Abstract

Development and Validation of the Incapacity Status Scale—Revised: a Novel, Multi-Dimensional Patient-Reported Measure of Disability in Multiple Sclerosis

Multiple sclerosis (MS) is associated with a wide variety of symptoms affecting patients' functioning and quality of life. Because of the heterogeneous clinical profile, existing methods of assessing disability and incapacity in MS suffer from limitations in psychometric validity, practicality of administration, and comprehensive representation of the MS illness experience. The most common primary outcome used in MS research, and subsequent scales based on it, rely on an outdated understanding of MS-related disability that overemphasizes ambulatory functioning at the expense of other impactful symptoms. Specifically, studies have shown that invisible elements of the disease profile have serious consequences for patients' well-being and ability to function. This study developed a new patient-reported instrument, the Incapacity Status Scale—Revised (ISS-R), which aimed to better reflect the complex, multi-dimensional aspects of MS disability. The ISS-R is available in both computerized and pen-and-paper formats and can be completed in approximately five minutes. It assesses 16 areas of functioning, using adaptive questioning with precise anchoring statements to minimize subjectivity. Principal component analysis of the ISS-R yielded a two-component solution, corresponding to Physical and Mental/Sensory functions, prompting the creation of two subscales. Item and scale analyses demonstrated strong reliability, consistency, and discrimination for the total scale and subscales. The ISS-R showed strong convergent validity with a performance-based composite ($r = -.547$, $p < .001$) and with an array of domain-specific objective and self-reported physical and

neuropsychiatric outcomes, reflecting the ISS-R's ability to capably represent both visible and invisible elements of MS disability. Discriminant validity was strong. Subscales and items similarly demonstrated excellent construct validity. Scores from the ISS-R were used to create predictive models using receiver operating characteristic (ROC) curves for employment status (AUC = .819, $p < .001$), fall risk (AUC = .805, $p < .001$), depressive (AUC = .845, $p < .001$) and anxiety disorders (AUC = .749, $p < .001$), and cognitive impairment (AUC = .736, $p < .001$), supporting criterion validity and generating practical interpretive cutoff scores. The ISS-R is a promising new patient-reported outcome allowing clinicians and researchers to assess the multi-dimensional aspects of disability in MS.

Development and Validation of the Incapacity Status Scale—Revised:

a Novel, Multi-Dimensional Patient-Reported Measure of Disability in Multiple Sclerosis

by

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Dedication

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Chapter I

Introduction

Multiple sclerosis (MS) is an immune-mediated disease affecting myelinated neurons within the central nervous system. Several subtypes of the disease have been described, classified by their differences in course of progression. Regardless of MS variant, the majority of cases show a long-term trend toward increasing presence of lesions and worsening symptoms over time (Filippi et al., 2018; Lublin et al., 2014).

Patients may present with a variety of symptoms depending on the location of lesions. The impact of symptoms has far-reaching consequences for patients' physical and mental health, as well as for their functional outcomes, including employment, social participation, and independence in completing activities of daily living. Although MS was once considered to be uncommon, epidemiological studies have documented a steady increase in rates of diagnosis. Large MS populations exist in North America and Europe, where current estimates indicate a prevalence of greater than 100 patients per 100,000 people (Howard, Trevick, & Younger, 2016). In the past five decades, estimated prevalence of MS in the United States has risen from 123,000 cases in 1976, to 300,000 cases in 1990, to more than 400,000 cases in 2009. Advances in diagnostic methods and technology have seen an even more precipitous rise in diagnosis over the past several years (Nelson et al., 2019); 2010 prevalence was estimated at 727,344 cases, representing a 309.2 per 100,000 rate, while the most recent estimates of data collected through 2017 suggest prevalence as high as 913,325 cases nationwide, a 362.6 per 100,000 rate (Wallin et al., 2019). Improvements in treatment have

also improved the survival rates of MS, leading to higher overall prevalence and a growing population of geriatric MS patients (Louapre, Papeix, Lubetzki, & Maillart, 2017).

Alongside the development of new immunotherapies targeted toward specific MS disease pathways has been an increase in attention from clinical researchers interested in accurately measuring patients' functioning, both in the natural course of the disease and as a direct response to specific MS treatments. While an extensive research network has contributed to the advancement of basic and clinical science in MS, the field has long suffered from a lack of optimal primary and secondary outcome measures for use with MS patients. The flaws in existing forms of measurement include impracticality, expense, psychometric and statistical limitations, and poor representation of the multifaceted elements impacting patients' experience of health and disability (van Munster & Uitdehaag, 2017; Cohen, Reingold, Polman, Wolinsky, & International Advisory Committee on Clinical Trials in Multiple Sclerosis, 2012).

The most commonly used primary outcome in clinical MS trials research is the Expanded Disability Status Scale (EDSS; Kurtzke, 1983). The EDSS is a 20-point ordinal rating scale that attempts to integrate scores from seven functional neurological systems: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral/mental. This scale, however, has numerous significant limitations that prevent it from serving as an ideal research measure, and have entirely precluded its use as a clinical instrument.

Contrary to its name, the EDSS has long been described as a measure of multifocal neurologic impairment rather than overall disability (Willoughby & Paty, 1988). As MS is a disease that inherently affects a wide range of capacities, the calculation of the total EDSS score based on functional systems scores is intended to adequately represent the broad

domains of disease activity and impairment found in patients. However, given the knowledge available to researchers in the 1970's and 1980's, when the scale was developed, a determination was made to weight the EDSS heavily toward lower motor functioning, as increasing difficulty with walking was considered the most prominent symptom of the disease (Thompson & Hobart, 1998). Although lower motor disturbance is a highly visible form of dysfunction in MS, it is far from the only sequela of MS, and is not necessarily the most disabling, or the most impactful on patients' quality of life and perception of their illness (Green, Cutter, Friendly, & Kister, 2017). As the EDSS is most reflective of walking and other related forms of physical disability, it may not be an ideal measure for gauging overall levels of disability, daily functioning, or risk of further decline. A measure that is more sensitive to other types of disability commonly found in MS would be better suited to evaluating patients comprehensively.

Learning to administer the EDSS also requires specialized, paid training; the assessment itself consists of a structured neurological examination which requires the clinical researcher to spend considerable time performing the standardized assessment protocol. Furthermore, because the scale is used exclusively for research purposes, those administering the EDSS must be paid out of a research budget rather than through patient insurance, and the score obtained from the evaluation serves a relatively meager role in ongoing patient care. The EDSS therefore adds considerable time and expense to any MS research in which it is utilized as an outcome measure, and can interrupt the normal flow of patient care in a research clinic without providing any corresponding benefit to the clinician or patient.

Clinicians and clinical researchers in the MS field would benefit from a new outcome measure that does not require the expense or specialized training of the EDSS, and which

provides a better representation of the broad variety of dysfunction that MS patients experience. In particular, an accurate self-report that acknowledges the subjective concerns of MS patients while maintaining validity in representing objective clinical data is needed to bridge the gap between patients' experience and externally measurable outcomes.

This study presents a new patient-reported outcome (PRO), the goal of which is to accurately assess and report disability across a multitude of neurological and symptomatic domains. This instrument, the Incapacity Status Scale—Revised (ISS-R), was inspired by an interview assessment protocol, the Incapacity Status Scale, originally formulated contemporaneously with the EDSS and appearing as part of the Minimal Record of Disability in MS ("IFMSS Minimal Record of Disability for Multiple Sclerosis," 1984). The present study sought to develop and validate this patient-reported, free-to-use scale, with the hope that it will provide considerable value as an outcome measure in future MS research and clinical practice.

Background and Significance

MS has a considerable impact on patient quality of life, and is responsible for an enormous financial burden to patients and healthcare systems (Rieckmann et al., 2013). One particular challenge in the effective treatment of the disease and its symptoms comes in the diagnosis and assessment of disease progression. One established method of qualifying clinical outcomes is through the standard of no evidence of disease activity (NEDA). Establishing this criterion involves the use of neuroimaging, primarily magnetic resonance imaging (MRI), to assess relapses or new disease activity in the brain. However, the most frequently selected forms of radiographic measurement, such as T2 hyperintense lesion burden, are poor correlates of clinical disability (Ziemssen et al., 2016).

Several factors may account for this discrepancy. The presence of T2 lesions is not directly reflective of neuroaxonal damage or death, which can contribute to lasting disability in MS. Additionally, radiological correlates of symptoms cannot always be found in MS. An inability to detect evidence of worsening disease is not proof of quiescence, and a patient can become increasingly disabled while still meeting the criteria to show NEDA. Therefore, it would be inappropriate to rely solely upon radiological findings and the NEDA standard in making treatment decisions or assessing results of research. This would fail to optimize patient outcomes, and would not maximally reduce the level of disability and impairment that patients experience on a daily basis.

Multiple methods of scientific inquiry are therefore required to investigate MS outcomes, and holistic interpretation of clinical and research data necessitates the use of instruments which do not neglect the potential diagnostic value of any symptom type. Pharmaceutical research, including a recent focus on monoclonal antibody development, has led to a surge in the number of disease modifying therapy (DMT) drugs approved by the U.S. Food and Drug Administration (FDA) to slow the progression of the disease (Multiple Sclerosis Coalition, 2018; Wingerchuk & Weinshenker, 2016). However, development of tools to properly measure the precise benefit of these medications has lagged far behind the creation of the DMTs themselves. Both the FDA and European Medicines Agency have published guidance papers calling for the use of PROs to evaluate medication benefits and support labeling claims (U.S. Food and Drug Administration, 2009; European Medicines Agency, 2005). However, the development of valid patient-reported instruments to represent disease progression, disability, and functional incapacity in clinical trials remains a clear area of weakness in MS (D'Amico, Haase, & Ziemssen, 2019).

One of the most significant challenges to the development of accurate disability PROs has been the difficulty in reflecting heterogeneous MS presentations within a single scale. Strategies to circumvent these challenges have included the administration of measures which reflect few or only one visible domain of functioning, such as walking; or the use of a large battery of symptom-specific scales, which can be burdensome to administer and which provide too many unique and psychometrically incompatible data points to be easily reconciled in clinical or research settings.

Opara, Jaracz, and Brola (2010), in reviewing the factors impacting quality of life in MS, list a wide variety of signs and symptoms, including: pain and other changes in sensation; muscle weakness; motor difficulties, such as impaired balance and coordination; depression and anxiety; visual problems; speech disturbance; cognitive impairment; and fatigue. Researchers have also observed an additive effect among these symptoms, many of which are comorbid and mutually contribute to worsening of function and quality of life. For example, both pain and depression are independently associated with psychosocial risk factors for mutual worsening (such as loss of work, social disruption, and general feelings of being unwell). As pain and depression frequently co-occur in MS, they can have a circular effect in which both become progressively more debilitating (Alschuler, Ehde, & Jensen, 2013). Considering incapacity from a multidimensional perspective is therefore of the utmost importance when conducting a complete patient-centered assessment.

Physical elements of the MS disease profile. The most immediately apparent types of dysfunction in MS are the physical forms of incapacity. Walking is affected in many patients, even in early stages of the disease and for those with relatively low overall levels of disability (Comber, Galvin, & Coote, 2017). MS lesions can produce difficulties with gait

initiation (Galli et al., 2015), smoothness (Pau et al., 2017), and consistency in stride length and timing (Kalron, 2016).

MS patients experience intrusive difficulties with upper limb functions, with more than half of patients reporting ownership of at least one upper motor assistive device (Marrie et al., 2017). Difficulty with limb functions, such as altered sensation, poor strength and dexterity, and rapid fatigability can emerge unilaterally or bilaterally at all stages of disease progression (Severijns, Van Geel, & Feys, 2018; Bertoni, Lamers, Chen, Feys, & Cattaneo, 2015). Postural control, gait problems, and upper limb impairments restrict patients' ability to participate in normal activities, including exercise, and therefore represent a significant detractor from health-related quality of life (Cetisli Korkmaz, Can Akman, Kilavuz Oren, & Bir, 2018; Cattaneo, Lamers, Bertoni, Feys, & Jonsdottir, 2017). These issues can be addressed through clinical intervention and lifestyle changes with potential neuroprotective benefit, making them important symptoms to assess thoroughly and regularly (Charron, McKay, & Tremlett, 2018; Reider, Salter, Cutter, Tyry, & Marrie, 2017).

Dysphagia and other physical difficulties with food consumption and preparation have serious consequences for patients' health. Dysphagia is a common symptom, affecting between 37% and 58% of patients (Aghaz, Alidad, Hemmati, Jadidi, & Ghelichi, 2018). In early to middle stages of MS, this can cause coughing, anxiety about meals, and reduced desire to eat, while in later stages swallowing difficulties can be a specific cause of MS mortality due to choking or complications of aspiration (Alali, Ballard, & Bogaardt, 2018). Overall, physical difficulties affecting efficient food intake are associated with poor nutritional health among MS patients (Redondo Robles et al., 2019).

