducting this research. Glenn Phillips is a former employee of Biogen. Robert Naismith has received compensation for consulting, advisory boards, and speaker's bureaus from the following companies: Alkermes, Biogen, Celgene, EMD Serono, Genentech, Genzyme, and Novartis. Philip Delio has received compensation for consulting from Biogen and Gore Pharmaceuticals. Drs. Naismith and Delio received funding for time spent consulting on this research, but received no funding for time spent contributing to this manuscript.

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## Ethical Guidelines

All patients who participated provided informed consent before completing study procedures. All study procedures and materials were approved by an independent institutional review board (Ethical & Independent Review Services; Study Number 14039-01).

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## Appendix: The Clinician Rating of Multiple Sclerosis (CRoMS)

Please use this questionnaire to rate severity of signs and symptoms **related to** multiple sclerosis (MS).

When completing these items, please consider only signs and symptoms that have been present in the **past month.**

Your answers should be based on your clinical judgment. Please consider **all sources of information** you gathered during the most recent office visit, including patient report, the neurological exam, your own observations, and neuropsychological testing.

When rating these items, please use the following **response options.**

**None:** Signs and symptoms are absent.

**Mild:** Signs or symptoms are present, but have minimal or no impact on function.

**Moderate:** Signs or symptoms have impact, placing some limitations on function.

**Severe:** Signs or symptoms have serious impact, substantially limiting function.

**Insufficient information:** You do not have enough information to rate an item.

| | | None | Mild | Moderate | Severe | Insufficient information |
|---|---|---|---|---|---|---|
| 1. | Cognition | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. | Depression | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. | Anxiety | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. | Fatigue | ☐ | ☐ | ☐ | ☐ | ☐ |
| 5. | Visual function | ☐ | ☐ | ☐ | ☐ | ☐ |
| 6. | Upper extremities | | | | | |
| | 6a. Weakness | ☐ | ☐ | ☐ | ☐ | ☐ |
| | 6b. Spasticity | ☐ | ☐ | ☐ | ☐ | ☐ |
| | 6c. Coordination | ☐ | ☐ | ☐ | ☐ | ☐ |
| 7. | Lower extremities | | | | | |
| | 7a. Weakness | ☐ | ☐ | ☐ | ☐ | ☐ |
| | 7b. Spasticity | ☐ | ☐ | ☐ | ☐ | ☐ |
| | 7c. Coordination | ☐ | ☐ | ☐ | ☐ | ☐ |
| 8. | Spasms | ☐ | ☐ | ☐ | ☐ | ☐ |
| 9. | Sensory symptoms (including numbness and tingling) | ☐ | ☐ | ☐ | ☐ | ☐ |
| 10. | Pain | ☐ | ☐ | ☐ | ☐ | ☐ |
| 11. | Balance | ☐ | ☐ | ☐ | ☐ | ☐ |
| 12. | Walking | ☐ | ☐ | ☐ | ☐ | ☐ |
| 13. | Bladder function | ☐ | ☐ | ☐ | ☐ | ☐ |
| 14. | Sexual function | ☐ | ☐ | ☐ | ☐ | ☐ |
| 15. | Sleep | ☐ | ☐ | ☐ | ☐ | ☐ |

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