Bowel and bladder functions are frequently affected by MS and have significant quality of life ramifications (Vitkova et al., 2014). Fecal incontinence and constipation can occur within the same patient, with root causes spanning neurological damage, behavioral factors, and polypharmacy. Because untreated problems can lead to infections or require surgery as a long-term intervention, it is important that bowel dysfunction be properly assessed in a timely fashion (Preziosi, Gordon-Dixon, & Emmanuel, 2018). Bladder control problems, such as urinary urgency, frequency, incontinence, and nocturia affect a majority of MS patients during their lifespan (Kisic Tepavcevic, Pekmezovic, Dujmovic Basuroski, Mesaros, & Drulovic, 2017; Akkoç et al., 2016). Therapeutic options exist, highlighting the need for evaluation of urological issues (Yang, 2013; Tubaro et al., 2012).

In conjunction with typical neurological examination and performance-based measures, the use of PROs is recommended to monitor changes over time, and to facilitate discussions between clinicians and their patients about the burden produced by the presence of physical symptoms (Smrtka, Brown, & Bjorklund, 2016).

Neuropsychiatric elements of the MS disease profile. Research since the initial publication of the EDSS indicates that invisible forms of disability may in fact be the most prominent elements of the disease profile from the patient's perspective (Green et al., 2017). Physician opinions of impairment tend to place far more emphasis on observable, physical factors when compared to the ratings of patients (Heesen et al., 2018). It is clear that there is a need, both for clinicians and researchers, to assess the progression of MS in a comprehensive but standardized manner that includes interpretation of all types of patient complaints.

Pain and altered sensation are significant aspects of disability in MS. It is estimated that half of MS patients experience pain chronically (Ferraro et al., 2018; O'Connor, Schwid, Herrmann, Markman, & Dworkin, 2008), with 73% reporting some level of acute pain, and 40% of MS patients endorsing pain as moderate or worse according to MS pain rating standards (Alschuler et al., 2013; Alschuler, Jensen, & Ehde, 2012).

Sleep disturbance is highly impactful in MS as well. Although disordered sleep is common, it remains underdiagnosed among MS patients (Braley & Boudreau, 2016; Brass, Li, & Auerbach, 2014), and is independently associated with overall disability (Vitkova et al., 2018). Unsurprisingly, fatigue is also among the most commonly reported MS symptoms, with prevalence estimates of approximately 75% (Lerdal, Celius, Krupp, & Dahl, 2007; Krupp, 2006). Historically, fatigue has been overlooked in MS treatment for a variety of reasons. It is difficult to assess objectively, and it is highly complex in both presentation and etiology.

Fatigue can be experienced in one or both of physical and cognitive domains, which can be difficult to parse during a standard patient evaluation. Braley and Chervin (2010) note that fatigue also stems from a variety of primary neurological causes, including the presence of proinflammatory cytokines, abnormal endocrine function, axonal loss, and other brain changes observed only on non-conventional forms of neuroimaging, such as positron emission tomography or functional MRI. Because these MRI sequences are not typically employed in routine MS follow-up, these organic causes of fatigue can easily be missed.

Secondary causes of fatigue include inadequate sleep and the presence of sleep-related disorders, depression, overall disability level, and iatrogenesis, given the prominent use of antispasmodic drugs, anxiolytics, pain medications, and immunomodulators.

Medications of these types are known to carry risks of fatigue and drowsiness. All of these primary and secondary factors are considerably more prevalent in MS than in the general population.

Studies have shown that impairment of mental functions, such as cognition and mood, is the strongest predictor of quality of life in MS, while fatigue is the most prevalent and severe individual symptom (Wynia, Middel, van Dijk, De Keyser, & Reijneveld, 2008). Cognitive dysfunction can appear very early in the course of the disease—even prior to the conversion of clinically isolated syndrome (a single demyelinating event) into diagnosable MS. Neuropsychological studies have demonstrated a relationship between diminished information processing speed, the core cognitive deficit in MS, and a decline in health-related quality of life, independent of patients' level of physical disability (Benedict et al., 2017; Wilski & Tasiemski, 2016; Lysandropoulos, Havrdova, & ParadigMS Group, 2015).

The MS cognitive profile is subtle and changes are gradual in onset, with general sparing of cerebral functions such as language and memory that are prominently affected in other neurocognitive disorders (Chiaravalloti & DeLuca, 2008). Even neurologists cannot identify cognitive impairment in their patients at better than chance levels based on the information obtained during a standard neurological examination and clinical interview (Romero, Shammi, & Feinstein, 2015). Because changes in cognition can be a sign of relapse, it is important that such complaints be properly evaluated and assessed through timely referral for formal neuropsychological testing (Foley & Portnoy, 2018; Giedraitiene, Kaubrys, & Kizlaitiene, 2018). Researchers suggest that early detection and intervention through cognitive remediation programs may improve quality of life for affected MS patients (Glanz et al., 2010).

Other work has highlighted the psychiatric component of MS-related quality of life, including patients' emotional adjustment to illness and perception of their disease. Researchers have long called for increased clinical recognition of the neuropsychiatric sequelae of MS, as well as "better quantification of treatment responses [to neuropsychiatric interventions] in clinical trials…to provide a complete picture of patients' health status." (Benito-León, Morales, Rivera-Navarro, & Mitchell, 2003, p. 1291).

Psychiatric illness is very common in MS, with recent systematic reviews placing the point prevalence of depression between 23.7% and 30.5%; anxiety between 21.9% and 22.1%, and alcohol abuse at 14.8% (Boeschoten et al., 2017; Marrie et al., 2017; Marrie et al., 2015). Lifetime prevalence estimates for depression are as high as half of all patients (Patten, Marrie, & Carta, 2017; Siegert & Abernethy, 2005), while a study of more than 115,000 individuals in Canada found that the point prevalence of depression in individuals with MS was more than twice that of unaffected individuals. Furthermore, prevalence was highest in the 18- to 45-year age group, at 25.7%, despite this younger MS population generally showing lower levels of physical disability (Patten, Beck, Williams, Barbui, & Metz, 2003).

These findings suggest that psychiatric dysfunction in MS may follow a different course from other forms of disability, particularly physical impairments. This introduces challenges in diagnosis and treatment of mental illness. The complexity and unpredictability of focal lesions in MS means that depression can easily be overlooked as coming from other MS symptoms (Minden, Orav, & Reich, 1987). For example, lack of energy, diminished motivation, and slowed movements can be attributed to fatigue or motor difficulties. In this way, the proper diagnosis of a mood disorder might be obscured, preventing the care

provider from beginning necessary treatment. Because of these challenges, mood disorders in MS are notoriously difficult to treat pharmacologically, and MS-specific guidelines for the prescription of psychotropic drugs are lacking (Nathoo & Mackie, 2017).

Visual disturbance can occur as the product of oculomotor difficulties or lesions anywhere in the afferent visual system, from the retina and optic nerve to thalamic or cortical tissue. The result can be a wide range of visual problems affecting quality of life, including diplopia, oscillopsia, depth perception weakness, and partial or complete visual field loss (Costello, 2016).

Communication can also be impaired in MS. This can result from cognitive deficits, such as expressive or receptive aphasic disorders (Renauld, Mohamed-Saïd, & Macoir, 2016). Speech apraxia and dysarthria also occur in MS (Noffs et al., 2018; Rusz et al., 2018). Hearing difficulties are associated with focal lesions in the brainstem or vestibulocochlear nerve (Kaytancı, Ozdamar, Acar, & Tekin, 2016; Furst & Levine, 2015). The prognosis for recovery of hearing is variable in such cases (Fernández-Menéndez, Redondo-Robles, García-Santiago, García-González, & Arés-Luque, 2014). Sudden sensorineural hearing loss, while still a rare symptom, occurs at considerably higher rates among MS patients than in the general population (Atula, Sinkkonen, Saat, Sairanen, & Atula, 2016).

Sexual health is an important and often under-assessed aspect of the MS symptom profile. Sexual dysfunction affects 33-75% of women and 47-75% of men with MS, and can stem from a variety of primary and secondary causes, including psychiatric and neuropsychological factors (Pöttgen et al., 2018; Marck et al., 2016; Lew-Starowicz & Gianotten, 2015). Difficulties with sexual health have significant repercussions for patients' mood, self-image, and relationships (Delaney & Donovan, 2017). A study of more than 9,000

MS patients found that only 20.6% were asked about sexual problems by their healthcare providers, resulting in inadequate treatment (Wang et al., 2018).

Given the significant impact of non-physical disability, particularly neuropsychiatric functioning, on quality of life and disease burden in MS, it is essential that tools used to measure patient status and treatment responsiveness incorporate a broader understanding of what disability really means to the patient living with MS.

Psychosocial and functional limitations among MS patients: the importance of assessment. The physical and mental components of MS produce a range of real-world difficulties. Physical and cognitive limitations impact patients' completion of daily living activities (Sebastião, Pilutti, & Motl, 2019; Goverover, Strober, Chiaravalloti, & DeLuca, 2015; Salter, Cutter, Tyry, Marrie, & Vollmer, 2010), with patients suffering significant detriment to their independence and overall quality of life (Cowan, Pierson, & Leggat, 2018). Tools that help patients better understand their own functional limitations and prepare for changes in their independence are recommended to improve collaborative decision-making with their care providers and enhance overall patient safety (Gerstenecker et al., 2017; Beer, Khan, & Kesselring, 2012).

Social deficits are also common in MS and are strongly related to patients' quality of life (Lex et al., 2018; Rimaz, Mohammad, Dastoorpoor, Jamshidi, & Majdzadeh, 2014). Pain and decreased physical functioning restrict patients' ability to engage in social activities (Kratz et al., 2017), while deficits in social cognition are increasingly recognized as a common manifestation of the disease (Bora, Özakbaş, Velakoulis, & Walterfang, 2016; Cotter et al., 2016). Feelings of loneliness and social isolation are common in patients struggling with significant disability profiles or single marital status (Freeman, Gorst, Gunn,

& Robens, 2019; Balto, Pilutti, & Motl, 2019). Social connectedness is also a potential protective factor against the development of depressive symptoms among MS patients, for whom as much as 52% of the relationship between stressors and depression is mediated by loss of social functions (Kirchner & Lara, 2011). Assessing risk factors for loss of social functioning is important to maximize patients' psychosocial wellbeing.

Loss of employment is a serious possible consequence of MS, affecting approximately half of all patients, and stemming from a variety of visible and invisible causes (Forslin, Fink, Hammar, von Koch, & Johansson, 2018; Lorefice et al., 2018; van der Hiele et al., 2015). Researchers have found that a majority of patients experience loss of productivity at work (Chen et al., 2019), while work absenteeism has been reported in as many as 73.3% of MS patients, including absences of greater than a month of work per year in 45.6% (Doesburg, Vennegoor, Uitdehaag, & van Oosten, 2019). Reductions or total inability to work has a deleterious impact on overall quality of life by limiting opportunities for social interaction, contributing to financial hardships, and producing loss of self-efficacy and sense of purpose (Krause et al., 2019). Because changes in employment status are difficult to address after they have occurred, it is imperative that holistic evaluation of patient status includes assessment of risk for change in employment status, both to inform targeted interventions (Gerhard, Dorstyn, Murphy, & Roberts, 2018) and to assess treatment effectiveness in research (Raggi et al., 2016).

Physical and cognitive forms of disability in MS are associated with an increased risk of falling (Gunn et al., 2018; Etemadi, 2017; Wajda, Motl, & Sosnoff, 2013; D'Orio et al., 2012). Falls represent a danger to patients' health and serve as an independent predictor of worsening disease status (Gunn, Newell, Haas, Marsden, & Freeman, 2013). Accordingly,

screening for fall risk would help to identify at-risk patients and target them for early intervention. In-office testing of walking functions has proven to be an ineffective method of assessing risk for falls (Fritz et al., 2018). However, there is precedent supporting the effectiveness of gait- and fatigue-based PROs for screening fall risk in MS patients (Tajali et al., 2017). A comprehensive PRO capable of detecting patients at risk of falling would be of obvious benefit to MS clinicians.

Existing PROs for disability in MS: virtues and limitations. In producing a new PRO for MS, it is important to acknowledge the large body of research using the EDSS, and to create a scale that can be interpreted conceptually in relation to the outcome measures used in existing studies, as well as one that is convenient and inexpensive to administer.

Patient Determined Disease Steps (PDDS). The PDDS is a single-item PRO intended for use as an outcome measure, and indeed as a surrogate for the EDSS, with which it shows very strong correlation. However, the authors note that despite the high correlation between the two scales, they are not isomorphic, and fail to demonstrate statistical agreement; that is, while higher EDSS scores are associated with higher PDDS scores, the scales do not provide similar ratings, particularly at the higher and lower ends of the disability spectrum (Yvonne C. Learmonth, Motl, Sandroff, Pula, & Cadavid, 2013). Furthermore, the single item in the PDDS addresses only walking and lower motor functioning. This unidimensional focus is what allows the PDDS to correlate so strongly with the EDSS, but it serves to highlight the fact that both scales do not provide a comprehensive assessment of disability in MS.

Patient-Reported Outcomes Measurement Information System (PROMIS) and Quality of Life in Neurological Disorders (Neuro-QOL). The National Institutes of Health has worked to develop PROMIS (Cella et al., 2010) and Neuro-QOL (Cella et al., 2012), data

banks of questionnaires assessing functional impairment and quality of life across medical conditions and neurological disorders, respectively. PROMIS and Neuro-QOL represent encouraging sets of tools, particularly in the standardized comparison of different disease groups, but the breadth of these measures is both an asset and a limitation. While various short- and long-form measurements within different domains are available, the individual choice remains with the clinician or researcher how to best use the measures. Accordingly, the administrator must either pre-screen the patient based on their complaints in order to know which scales to administer (thereby adding to the time required and reducing the impartiality of unbiased PRO administration), or force the patient to complete a longer battery of scales assessing different symptom types.

Additionally, comprehensive measurement of dysfunction across domains remains somewhat unwieldy given the sheer number of different instruments that would need to be administered in order to produce a comprehensive evaluation of patient complaints. Furthermore, the scales trend more in the direction of assessing quality of life than overt functional incapacity. These tools also provide accurate intra-domain measurements, but not a psychometrically validated single score assessing overall disability for a specific disease population such as MS.

Multiple Sclerosis Impact Scale (MSIS-29). The MSIS-29 is comprised of 29 1-to-5 Likert items, inquiring about physical limitations and the degree to which MS symptoms and restriction in activities are bothersome to the patient (Hobart, Lamping, Fitzpatrick, Riazi, & Thompson, 2001). The scale, which was designed for use in clinical trials and epidemiological studies, provides a unitary outcome score following a straightforward and relatively quick administration. However, it suffers from several limitations.

First is the use of ordinal number ratings tied to vague general statements (e.g., “a little,” “moderately,” quite a bit”). Such methodology adds to the subjectivity of patient-reported data, and fosters the potential for increased error stemming from inconsistencies in patients’ internal rating schemata, or biased ratings due to affective disposition unrelated to the content of the question. Additionally, subsequent studies found weak correlations between the psychological components of the scale and external measures, including other functional and performance-based outcomes (Hoogervorst, Zwemmer, Jelles, Polman, & Uitdehaag, 2004).

Rasch analyses also indicated psychometric concerns with the scale’s representation at the lower-functioning end, and poor fitting of items to dichotomous physical and non-physical subscales. Rather, the underlying constructs would more accurately be conceptualized as symptoms, limitations, and psychological impact (Cleanthous et al., 2017). Other researchers have taken issue with combining all items from the MSIS-29 into a single scale score, which they found to be psychometrically unjustified (Ramp, Khan, Misajon, & Pallant, 2009).

MS Rating Scale—Revised (MSRS-R). The MSRS-R is an adapted neurological rating measure which asks patients to self-rate in eight areas: walking, arm/hand function, vision, speaking clearly, swallowing, thinking/memory/cognition, numbness/tingling/burning/pain, and bowel/bladder function (Wicks, Vaughan, & Massagli, 2012). Each area is rated ordinally to reflect the absence of symptoms; the presence of symptoms without disability; and mild, moderate, and severe levels of disability. The emphasis on degree of impairment is a clear strength of the scale, but there are several clear concerns which have not been addressed or further evaluated in follow-up studies.

There are apparent weighting issues in the MSRS-R, as each symptom contributes equally to the total score despite highly unequal reporting of scores by patients. For example, 18% of respondents considered their walking to be severely disabled and 13% reported severe disability due to altered sensation; however, only 4% of patients reported severe cognitive problems, only 3% reported severe vision difficulties, and only 1% reported each of upper motor, speaking, and swallowing trouble. Only a single component was extracted from the relatively few items, so no subscales were created. Given the physiological overlap in the domains supposedly being measured (for example, cerebellar and pyramidal tracts affecting both upper and lower limb function), this raises some concerns regarding the validity of these items in representing neurological functions.

The inclusion of two separate items to measure speaking and swallowing, thereby comprising 25% of the full scale, is also somewhat curious given the comorbidity of these symptoms and their comparatively low contribution to patients' perceptions of disability compared to neuropsychiatric and other forms of physical disability. Most concerning is the absence of any measure of mood or psychosocial functioning, given that such symptoms represent a vital area of impact on MS patients' sense of wellness.

SymptoMScreen. The SymptoMScreen was developed as a very brief assessment of patients' symptom severity for use in clinical practice (Green, Kalina, Ford, Pandey, & Kister, 2017). The instrument is presented on a single page and consists of 0-to-6 Likert items assessing various areas of symptomatology. The SymptoMScreen shows good correlative validity with external measures among patients with mild-to-moderate levels of disability (Fitzgerald et al., 2019). However, like many other scales, it relies on general designations of symptom severity in the middle ranges (e.g., rankings 1-5 correspond to

"very mild," "mild," "moderate," "severe," "very severe" symptoms). The guiding statements provided to patients provide similarly ambiguous anchors (e.g., "I make frequent adjustments," "I reduced my daily activities," "I gave up some activities").

As noted previously, such rankings are prone to very different interpretation by different patients. While the scale was designed for clinical tracking of individual patient complaints, intra- and inter-individual differences may be a source of uncontrolled error in longitudinal clinical assessment or cross-sectional research. Further studies would be needed to support the scale's use as a clinical assessment for longer than a three-month interval (Green et al., 2017). Its utility in disability research is also limited by its intended design as a symptom inventory, as opposed to a measure more explicitly assessing incapacity or disability constructs.

Innovation

The following key points were addressed in this study based on the current needs of the field and the limitations of existing instruments. First, the assessment tool that was developed needed to be practical to administer for both clinical and research purposes. Second, it needed to comprehensively evaluate both visible and invisible elements of MS-related disease burden, given the important manifestations of both on functional outcomes and quality of life. Most existing tools operate with a far more limited model of MS disability, and our current understanding highlights the antiquated nature of past instruments' approach to monitoring dysfunction. Finally, the instrument needed to accomplish these tasks in a manner that conceptually links disease activity with functional outcomes. In the short-term, substantial changes to the EDSS might force regulatory agencies to no longer accept any individual measure as a gold standard, which would hamper researchers' ability to

conduct research with treatment efficacy as the primary outcome. Instead, researchers promote the use of methodological refinements and adjunctive forms of measurement (Cohen et al., 2012). The ISS-R was therefore designed in a manner that would help bridge the gaps between past and current measures, and between objective test results and patient experience.

Achieving accurate self-assessment across functional neurological systems presents obvious challenges (Collins et al., 2016; Bowen, Gibbons, Gianas, & Kraft, 2001). The ISS-R was created in an attempt to improve upon PRO methods whose core structure dates back nearly forty years to the development of the EDSS, when modern knowledge of MS was not yet available to researchers. The ISS-R evaluates 16 common areas of disability, with gradations in score also reflecting current standards of MS care, including the use of modern medications, newer assistive devices, and compensatory strategies frequently employed by patients. This scale was designed to provide researchers and clinicians with a free-to-use PRO that can be completed in minutes. It was validated extensively against a wide range of objective and subjective measures, and is sensitive to the many elements of disability that are not well assessed by other available forms of measurement. It is anticipated that this scale will reduce the cost of future research compared to paid outcome measures and minimize the time burden on patients and clinical researchers.

Aims and Hypotheses

Consistent with the above-stated goals, this study had the following aims and hypotheses:

Aim 1: To expand upon study of the domains underlying neurological and neuropsychiatric dysfunction in MS.

Hypothesis 1: The different types of disability measured by the ISS-R will show a component structure analogous to functional systems and outcomes. In this way, it will be possible to make appropriate comparisons between the ISS-R, clinical data, and existing scales measuring disease status and illness burden, and to contribute to broader understanding of MS symptom comorbidity.

Aim 2: To evaluate the psychometric properties of the ISS-R using a sample of the MS population, and determine its validity as a comprehensive PRO.

Hypothesis 2a: The scale will be an internally reliable measure of incapacity.

Hypothesis 2b: Items, subscales, and the total scale score will demonstrate construct validity through strong relationships with related objective and subjective symptom and function measures.

Hypothesis 2c: Items, subscales, and the total scale score will demonstrate discriminant validity through weak associations with unrelated measures or measures of different disability constructs.

Aim 3: To assess the accuracy of self-rated impairment in MS, and examine discrepancies between patient complaints and the types of disability historically prioritized in MS care.

In prior research, self-report instruments measuring disability show strong correlation with physician estimates and objective measurements of physical functioning (Stuifbergen, Morris, Becker, Chen, & Lee, 2014; Bowen et al., 2001). Mental and non-physical functions are incompletely assessed and often underestimated in routine care.

Hypothesis 3a: The ISS-R will demonstrate criterion validity through comparison with functional and disability-based outcomes, and will outperform a widely used MS PRO

(the PDDS) in reflecting multi-dimensional aspects of the MS disability profile, including both visible and invisible forms of illness.

Hypothesis 3b: The classification properties of the ISS-R will demonstrate its merit as an incapacity screening instrument, and provide meaningful interpretive values for its use in this role.

Chapter II

Methods

Data were collected from the MS Center at Holy Name Medical Center (HNMC) in Teaneck, New Jersey, one of the largest clinical and research facilities for MS in the greater New York City metropolitan area. The facility serves approximately 1,800 patients each year, and has over 3,000 total individuals registered in its patient database. The center possesses a large full-time staff of MS specialty neurologists and nurses, including a dedicated research nurse. Data were collected by graduate student researchers in the lab of Frederick W. Foley, Ph.D., the MS Center's director of clinical psychology. All students received appropriate training in the administration and scoring of psychological, neuropsychological, and rehabilitation instruments, and in interviewing and coding procedures for collecting clinical data from patients. Where necessary, additional specialty training for instruments in this study was provided by the lab supervisor or by a senior graduate student. An ethical review of the study protocol and procedures for obtaining informed consent was conducted by the Institutional Review Board of the Albert Einstein College of Medicine. The protocol was approved as IRB #2009-519.

Participants and Recruitment

Patients referred for neuropsychological testing by their physician at the MS Center at HNMC are provided this service on-site, and are offered the opportunity to participate in ongoing research by consenting to the addition of their de-identified data to an MS research database. One to two patients are seen at the clinic per week on average, and patients

complete a clinical interview and battery of psychological and neuropsychological tests. The pen-and-paper version of the ISS-R was administered in conjunction with this test battery. 51 patients ultimately participated in this study via this recruitment method.

Additional patients receiving DMT infusions at HNMC's on-site infusion center were approached and screened for eligibility, per the inclusion and exclusion criteria described in the following section. These patients completed an abbreviated set of measures to assess physical and neuropsychological status in conjunction with their responses to the digital version of the ISS-R. Supplementary data were collected via review of patients' electronic medical records. Seven patients were screened but considered ineligible to participate. 13 patients were approached but declined to participate. 109 patients ultimately participated via this recruitment method. Therefore, a total of 160 patients participated in this study.

Informed consent procedures. Prior to enrollment in the study, all patients reviewed and signed an informed consent protocol discussing confidentiality and its limits; risks and benefits of involvement in this study; the purpose of the research; eligibility criteria for participation; and information allowing them to contact the research coordinator with additional questions or requests to discontinue participation for any reason at any time.

Risks and benefits to participants. Minimal risk was involved to patients. Standard risks of neuropsychological testing were described to patients undergoing neuropsychological evaluation, including test frustration and potential exposure to psychologically aversive issues during the interview and when completing self-report measures. Patients undergoing the abbreviated set of procedures were informed of similar risks, though risk was further attenuated by the brevity of the evaluation.

As the goal of the project in the long-term was the development of an evaluative instrument, there was little proximal benefit to participants. Patients received standard of neuropsychological care during their participation in the study, and relevant clinical data were made available to patients and to their MS care team.

Data security. Paper copies of study-related materials were kept in a secure environment alongside other research and clinical data within the MS Center. Digital ISS-R data were collected from participants using Qualtrics, a HIPAA-compliant online survey system. Patient electronic medical records were accessed exclusively on-site at HNMC, and were thereby safeguarded through the local encryption system on the hospital network, in compliance with state and federal law, and HNMCs protocols for patient data privacy and security. Digital files and databases accessed off-site were stored in an online cloud storage system under a HIPAA-compliant 1024-bit Digital Signature Algorithm-based encryption protocol.

Eligibility and Exclusion Criteria

Patients were eligible to participate if they were between the ages of 18 and 80 at the time of participation. Patients were required to be fluent speakers of English in order to standardize responses to written questionnaires and test administration procedures.

All patients were required to have a confirmed diagnosis of MS, as recorded by their neurologist in their electronic medical record. Patients with other conditions treated at the MS Center at HNMC were considered ineligible. The list of excluded conditions included: suspected but unconfirmed MS; clinically isolated syndrome; radiologically isolated syndrome; and other immune-mediated or demyelinating disorders, such as neuromyelitis optica and transverse myelitis.

As the study involved development of an instrument intended to monitor functional incapacity and impairment, patients were considered ineligible for this study if they were experiencing an active exacerbation or relapse of their MS. This status was determined by consultation with the MS nursing staff, review of current medical records, and direct querying of patients. Patients who were unsure of their exacerbation or relapse status, or whose status could otherwise not be determined as negative with appropriate clinical certainty, were considered ineligible for this study.

Patients were considered ineligible to participate if they had a history of any of the following conditions: traumatic brain injury more severe or more frequent than a single concussion/mild traumatic brain injury; epilepsy; Parkinson's disease or other movement disorder; Alzheimer's disease or other neurodegenerative disorder; vascular neurocognitive disorder, or another neurocognitive disorder not etiologically attributed exclusively to the effects of MS; or another major neurological illness other than MS not otherwise specified.

Measures and Procedures

The original Incapacity Status Scale showed strong correlation with the EDSS (Provinciali, Ceravolo, Bartolini, Logullo, & Danni, 1999; Slater, LaRocca, & Scheinberg, 1984), but it contained several methodological shortcomings. As an interview measure, it required administration by knowledgeable personnel, thereby introducing the potential for observer effects to influence the responses that were ultimately recorded. Furthermore, investigations by this research group found high non-response rates to certain items, such as sexual function (64.5% non-response; Portnoy, Archetti, Stimmel, & Foley, 2016), suggesting a lack of comfort, either on the part of patients or interviewers, in discussing such sensitive issues. The resulting incomplete administration of the scale not only generates

statistical and psychometric problems, but also leads to under-evaluation of important areas of incapacity that may be difficult to discuss. Field testing has also shown that, for certain items in the original Incapacity Status Scale, very few patients endorsed particular answer choices, which may imply that the items are not fully representative of patients' experiences with disability (Battaglia, Serpero, Bordo, & Garello, 1984).

Development of the ISS-R. The ISS-R contains 16 items, each asking the patient to assess their ability to complete a common daily activity independently or with aid or assistance; or to report their degree of symptomatology in a different area. Patients choose the statement that best describes their functional ability, and statements are coded in a 5-point ordinal fashion reflecting the following general hierarchy: 0 for no incapacity or disruption of activities; 1 for mild incapacity; 2 for moderate incapacity; 3 for severe incapacity; and 4 for very severe or total incapacity in the specified area of function.

The grading criteria for each item are summarized in Table 1. Contemporary trends in formulating diagnostic and severity criteria, such as those appearing in the DSM-5 (American Psychiatric Association, 2013), qualify degree of functional impairment and disability based on loss of independence and reliance on others to perform daily functions. Within MS specifically, composite functional status scores have been noted to reflect worsening disability alongside increased dependence on others (Hoogervorst, Kalkers, Cutter, Uitdehaag, & Polman, 2004). The ISS-R therefore uses this conceptual framework in qualifying levels of incapacity.

Because the ISS-R provides written descriptions of incapacity in ecologically meaningful activities, it also serves as a multi-domain screening measure for specific complaints in addition to a generalized measure of disability. The patient's care providers can

Table 1. *ISS-R items and corresponding functional systems.*

Item number	Domain	Incapacity Grading Criteria	Related Functional System(s)
1	Stair Climbing	• Difficulty climbing stairs • Need for tools or railings • Independence from human or machine assistance	Pyramidal
2	Grooming	• Difficulty grooming self • Need for extra time or special tools • Independence from human assistance	Cerebellar
3	Sensation	• Tingling, numbness, or pain • Interference with activities or relationships • Medication or compensatory behaviors	Sensory
4	Bowel Function	• Constipation, need for medication • Fecal incontinence • Independent management of colostomy	Bowel and Bladder
5	Bladder Function	• Urinary retention, catheters, manual compression • Urinary incontinence • Independent management of urostomy	Bowel and Bladder
6	Fatigue	• Frequency and severity of fatigue • Interference with physical and mental function	Cerebral, Pyramidal
7	Ambulation	• Difficulty walking 50 meters without stopping • Need for assistive devices or wheelchair	Pyramidal, Cerebellar
8	Speech/Hearing	• Interference with ability to communicate • Need for assistive devices	Brainstem, Cerebral
9	Mood	• Interference with activities or relationships • Need for psychological or psychiatric treatment	Cerebral
10	Dressing	• Difficulty dressing self • Need for special tools or clothing • Independence from human assistance	Cerebellar
11	Transfers	• Difficulty making transfers • Need for tools or assistive devices • Independence from human assistance	Pyramidal
12	Cognition	• Difficulty with activities due to problems thinking • Compensation and need for human assistance	Cerebral
13	Bathing	• Difficulty bathing • Need for special tools or assistive devices • Independence from human assistance	Cerebellar, Pyramidal
14	Feeding	• Difficulty eating, drinking, swallowing • Need for special tools or preparation of food • Independence, management of feeding tube	Brainstem, Cerebellar
15	Vision	• Difficulty with visual acuity, diplopia, oscillopsia • Independence from human assistance	Visual
16	Sexual Function	• Difficulty engaging in sexual activities • Effectiveness of compensatory behaviors • Need for medication or sexual aids	None

use individual item scores in this manner during follow up. Use of specific anchoring statements, rather than numerical or nonspecific qualitative Likert ratings, as in other scales, was employed to promote standardization by minimizing subjectivity and interpersonal differences in rating items. For example, there are known limitations in the way that self-reports tend to assess cognitive functioning, where mood factors and ruminative tendencies can influence ratings (Malivoire, Hare, & Hart, 2018; Kim et al., 2017). Descriptive designations of the impact of each symptom on day-to-day life, and the methods through which patients make accommodations for these difficulties, were intended to provide a less subjective form of inquiry.

As shown in Table 1, the ISS-R has at least one item corresponding conceptually to each of the seven functional neurological systems used in scoring the EDSS. Because responses on the scale are patient-reported, the language in the ISS-R was made as simple as possible in order to allow patients to easily understand items while still reflecting the complex symptom profile of MS. A readability estimate, the Flesch-Kincaid Grade Level, was calculated using Microsoft Word (Microsoft Office Professional Plus 2010, v14.0), which rated the scale at 8.3, suggesting that it would be well comprehended by patients reading at or above an eighth grade level in the United States.

Core measures. The following variables were considered part of the primary analyses. Data for these variables were therefore collected from participants in both recruitment methods.

- *ISS-R.* In addition to scores on each item, the time required to complete the scale was recorded to help describe the practicality of scale administration.

- Demographic and background data, including patient age, race, sex, length of education, marital status, employment/student status, and length of MS diagnosis, were collected.
- *Multiple Sclerosis Functional Composite* (MSFC; Fischer et al., 2001). The Multiple Sclerosis Functional Composite (MSFC) is a clinical and research measure that was designed to assess multiple domains of function (Cutter et al., 1999). Among the key aspects of its development was the inclusion of a cognitive measure, so as not to overlook this type of dysfunction; and for the score to be sensitive to changes in MS over time (Fischer et al., 2001). The MSFC consists of three objective measures, assessing lower extremity, upper extremity, and cognitive functions. In each of these tasks, a *z*-score is calculated to compare performance either to other participants in a study or to a set of norms used for cross-study comparison. The average of these three *z*-scores produces the MSFC total, which is more sensitive to change from different neurological dimensions than the EDSS (Hoogervorst, Kalkers, Uitdehaag, & Polman, 2002), and more sensitive than the EDSS to changes in quality of life (Ozakbas, Cagiran, Ormeci, & Idiman, 2004; Miller, Rudick, Cutter, Baier, & Fischer, 2000). The MSFC and each of its three components have been established as reliable and valid measures of MS functioning, with strong intra- and interrater reliability and test-retest reliability, despite some observed practice effects (Meyer-Moock, Feng, Maeurer, Dippel, & Kohlmann, 2014; Polman & Rudick, 2010; E. Rosti-Otajärvi, Hämäläinen, Koivisto, & Hokkanen, 2008; J. A. Cohen et al., 2000).
    - Upper motor functioning is measured by the time required to complete a 3-by-3 pegboard dexterity test using each hand (9HPT; Goodkin, Hertsgaard, & Seminary, 1988).

- Lower motor functioning is measured by the time required for the patient to walk 25 feet (T25FW).
- There has been debate among researchers about whether to use the Paced Auditory Serial Addition Test (Gronwall, 1977) or the Symbol Digit Modalities Test (SDMT; Smith, 1982) as the estimate of cognitive functioning in the MSFC, or whether both should be used in a complementary fashion (Brochet et al., 2008). The PASAT, an auditory *n*-back test requiring working memory and rapid digit addition, is the measure originally described in the MSFC. However, the PASAT is poorly tolerated by patients, who find the task demands overly frustrating and often refuse the task, discontinue prematurely, or employ an alternating-response approach that circumvents the test's working memory component at the expense of maximizing performance (Cortés-Martínez et al., 2019; Hansen et al., 2017; Locke, Stonnington, Thomas, & Caselli, 2011; Tombaugh, 2006; Fisk et al., 2005). The SDMT, a measure of visual processing speed and attention, is among the most widely used and well-validated individual cognitive tests in MS (Ruet & Brochet, 2018; Strober et al., 2018; Benedict et al., 2017; Van Schependom et al., 2014). The SDMT demonstrates superior validity, tolerability, and ease of administration compared to the PASAT when used as the measure of cognitive function in the MSFC (López-Góngora, Querol, & Escartín, 2015; Karabudak et al., 2015; Drake et al., 2010). Accordingly, the SDMT was used as the measure of cognitive functioning for calculating the MSFC in this study. The oral version of the SDMT was administered, as it eliminates potential variance stemming from the upper motor demands of the written version.

- *Patient Determined Disease Steps* (PDDS; Learmonth et al., 2013). This measure served as a surrogate for the EDSS, as well as a valid self-reported measure of ambulation and independent measure of generalized disability. PDDS and EDSS scores are strongly associated (r_s = .784), and the scale also correlates significantly with other self-reported and objective measures of walking ability cross-sectionally. Despite some validity weaknesses in longitudinal measurement of walking due to fluctuations in self-reported ambulatory capacity (Motl, Putzki, Pilutti, & Cadavid, 2015), the PDDS is generally considered valid and reliable, with studies supporting its use cross-culturally and through different modalities, including phone and digital administration (Kahraman, Özdoğar, & Özakbaş, 2019; Lavorgna, Miele, Petruzzo, Lanzillo, & Bonavita, 2018; Lavorgna et al., 2017).

Supplemental measures. Patients undergoing neuropsychological testing also completed the following measures.

- *Structured Clinical Interview for DSM-IV Axis I Disorders* (SCID-I; First, Spitzer, Gibbon, & Williams, 1996). A standardized interview to determine the presence of common types of mental disorders. In this study, patients were coded dichotomously for the presence or absence of any depressive or any anxiety disorder.
- *Wisconsin Card Sorting Test* (WCST; Heaton & PAR Staff, 2003). The 128-card computerized version of this test was administered to assess patients' executive functioning capacities. The WCST is a reliable and valid detector of cognitive impairment in MS, and has been associated specifically with the presence of frontal-subcortical network lesions among MS patients (Parmenter et al., 2007; Beatty & Monson, 1996; Arnett et al., 1994). The WCST generates several scores, reflecting

different possible dysexecutive task approaches. Patients who demonstrate poor cognitive flexibility would have high numbers of perseverative errors, while patients who inefficiently generate conceptual problem-solving strategies would be expected to have high numbers of non-perseverative errors. Total errors standard scores were used as the outcome of this test. This value necessarily regresses toward the mean standard score of 100 compared to either of the specific errors scores, thereby making it more difficult to significantly associate it with any other variable. However, this approach was chosen in order to more accurately reflect when any form of executive dysfunction resulted in poor WCST performance.

- *Illness Intrusiveness Ratings Scale* (IIRS; Devins, 2010). A measure of the degree to which illness and management of illness affect the patient's life, with published norms for 36 chronic conditions, including MS. In addition to a total score, the scale provides three subscales, describing the intrusive effects of illness on social relationships, intimacy, and instrumental activities. Analyses of the scale have provided evidence of its ability to represent both physical and emotional aspects of illness burden among MS patients (Bouchard, Duquette, & Mayo, 2017). Other studies have explored the connections among the IIRS, self-reported quality of life and functional ability, and performance-based metrics, including differences and similarities between the sexes (Neto, Gromisch, Sloan, Tyry, & Foley, 2019; Snyder, Foley, Farrell, Beier, & Zemon, 2013; Turpin, Carroll, Cassidy, & Hader, 2007; Shawaryn, Schiaffino, LaRocca, & Johnston, 2002).
- *Fatigue Severity Scale* (FSS; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989). A commonly used clinical assessment that provides a continuous value quantifying fatigue

symptoms. Psychometric studies of the FSS suggest adequate reliability and ability to detect change (Learmonth et al., 2013; Armutlu et al., 2007), while confirmatory factor analysis supports its unidimensionality and construct validity (Eija Rosti-Otajärvi, Hämäläinen, Wiksten, Hakkarainen, & Ruutiainen, 2017).

- *Fatigue Scale for Motor and Cognitive Functions* (FSMC; Penner et al., 2009). A more recently developed fatigue measure, which provides subscales separating motor and cognitive fatigue in addition to a total fatigue score. In addition to strong test-retest reliability and capacity to discriminate between MS patients and healthy controls, research also provides evidence of its structural and convergent validity (Oervik, Sejbaek, Penner, Roar, & Blaabjerg, 2017; Elbers et al., 2012).
- *Patient Health Questionnaire-9* (PHQ; Kroenke, Spitzer, & Williams, 2001). A measure of depression commonly employed in clinical and research settings. The PHQ has an extensive history of use in MS specifically, where its ease of administration and high sensitivity are cited as important benefits (Marrie et al., 2018; Patten et al., 2015). Studies support the use of the PHQ as a depression screener in MS, and have allayed concerns that the presence of other common MS symptoms, such as fatigue or difficulties with concentration, might contaminate depression scores (Patrick & Connick, 2019; Sjonnesen et al., 2012).
- *Hospital Anxiety and Depression Scale – Anxiety subscale* (HADS-A; Zigmond & Snaith, 1983). A well-validated 7-item subscale quantifying symptoms of anxiety. Research supports the validity and reliability of the HADS-A in MS (Honarmand & Feinstein, 2009), and among existing anxiety screeners, the HADS-A is particularly recommended

for use with MS patients based on its superior diagnostic sensitivity and specificity (Litster et al., 2016).

- *Eating Assessment Tool-10* (EAT; Belafsky et al., 2008). A scale measuring the symptoms and impact of dysphagia, including difficulty swallowing solids and liquids, pain involved in swallowing, weight loss associated with difficulty swallowing, and daily intrusiveness of swallowing problems. The original validation study established the internal consistency, test-retest reliability, and criterion validity of the scale. More recent research, including Rasch and differential item functioning analyses, confirmed unidimensionality of the scale, but also raised concerns regarding structural validity weaknesses, a lack of range in item difficulties, and item redundancy (Cordier et al., 2017; Wilmskoetter et al., 2019). It should be noted that the decision to use the EAT and data collection for present study began prior to the publication of the latter two studies.
- *Selected short-form scales from the Multiple Sclerosis Quality of Life Inventory* (MSQLI; Ritvo et al., 1997). The Pain Effects Scale (PES), Bladder Control Scale (BLCS), Bowel Control Scale (BWCS), Impact of Visual Impairment Scale (IVIS), and Perceived Deficits Questionnaire (PDQ) were used as validated self-reports of sensory disturbance, urinary dysfunction, bowel dysfunction, visual disability, and cognitive dysfunction, respectively. Subsequent research has supported the reliability and construct validity of the MSQLI scales through correlational analyses with disease status, EDSS scores, objective function measures, and other validated health-related quality of life scales (Marrie, Miller, Chelune, & Cohen, 2003; Dilorenzo, Halper, & Picone, 2003; Fischer et al., 1999).

- *Multiple Sclerosis Intimacy and Sexuality Questionnaire-15* (MSISQ; Foley et al., 2013). A valid self-report of sexual function in MS, reflecting primary, secondary, and tertiary forms of sexual dysfunction. The 15-item MSISQ was developed from a 19-item original scale. The psychometric properties of the two versions have been well established, with multiple studies identifying the same three-component structure and supporting strong reliability and consistency cross-culturally (see, e.g., Noordhoff, Scheepe, ’t Hoen, Sluis, & Blok, 2018; Silva et al., 2015; Mohammadi, Rahnama, Montazeri, & Foley, 2014). A systematic review found that the MSISQ is currently the only valid tool for assessing sexual dysfunction in the MS population (’t Hoen et al., 2017).
- A standardized fall risk assessment was conducted during the interview to determine whether patients had fallen at least once in the two months prior to evaluation.

Data Analysis Plan

Demographic characteristics of the sample were calculated. Characteristics were compared across the two recruitment methods to ensure similarity of the two subsamples and suitability for combined analysis. Completion time was calculated for the total sample and compared for each of the two ISS-R administration methods (paper and digital). Comparison analyses were conducted using Welch’s *t*-tests for continuous variables and exact test for discrete variables.

Principal component analysis was used to reveal the component structure underlying the ISS-R. Kaiser-Meyer-Olkin (KMO) Measure of Sampling Adequacy was calculated, and Bartlett’s Test of Sphericity was conducted to determine the sample’s suitability for such analysis. Number of components to extract was determined using data set permutation-modified Monte Carlo eigenvalue simulation (O’Connor, 2018, 2000), where components

corresponding to eigenvalues greater than those randomly produced at the 95th percentile of the simulation were retained. Scree plot was generated for visual inspection of eigenvalues. Oblique rotation of the component solution was employed, as the extracted components were expected to be intercorrelated. Each extracted component informed the creation of a subscale, measuring a different element of incapacity. Individual items were assigned to a subscale based on highest component loading.

Reliability and item analyses were conducted. Cronbach's α was calculated for the ISS-R total and subscales as a measure of internal consistency. Spearman-Brown split-half coefficients based on odd-even item pairings were calculated to measure reliability within and between sections of the scale. Mean scores were calculated for each of the 16 items. Item consistency was measured using the mean inter-item correlation (IIC). Item discrimination was measured using corrected item-total correlations (ITC). Items were further assessed by calculating internal consistency if the item was deleted.

Pearson correlations between the ISS-R scales and performance-based outcomes were calculated. Correlations were calculated for the ISS-R scales and PDDS against the previously described self-report inventories, and against performance on the WCST. Spearman rank-order correlations were calculated to compare ISS-R items to corresponding outcome measures. These analyses were intended to ascertain which objective and subjective disability constructs were adequately reflected by the different scales and items, including areas in which the ISS-R and PDDS performed differently, and to assess convergent validity. Discriminant validity was assessed through correlation with years of education, which was expected to be weak or non-significant.

ISS-R scale scores and PDDS scores were compared across dichotomous employment/student status, history of falls, depressive disorder diagnosis, anxiety disorder diagnosis, and cognitive impairment using Mann-Whitney *U* test. As the median and mode age of retirement in the United States is 62 (Board of Governors of the Federal Reserve System, 2018), analysis of employment data excluded patients age 63 or older (n = 12) in order to minimize confounding effects with retirement unrelated to disability. Receiver operating characteristic (ROC) analyses were conducted for each of these five dichotomous variables using the ISS-R and PDDS in order to compare accuracy in predicting these outcomes and assess criterion validity. For ROC analyses yielding a significant overall model by area under the curve, threshold criteria were evaluated based on the coordinates producing maximum Youden index (J) and maximum specificity at sensitivity greater than or equal to 80.0%. Each criterion was further evaluated based on its associated relative risk value. Relative risk was calculated rather than odds ratio to minimize statistical volatility.

Power Analysis

Power analyses were conducted using G*Power v3.1 and MedCalc v14. The required sample size for principal component and factor analyses remains the subject of considerable mathematical debate. Some researchers have argued in favor of absolute minimum sample thresholds, such as the rule of 100 (Gorsuch, 1983). MacCallum, Widaman, Zhang, & Hong (1999), who reviewed the vast body of literature, reported that other suggestions have included the greater of 100 participants or 20 times the number of variables, and minimum cutoffs ranging as high as 150, 200, or 500. Other suggestions described in the literature have included fixed variable-to-subject ratios, including 2:1 (Kline, 1979), between 3:1 and 6:1 (Cattell, 1978), 5:1 (Bryant & Yarnold, 1995), and 20:1 (Hair, Anderson, Tatham, & Black,

1995). Subsequent research regarding factor analysis was well summarized by Costello & Osborne (2005; Osborne & Costello, 2004), who also described the lack of consensus in both principal component analysis and factor analysis. The authors' 2005 review showed that the majority of published studies using principal component or factor analysis used a fixed subject-to-variable ratio less than or equal to 10:1.

More recently, authors have found success conducting analyses with smaller samples. De Winter, Dodou, & Wieringa (2009) considered 50 subjects to be a reasonable minimum cutoff, and demonstrated that under certain data conditions, such as a low number of expected factors or high degree of difference in loadings across variables, may allow for effective extraction at even smaller sample sizes. Additional techniques have also been described for analysis on samples smaller than 50 (Jung, 2013; Jung & Lee, 2011).

In this study, given the small number of variables and low number of expected components to be extracted, a 10:1 subject-to-item ratio was considered at least sufficient to reveal the component structure of the ISS-R. For the 16-item scale, this required a total sample size of 160.

Two-tailed inter-subsample comparisons capable of detecting medium-sized effects ($d = 0.50$, $\alpha = .05$, $\beta = .20$) required a total sample size of 148; specifically, at least 47 patients in the smaller subsample, and 101 in the larger subsample. For bivariate correlations ($\alpha = .05$, $\beta = .20$) capable of detecting an effect of medium size by established criteria ($r = 0.35$; Cohen, 1988), a sample size of 49 was required. This effect size was relatively modest compared to the correlations for similar disability constructs observed in validation of the PDDS, which ranged in magnitude from $r_s = 0.501$ to $r_s = 0.805$ (Learmonth et al., 2013). A

minimum of 49 participants were therefore needed to complete the measures used in convergence analysis.

ROC power analysis was conducted for each of the five dichotomous outcomes. Acceptable ROC was defined as capable of detecting at least a moderate-sized area under the curve (AUC = 0.750, null hypothesized AUC = 0.500, $\alpha = .05$, $\beta = .20$; see Youngstrom, 2014; Swets, Dawes, & Monahan, 2000; and Swets, 1988). For employment/student status, a total sample size of 40 (20 positive and 20 negative cases) was required. For history of falls, a sample size of 50 (14 positive and 36 negative cases) was required. For depressive disorders, a sample size of 39 (19 positive and 20 negative cases) was required. For anxiety disorders, a sample size of 51 (14 positive and 37 negative cases) was required. For cognitive impairment, a sample size of 88 (12 positive and 76 negative cases) was required.

Chapter III

Results

Statistical analyses were conducted using IBM SPSS Statistics v20 and MedCalc v14. Descriptive statistics for the sample's demographic variables (age, education, length of diagnosis, sex, race, marital status, and employment/student status) were calculated. The two subsamples were compared to assess homogeneity of the full sample. Welch's *t*-test was used to compare continuous variables. Exact test was used to compare discrete variables.

Age for the sample ($M = 46.79$, $SD = 11.95$) did not differ significantly between the subsamples, $t(93.325) = 1.459$, $p = .148$. Years of education ($M = 14.82$, $SD = 2.31$) did not significantly differ between subsamples, $t(117.084) = -0.390$, $p = .697$. Length of diagnosis ($M = 11.50$, $SD = 8.95$) was 3.05 years shorter for those completing the digital questionnaire versus the paper questionnaire, representing a significant difference, $t(101.614) = -2.079$, $p = .040$. The subsamples did not differ significantly in sex ($p = .856$), race ($p = .236$), marital status ($p = .395$), or employment/student status ($p = .175$). These results are summarized in Table 2.

PDDS for the sample ($M = 2.47$, $SD = 2.24$) did not differ significantly between the subsamples, $t(97.027) = -1.264$, $p = .209$. Raw SDMT scores ($M = 49.74$, $SD = 12.62$) did not differ significantly between the subsamples, $t(105.903) = -1.232$, $p = .221$. Average 9HPT ($M = 26.18$, $SD = 7.13$) did not differ significantly between the subsamples, $t(68.709) = -0.214$, $p = .831$. Average T25FW ($M = 6.11$, $SD = 3.04$) did not differ significantly between the subsamples, $t(137.554) = -0.892$, $p = .374$. ISS-R completion time was

significantly lower for the digital version (M = 292.20, SD = 136.57) than for the paper version (M = 368.77, SD = 135.54), $t(79.887) = -3.095$, $p = .003$. These results are summarized in Table 3.

Table 2. *Total sample demographics and comparison of subsamples.*

	N = 160				
	M	*SD*	Min.	Max.	*p*
Age (yrs)	46.79	11.95	21	71	.148
Education (yrs)	14.82	2.31	10	20	.697
Length of diagnosis (yrs)	11.50	8.95	0	38	.040*
Digital	9.39	8.11	1	31	
Paper	12.44	9.18	0	38	
	n	% of sample	*p*		
Sex			.856		
Female	111	(69.4)			
Male	49	(30.6)			
Race			.236		
White/Caucasian	120	(75.0)			
Hispanic/Latino	22	(13.8)			
Black/African-American	15	(9.4)			
Other	3	(1.9)			
Marital status			.395		
Married/cohabitating	95	(59.4)			
Single	45	(28.1)			
Divorced	16	(10.0)			
Widowed	4	(2.5)			
Employment/student status			.175		
None	78	(48.8)			
Full-time	71	(44.4)			
Part-time	11	(6.9)			

Paper administration n = 51. Digital administration n = 109. Listed p values represent comparison of subsamples using Welch's t-test (age, education, length of diagnosis) and exact test (sex, race, marital status, employment/student status).
*$p < .05$.

The minimum completion time for the ISS-R was 90 seconds, while the maximum completion time was 708 seconds. Of note, these values are ecologically representative for scale administration in a busy clinic setting. Patients were permitted to complete the scale at their own pace, and these statistics include instances of administration when patients were

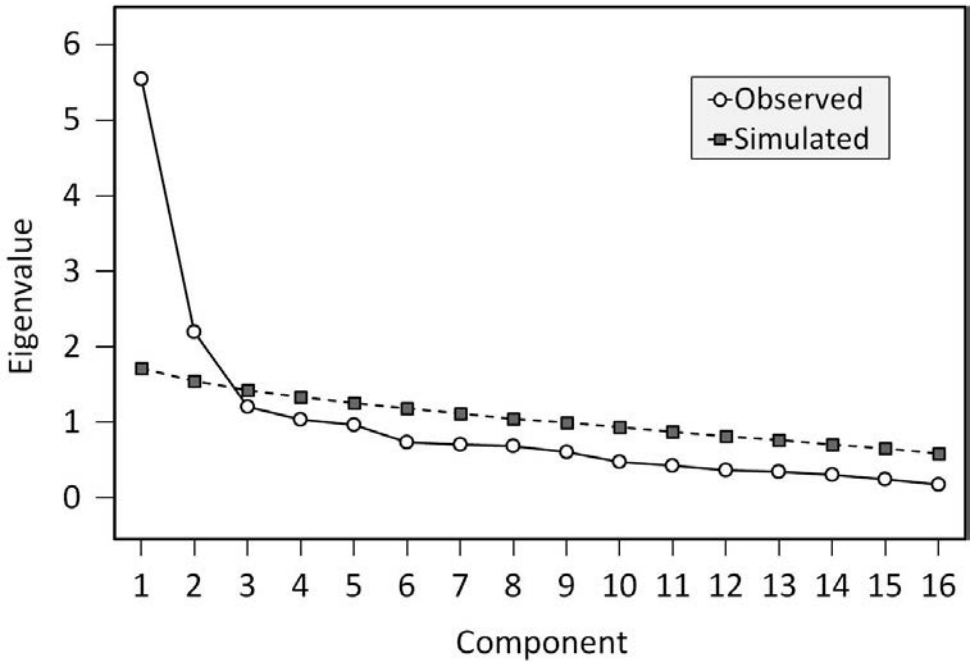
temporarily interrupted by cell phone use or conversations with family members or nursing staff. A sum of the scores on ISS-R items was calculated for each participant. These totals did not differ significantly between the subsamples, $t(107.134) = 1.214$, $p = .228$.

Table 3. *Total sample raw primary outcome variables and comparison of subsamples.*

	M (SD)	*Mdn (IQR)*	*p*
PDDS	2.47 (2.24)	2 (3.0)	.209
SDMT (raw)	49.74 (12.62)	50 (15.5)	.221
Average 9HPT (s)	26.18 (7.13)	24.88 (6.40)	.831
Average T25FW (s)	6.11 (3.04)	5.19 (2.30)	.374
ISS-R Completion Time (s)	315.06 (140.27)	291 (185.5)	.003**
Digital	292.20 (136.57)	269 (193.5)	
Paper	368.77 (135.54)	328 (162.0)	

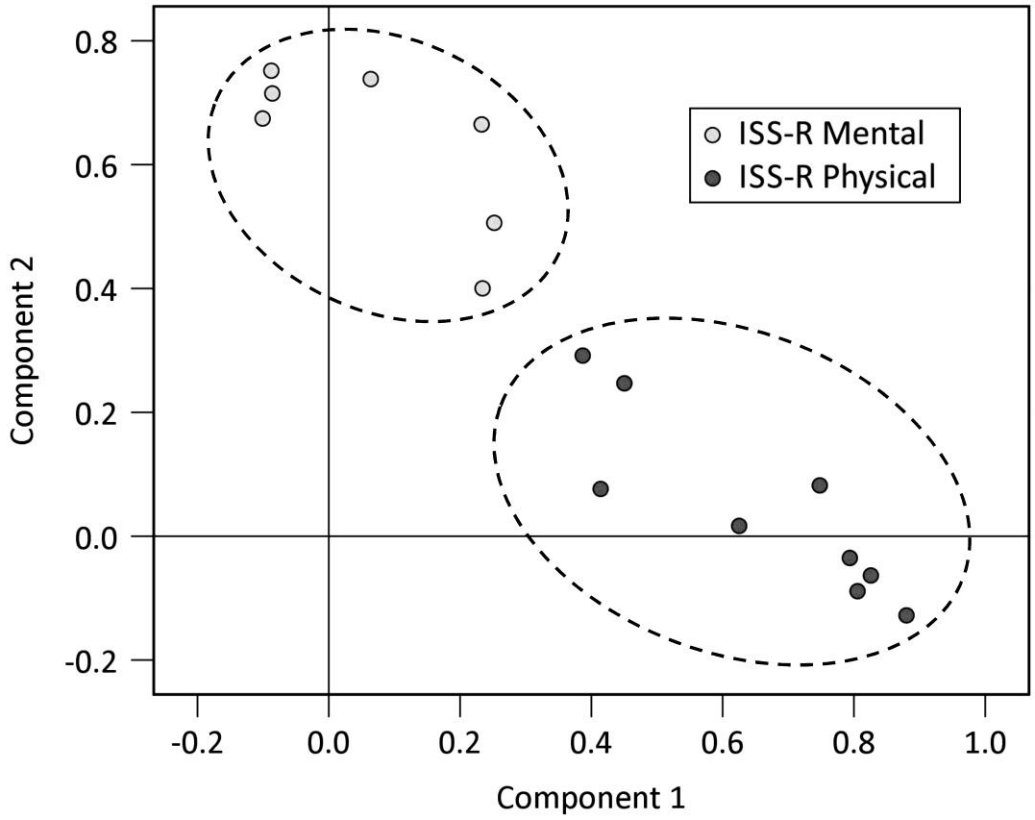
PDDS = Patient Determined Disease Steps; SDMT = Symbol Digit Modalities Test; 9HPT = 9-Hole Peg Test; T25FW = Timed 25-Foot Walk.
Listed *p* values represent comparison of subsamples using Welch's *t*-test.
**$p < .01$.

Figure 1. *Scree plot for the ISS-R and random eigenvalue simulation at the 95th percentile.*



Suitability metrics for principal component analysis were calculated. Sampling adequacy was meritorious (KMO = .831; Kaiser, 1974). Bartlett's test verified that the assumption of homoscedasticity was met, $\chi^2(120) = 1049.477$, $p < .001$. Data set permutation-modified Monte Carlo eigenvalue simulation suggested retention of two components (see Figure 1 and Table 4). The first component explained 34.63% of total variance, and the second component explained 13.69% of total variance, for a cumulative total of 48.32% of variance explained.

Figure 2. *Component loading plot for the ISS-R after direct oblimin rotation.*



Direct oblimin rotation was applied to the component solution, and the resulting pattern matrix was examined. Items were assigned to one of the two subscales based on highest component loading, as shown in Table 5. Based on the items assigned to each subscale, the scales were termed Physical Incapacity (ISS-R Physical subscale) and

Mental/Sensory Incapacity (ISS-R Mental subscale) according to the apparent underlying constructs that each subscale measured. The component loadings are plotted in Figure 2. Scores for the ISS-R total scale and subscales, and for the MSFC, were calculated. Descriptive statistics for the ISS-R and MSFC are shown in Table 6.

Table 4. *Data set permutation-modified Monte Carlo eigenvalue simulation.*

Component	Observed eigenvalue	Simulated eigenvalue
1	5.541	1.714
2	2.190	1.542
3	1.202	1.429
4	1.032	1.336
5	0.962	1.255
6	0.738	1.182
7	0.707	1.114
8	0.684	1.051
9	0.609	0.991
10	0.473	0.933
11	0.431	0.877
12	0.363	0.820
13	0.342	0.766
14	0.309	0.711
15	0.244	0.654
16	0.174	0.591

Unshaded cells indicate that the observed eigenvalue for the component exceed the eigenvalue at the 95th percentile of the random simulation.

Table 5. *Pattern matrix for the ISS-R scale and assignment of items to subscales.*

Item name	Component		Assigned Subscale
	1	2	
Stair Climbing	.748	.082	Physical Incapacity
Grooming	.625	.017	Physical Incapacity
Sensation	.252	.506	Mental/Sensory Incapacity
Bowel Function	.414	.076	Physical Incapacity
Bladder Function	.387	.292	Physical Incapacity
Fatigue	.064	.738	Mental/Sensory Incapacity
Ambulation	.806	−.089	Physical Incapacity
Speech/ Hearing	−.086	.715	Mental/Sensory Incapacity
Mood	−.088	.752	Mental/Sensory Incapacity
Dressing	.826	−.063	Physical Incapacity
Transfers	.794	−.035	Physical Incapacity
Cognition	.233	.665	Mental/Sensory Incapacity
Bathing	.880	−.128	Physical Incapacity
Feeding	.450	.247	Physical Incapacity
Vision	−.101	.674	Mental/Sensory Incapacity
Sexual Function	.234	.400	Mental/Sensory Incapacity

The higher component loading for each item appears in the unshaded cell.

Table 6. *Descriptive statistics for the ISS-R scales and MSFC.*

	M (SD)	*Mdn (IQR)*	Min.	Max.
ISS-R Total (0–64)[†]	13.74 (9.29)	12.5 (13.0)	0	50
Physical (0–36)[†]	6.06 (5.86)	4.5 (7.0)	0	32
Mental (0–28)[†]	7.68 (4.96)	7.0 (8.0)	0	20
MSFC	0.06 (0.78)	0.08 (1.02)	−2.07	1.83

ISS-R = Incapacity Status Scale–Revised; MSFC = Multiple Sclerosis Functional Composite.
[†]Values in parentheses indicate the range of possible scores.

Table 7. *Item analysis for the ISS-R total scale.*

Item name	Mean	Consistency (IIC)	Cronbach's α if deleted	Discrimination (Corrected ITC)
Stair Climbing	1.16	0.368	.842	.641
Grooming	0.29	0.282	.851	.473
Sensation	1.73	0.303	.848	.541
Bowel Function	0.92	0.210	.856	.368
Bladder Function	1.74	0.285	.851	.500
Fatigue	1.97	0.307	.848	.538
Ambulation	0.78	0.321	.847	.551
Speech/ Hearing	0.31	0.225	.856	.385
Mood	1.28	0.235	.856	.394
Dressing	0.29	0.347	.847	.565
Transfers	0.28	0.344	.848	.569
Cognition	1.08	0.361	.844	.622
Bathing	0.37	0.347	.846	.591
Feeding	0.24	0.290	.853	.485
Vision	0.44	0.203	.856	.337
Sexual Function	0.87	0.254	.853	.441

IIC = Inter-item correlation; ITC = Item-total correlation

Reliability analysis suggested good internal consistency for the ISS-R total scale (Cronbach's α = .869), Physical subscale (Cronbach's α = .856), and Mental subscale (Cronbach's α = .797). Split-half reliability was strong for the total scale (ρ_{SB} = .881), Physical subscale (ρ_{SB} = .882), and Mental subscale (ρ_{SB} = .824).

Item analysis for the total scale and subscales suggested retention of all items, as Cronbach's α decreased with the removal of any item. Consistency was strong for the total

scale (mean IIC = .293), Physical subscale (mean IIC = .398), and Mental subscale (mean IIC = .359). Item discrimination was very strong for the total scale (mean corrected ITC = .500), Physical subscale (mean corrected ITC = .576), and Mental subscale (mean corrected ITC = .523). The item analysis results for the total scale, Physical subscale, and Mental subscale are shown in Tables 7, 8, and 9.

Table 8. *Item analysis for the ISS-R Physical subscale.*

Item name	Mean	Consistency (IIC)	Cronbach's α if deleted	Discrimination (Corrected ITC)
Stair Climbing	1.16	0.465	.806	.702
Grooming	0.29	0.363	.829	.508
Bowel Function	0.92	0.259	.842	.386
Bladder Function	1.74	0.309	.848	.459
Ambulation	0.78	0.458	.808	.685
Dressing	0.29	0.470	.815	.657
Transfers	0.28	0.456	.818	.643
Bathing	0.37	0.483	.811	.692
Feeding	0.24	0.322	.836	.450

IIC = Inter-item correlation; ITC = Item-total correlation

The ISS-R total score demonstrated strong correlation with the MSFC ($r = -.547$, $p < .001$), as did the ISS-R Physical subscale ($r = -.657$, $p < .001$). The ISS-R Mental subscale demonstrated moderate correlation with the MSFC ($r = -.309$, $p = .004$). Correlations were calculated between the ISS-R and the measures comprising the MSFC. The ISS-R total score was significantly correlated with SDMT raw score ($r = -.479$, $p < .001$), upper motor dexterity ($r = .381$, $p < .001$), and walking speed ($r = .413$, $p < .001$). The Physical subscale was significantly correlated with SDMT raw score ($r = -.500$, $p < .001$), upper motor

dexterity ($r = .494$, $p < .001$), and walking speed ($r = -.605$, $p < .001$). The Mental subscale was significantly correlated with SDMT raw score ($r = -.301$, $p < .001$), but not with upper motor dexterity ($r = .187$, $p = .077$) or walking speed ($r = .139$, $p = .099$).

Table 9. *Item analysis for the ISS-R Mental subscale.*

Item name	Mean	Consistency (IIC)	Cronbach's α if deleted	Discrimination (Corrected ITC)
Sensation	1.73	0.342	.748	.521
Fatigue	1.97	0.418	.724	.619
Speech/ Hearing	0.31	0.343	.769	.482
Mood	1.28	0.385	.735	.572
Cognition	1.08	0.422	.729	.622
Vision	0.44	0.325	.765	.433
Sexual Function	0.87	0.280	.771	.415

IIC = Inter-item correlation; ITC = Item-total correlation

The ISS-R total score was strongly correlated with both the Physical ($r = .883$, $p < .001$) and Mental subscales ($r = .831$, $p < .001$). The Mental and Physical subscales were moderately-to-strongly intercorrelated ($r = .472$, $p < .001$). These results are summarized in Table 10.

Patient-reported outcomes were measured for association with the three ISS-R scales and PDDS using Pearson product-moment correlations in order to evaluate which constructs were adequately represented by scores on each of those four measurements. As shown in Table 11, the PDDS correlated significantly with the ISS-R total score and subscales, though more strongly with the total score and Physical subscale than the Mental subscale. Total illness intrusiveness correlated significantly with the ISS-R total and subscales and with the PDDS. Relationship illness intrusiveness was significantly correlated with all four measures,

though more strongly with the ISS-R total and Mental subscale than the Physical subscale or PDDS. Intimacy illness intrusiveness was significantly correlated with the ISS-R total and Mental subscale, but not the Physical subscale or PDDS. Instrumental activity illness intrusiveness was significantly correlated with all four measures.

Table 10. *Correlations between ISS-R scales and MSFC scores.*

	ISS-R Total	ISS-R Physical	ISS-R Mental
MSFC	−.547**	−.657**	−.309*
SDMT (raw)	−.479**	−.500**	−.301**
Average 9HPT	.381**	.494**	.187
Average T25FW	.413**	.605**	.139
ISS-R Physical	.883**	--	--
ISS-R Mental	.831**	.472**	--

ISS-R = Incapacity Status Scale–Revised; MSFC = Multiple Sclerosis Functional Composite; SDMT = Symbol Digit Modalities Test; 9HPT = 9-Hole Peg Test; T25FW = Timed 25-Foot Walk.
*$p < .005$; **$p < .001$.

Each of anxiety, depression, and perceived cognitive deficits was significantly correlated with the ISS-R total and Mental subscale scores, but not with the ISS-R Physical subscale or PDDS. Effects of pain and altered sensation were significantly correlated with all four measures. General fatigue, measured by the FSS and FSMC total scores, was significantly correlated with all four measures, though more strongly with the ISS-R total and Mental subscale than the Physical subscale or PDDS. Motor fatigue significantly correlated with each of the four measures. Cognitive fatigue was significantly correlated with the ISS-R total and Mental subscale scores, but not with the ISS-R Physical subscale or PDDS.

Bladder control was significantly correlated with all four measures. Bowel control was significantly correlated with each of the three ISS-R scales, but not the PDDS.

Swallowing problems were not significantly correlated with any of the four measures. Functional visual impairment was significantly correlated with the three ISS-R scales but not the PDDS. Sexual dysfunction was correlated with each of the four measures.

Table 11. *Correlations between ISS-R scales, PDDS, and other patient-reported outcomes.*

	ISS-R Total	ISS-R Physical	ISS-R Mental	PDDS
PDDS	.705***	.797***	.382***	--
IIRS Total†	.735***	.492***	.788***	.556***
IIRS–Relationship	.616***	.365*	.708***	.418**
IIRS–Intimacy	.484***	.253	.589***	.185
IIRS–Instrumental	.761***	.621***	.714***	.677***
HADS-A	.387**	.231	.443**	−.061
PHQ-9	.580***	.259	.742***	.195
PDQ	.510***	.286	.616***	.091
PES	.703***	.499***	.743***	.614***
FSS	.632***	.380**	.716***	.402*
FSMC Total	.621***	.386**	.696***	.382*
FSMC–Motor	.640***	.462***	.657***	.497***
FSMC-Cognitive	.562***	.279	.693***	.248
BLCS	.526***	.529***	.409**	.573***
BWCS	.475**	.423**	.420**	.304
EAT	.264	.195	.272	.135
IVIS	.405**	.344*	.374*	.211
MSISQ	.594***	.498***	.556***	.541***

ISS-R = Incapacity Status Scale–Revised; PDDS = Patient Determined Disease Steps; IIRS = Illness Intrusiveness Ratings Scale; HADS-A = Hospital Anxiety and Depression Scale, Anxiety; PHQ = Patient Health Questionnaire; PDQ = Perceived Deficits Questionnaire; FSS = Fatigue Severity Scale; FSMC = Fatigue Scale for Motor and Cognitive Functions; BLCS = Bladder Control Scale; BWCS = Bowel Control Scale; EAT = Eating Assessment Tool; PES = Pain Effects Scale; IVIS = Impact of Visual Impairment Scale; MSISQ = Multiple Sclerosis Intimacy and Sexuality Questionnaire.

†Values used in analysis reflect demographically adjusted *z*-scores for the total scale and subscales.

*$p < .05$; **$p < .01$; ***$p < .001$.

Executive functioning, as measured by the WCST total errors standard score, was significantly correlated with ISS-R total, Mental subscale, and Cognition item scores. Executive functioning was not significantly correlated with the ISS-R Physical subscale or PDDS scores. These results are summarized in Table 12.

Table 12. *Correlations between WCST performance and ISS-R and PDDS.*

	ISS-R Total	ISS-R Physical	ISS-R Mental	ISS-R Cognition	PDDS
WCST Total Errors[†]	−.318*	−.243	−.320*	−.412**	−.163

ISS-R = Incapacity Status Scale–Revised; PDDS = Patient Determined Disease Steps; WCST = Wisconsin Card Sorting Test.
[†]Values used in analysis reflect demographically adjusted standard scores.
*$p < .05$; **$p < .01$.

Spearman rank-order correlations were calculated between validated self-report measures and corresponding ISS-R items. Lower motor function, measured by the PDDS, was significantly correlated with ISS-R Stair Climbing ($r_s = .757$, $p < .001$), Ambulation ($r_s = .731$, $p < .001$), Transfers ($r_s = .470$, $p < .001$), and Bathing ($r_s = .566$, $p < .001$). Anxiety, measured by the HADS-A, was significantly correlated with ISS-R Mood ($r_s = .757$, $p < .001$), as was depression, measured by the PHQ-9 ($r_s = .768$, $p < .001$). Cognitive complaints, measured by the PDQ, were significantly correlated with ISS-R Cognition ($r_s = .670$, $p < .001$). Pain and altered sensation, measured by the PES, were significantly correlated with ISS-R Sensation ($r_s = .578$, $p < .001$). ISS-R Fatigue was significantly correlated with generalized fatigue, measured by the FSS ($r_s = .786$, $p < .001$) and FSMC total score ($r_s = .695$, $p < .001$), as well as with FSMC Motor ($r_s = .660$, $p < .001$) and Cognitive fatigue scores ($r_s = .696$, $p < .001$).

Bladder control, measured by the BLCS, was significantly correlated with ISS-R Bladder Function ($r_s = .642$, $p < .001$). Bowel control, measured by the BWCS, was

significantly correlated with ISS-R Bowel Function (r_s = .633, p < .001). Swallowing difficulty, measured by the EAT, was significantly correlated with ISS-R Feeding (r_s = .506, p = .001). Effects of visual impairment, measured by the IVIS, were significantly correlated with ISS-R Vision (r_s = .421, p = .006). Sexual problems, measured by the MSISQ, were significantly correlated with ISS-R Sexual Function (r_s = .576, p < .001).

Correlations between ISS-R metrics and years of education were calculated to evaluate discriminant validity. Education was weakly but significantly associated with the ISS-R total score (r = −.181, p = .023) and Physical subscale (r = −.180, p = .024). Education was not significantly associated with the Mental subscale (r = −.127, p = .112). Education was significantly but weakly associated with ISS-R Fatigue (r_s = −.180, p = .024), Ambulation (r_s = −.229, p = .004), and Speech/Hearing (r_s = −.193, p = .015). Education was not significantly associated with ISS-R Stair Climbing (r_s = −.130 p = .104), Grooming (r_s = −.067, p = .405), Sensation (r_s = −.119, p = .135), Bowel Function (r_s = −.121, p = .130), Bladder Function (r_s = −.144, p = .071), Mood (r_s = −.091, p = .257), Dressing (r_s = −.144, p = .071), Transfers (r_s = −.121, p = .131), Cognition (r_s = −.082, p = .305), Bathing (r_s = −.107, p = .180), Feeding (r_s = −.147, p = .065), Vision (r_s = −.016, p = .844), or Sexual Function (r_s = −.011, p = .890).

Mann-Whitney U test was conducted to compare ISS-R scales and PDDS across each of dichotomous employment status, history of falls in the prior two months, presence of a depressive disorder, presence of an anxiety disorder, and cognitive impairment.

Across employment status, scores on each of the ISS-R scales and PDDS were significantly different. Across falls history, scores on each of the four measures were significantly different. Across diagnoses of depressive and anxiety disorders, ISS-R total

scores and Mental subscale scores were significantly different, but Physical subscale scores and PDDS scores were not. Across cognitive impairment, scores on each of the four measures were significantly different. These results are summarized in Table 13.

Table 13. *Mann-Whitney U tests for the ISS-R scales and PDDS across employment status, falls history, diagnosis of a depressive disorder, diagnosis of an anxiety disorder, and cognitive status.*

	Employed or student					
	Yes		No			
	Mdn	*IQR*	*Mdn*	*IQR*	*U*	*p*
ISS-R Total	8.00	9.00	18.00	12.00	987.0	< .001
ISS-R Physical	2.00	0.50	8.00	7.00	1043.0	< .001
ISS-R Mental	5.00	6.00	10.00	8.00	1320.0	< .001
PDDS	1.00	2.00	3.00	3.25	1096.5	< .001

Employment status was compared only for patients under age 63 (n = 148) to minimize confounds with retirement unrelated to disability.

	Falls in prior two months					
	No		Yes			
	Mdn	*IQR*	*Mdn*	*IQR*	*U*	*p*
ISS-R Total	12.50	12.00	23.00	16.00	60.0	.002
ISS-R Physical	3.00	6.75	10.00	10.00	64.5	.004
ISS-R Mental	9.00	6.75	14.00	4.00	68.5	.006
PDDS	1.00	3.50	4.00	1.50	52.5	.015

	Depressive disorder					
	No		Yes			
	Mdn	*IQR*	*Mdn*	*IQR*	*U*	*p*
ISS-R Total	10.50	11.25	18.00	14.50	174.0	.004
ISS-R Physical	3.00	8.00	5.00	9.00	273.5	.334
ISS-R Mental	5.00	6.50	14.00	6.50	100.5	< .001
PDDS	1.00	3.00	2.50	3.00	163.5	.061

Table 13 (continued).

	Anxiety disorder					
	No		Yes			
	Mdn	*IQR*	*Mdn*	*IQR*	*U*	*p*
ISS-R Total	14.00	11.00	21.50	18.00	130.0	.006
ISS-R Physical	3.00	7.00	8.50	11.00	173.0	.068
ISS-R Mental	8.00	7.50	14.50	7.50	110.5	.001
PDDS	2.00	3.00	4.00	3.50	143.0	.127

	Cognitive impairment					
	No		Yes			
	Mdn	*IQR*	*Mdn*	*IQR*	*U*	*p*
ISS-R Total	11.00	12.25	19.00	10.25	800.5	< .001
ISS-R Physical	4.00	6.25	8.00	10.00	840.0	.001
ISS-R Mental	7.00	8.25	10.00	7.00	930.0	.003
PDDS	2.00	3.00	4.00	3.00	609.0	< .001

Cognitive impairment was defined as demographically adjusted *z*-score less than or equal to −2.00 on the Symbol Digit Modalities Test.

Across employment status, scores on each of the ISS-R scales and PDDS were significantly different. Across falls history, scores on each of the four measures were significantly different. Across diagnoses of depressive and anxiety disorders, ISS-R total scores and Mental subscale scores were significantly different, but Physical subscale scores and PDDS scores were not. Across cognitive impairment, scores on each of the four measures were significantly different. These results are summarized in Table 13.

ROC curve analysis was conducted to assess the ability of the ISS-R total score and PDDS to determine each dichotomous outcome. Analysis was also conducted using the ISS-R mental score for presence of depressive and anxiety disorders.

ISS-R total score produced a strong overall model of employment status (AUC = .819, $p < .001$). Maximum *J* yielded a criterion of score greater than or equal to 16, corresponding to a significantly elevated risk of unemployment (RR = 3.089, $p < .001$).

Maximum specificity at sensitivity greater than or equal to 80.0% yielded a criterion of score greater than or equal to 10, corresponding to a significantly elevated risk of unemployment (RR = 2.935, $p < .001$).

Table 14. *Receiver operating characteristic analysis for dichotomous employment.*

	AUC	95% CI	*p*		
ISS-R Total	.819	[.753, .886]	< .001		
Criterion	Sensitivity	Specificity	*J*	RR	95% CI
≥ 16	69.0	83.1	.521	3.089*	[2.107, 4.529]
≥ 10	80.3	62.3	.426	2.935*	[1.807, 4.767]
	AUC	95% CI	*p*		
PDDS	.776	[.701, .852]	< .001		
Criterion	Sensitivity	Specificity	*J*	RR	95% CI
≥ 2	75.7	70.0	.457	2.781*	[1.802, 4.292]
≥ 1	91.4	41.4	.329	3.556*	[1.689, 7.484]

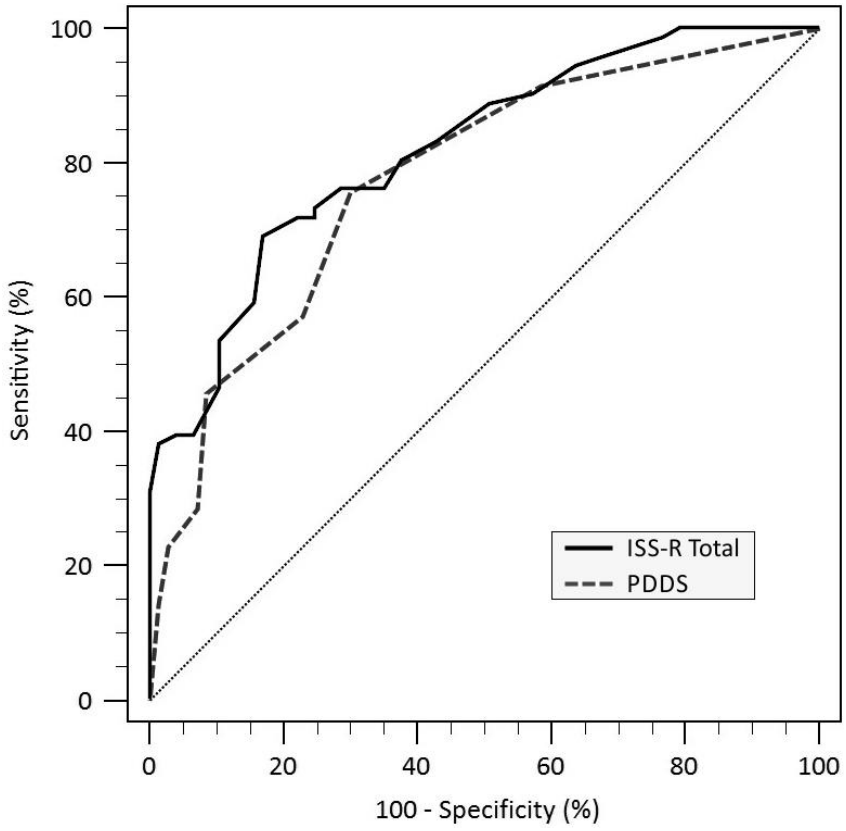
ISS-R = Incapacity Status Scale–Revised; PDDS = Patient Determined Disease Steps; AUC = Area under curve; *J* = Youden index; RR = Relative risk.
Threshold criteria were evaluated for coordinates yielding the maximum Youden index, and the coordinate producing the highest-specificity value at sensitivity greater than or equal to 80.00%.
*Relative risk was statistically significant at the α = .05 level.

PDDS produced a moderately strong overall model of employment status (AUC = .776, $p < .001$). Maximum *J* yielded a criterion of score greater than or equal to 2, corresponding to a significantly elevated risk of unemployment (RR = 2.781, $p < .001$). Maximum specificity at sensitivity greater than or equal to 80.0% yielded a criterion of score greater than or equal to 1, corresponding to a significantly elevated risk of unemployment (RR = 3.556, $p = .001$). These results are summarized in Table 14. The ROC curves are plotted in Figure 3.

ISS-R total score produced a strong overall model of falls history (AUC = .805, $p <$ .001). Maximum *J* yielded a criterion of score greater than or equal to 22, corresponding to a

significantly elevated risk of having experienced a fall (RR = 5.075, p = .001). Maximum specificity at sensitivity greater than or equal to 80.0% yielded a criterion of score greater than or equal to 15, at which risk of having experienced a fall was not significantly elevated (RR = 3.857, p = .058).

Figure 3. *Receiver operating characteristic curves for employment status.*



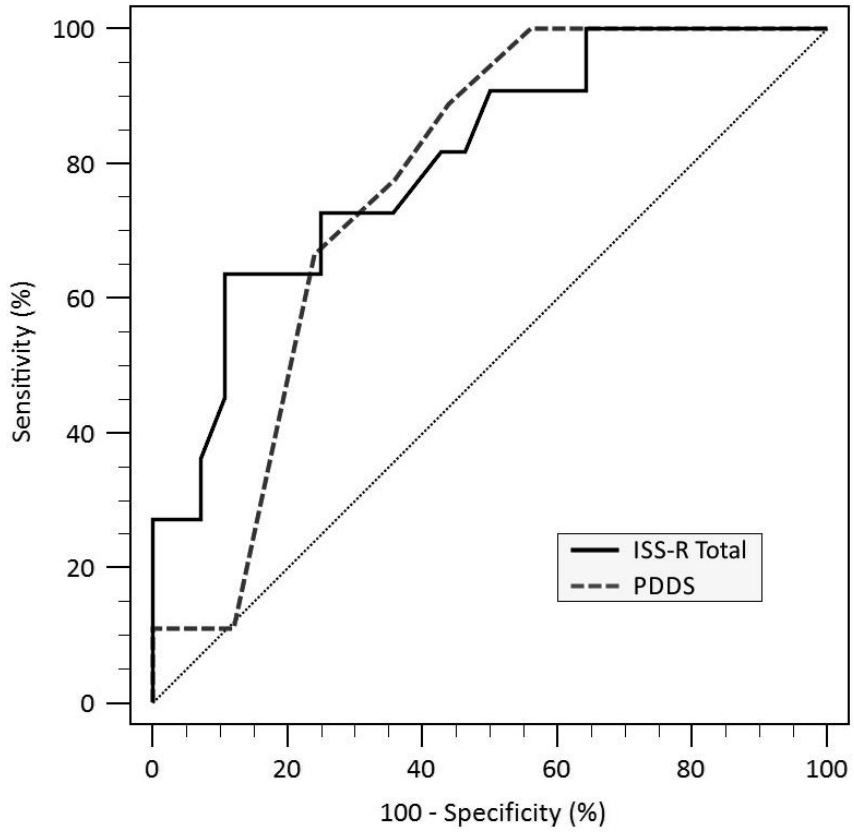
PDDS produced a moderately strong overall model of falls history (AUC = .767, p < .001). Maximum J yielded a criterion of score greater than or equal to 2, at which risk of having experienced a fall was not significantly elevated (RR = 6.316, p = .066). Maximum specificity at sensitivity greater than or equal to 80.0% yielded the same criterion. These results are summarized in Table 15. The ROC curves are plotted in Figure 4.

Table 15. *Receiver operating characteristic analysis for dichotomous falls within the prior two months.*

	AUC	95% CI	*p*		
ISS-R Total	.805	[.652, .958]	< .001		
Criterion	Sensitivity	Specificity	*J*	RR	95% CI
≥ 22	63.6	89.3	.529	5.075*	[1.874, 13.744]
≥ 15	81.8	57.1	.390	3.857	[0.954, 15.592]
	AUC	95% CI	*p*		
PDDS	.767	[.609, .924]	< .001		
Criterion	Sensitivity	Specificity	*J*	RR	95% CI
≥ 2	88.9	56.0	.449	6.316	[0.885, 45.089]

ISS-R = Incapacity Status Scale–Revised; PDDS = Patient Determined Disease Steps; AUC = Area under curve; *J* = Youden index; RR = Relative risk.
Threshold criteria were evaluated for coordinates yielding the maximum Youden index, and the coordinate producing the highest-specificity value at sensitivity greater than or equal to 80.00%.
*Relative risk was statistically significant at the .05 α-level.

Figure 4. *Receiver operating characteristic curves for falls history.*



ISS-R total score produced a moderately strong overall model of depressive disorder diagnosis (AUC = .732, $p < .001$). Maximum *J* yielded a criterion of score greater than or equal to 18, corresponding to a significantly elevated risk of having a depressive disorder (RR = 2.167, $p = .004$). Maximum specificity at sensitivity greater than or equal to 80.0% yielded a criterion of score greater than or equal to 12, corresponding to a significantly elevated risk of having a depressive disorder (RR = 2.375, $p = .034$).

Table 16. *Receiver operating characteristic analysis for diagnosis of a depressive disorder.*

	AUC	95% CI	*p*		
ISS-R Total	.732	[.595, .869]	< .001		
Criterion	Sensitivity	Specificity	*J*	RR	95% CI
≥ 18	52.0	84.6	.366	2.167*	[1.280, 3.666]
≥ 12	80.0	53.9	.339	2.375*	[1.068, 5.280]
	AUC	95% CI	*p*		
ISS-R Mental	.845	[.743, .948]	< .001		
Criterion	Sensitivity	Specificity	*J*	RR	95% CI
≥ 14	52.0	100.0	.520	3.009*	[1.884, 4.804]
≥ 9	80.0	65.38	.454	3.035*	[1.352, 6.810]
	AUC	95% CI	*p*		
PDDS	.625	[.400, .850]	.276		

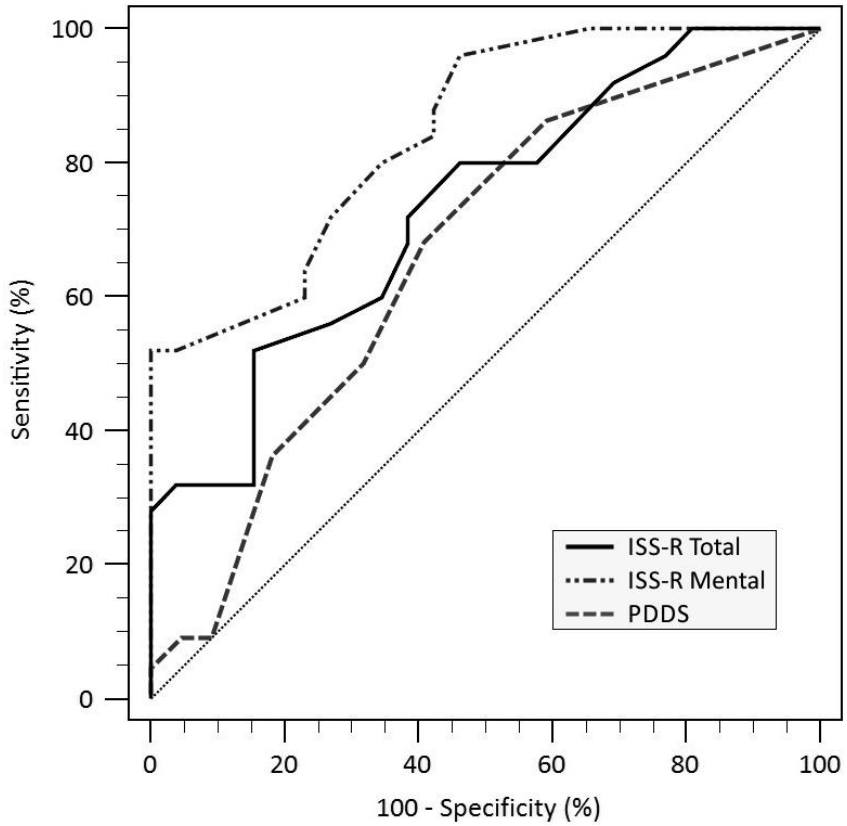
ISS-R = Incapacity Status Scale–Revised; PDDS = Patient Determined Disease Steps; AUC = Area under curve; *J* = Youden index; RR = Relative risk.
Threshold criteria were evaluated for coordinates yielding the maximum Youden index, and the coordinate producing the highest-specificity value at sensitivity greater than or equal to 80.00%.
*Relative risk was statistically significant at the .05 α-level.

The ISS-R Mental subscale produced a strong overall model of depressive disorder diagnosis (AUC = .845, $p < .001$). Maximum *J* yielded a criterion of score greater than or equal to 14, corresponding to a significantly elevated risk of having a depressive disorder (RR = 3.009, $p < .001$). Maximum specificity at sensitivity greater than or equal to 80.0%

yielded a criterion of score greater than or equal to 9, corresponding to a significantly elevated risk of having a depressive disorder (RR = 3.035, p = .007).

PDDS did not produce a significant model of depressive disorders (AUC = .625, p = .276). These results are summarized in Table 16. The ROC curves are plotted in Figure 5.

Figure 5. *Receiver operating characteristic curves for depressive disorders.*



ISS-R total score produced a moderately strong overall model of anxiety disorder diagnosis (AUC = .749, p = .003). Maximum J yielded a criterion of score greater than or equal to 24, corresponding to a significantly elevated risk of having an anxiety disorder (RR = 4.667, p < .001). Maximum specificity at sensitivity greater than or equal to 80.0% yielded a criterion of score greater than or equal to 10, at which risk of having an anxiety disorder was not significantly elevated (RR = 3.000, p = .118).

The ISS-R Mental subscale produced a moderately strong overall model of anxiety disorder diagnosis (AUC = .787, $p < .001$). Maximum *J* yielded a criterion of score greater than or equal to 7, corresponding to a significantly elevated risk of having an anxiety disorder (RR = 16.206, $p = .048$). Maximum specificity at sensitivity greater than or equal to 80.0% yielded the same criterion.

Table 17. *Receiver operating characteristic analysis for diagnosis of an anxiety disorder.*

	AUC	95% CI	*p*		
ISS-R Total	.749	[.586, .912]	.003		
Criterion	Sensitivity	Specificity	*J*	RR	95% CI
≥ 24	50.0	94.6	.446	4.667*	[2.180, 9.990]
≥ 10	85.7	40.5	.263	3.000	[0.755, 11.914]
	AUC	95% CI	*p*		
ISS-R Mental	.787	[.648, .926]	< .001		
Criterion	Sensitivity	Specificity	*J*	RR	95% CI
≥ 7	100.0	48.7	.487	16.206*	[1.023, 256.764]
	AUC	95% CI	*p*		
PDDS	.645	[.443, .847]	.159		

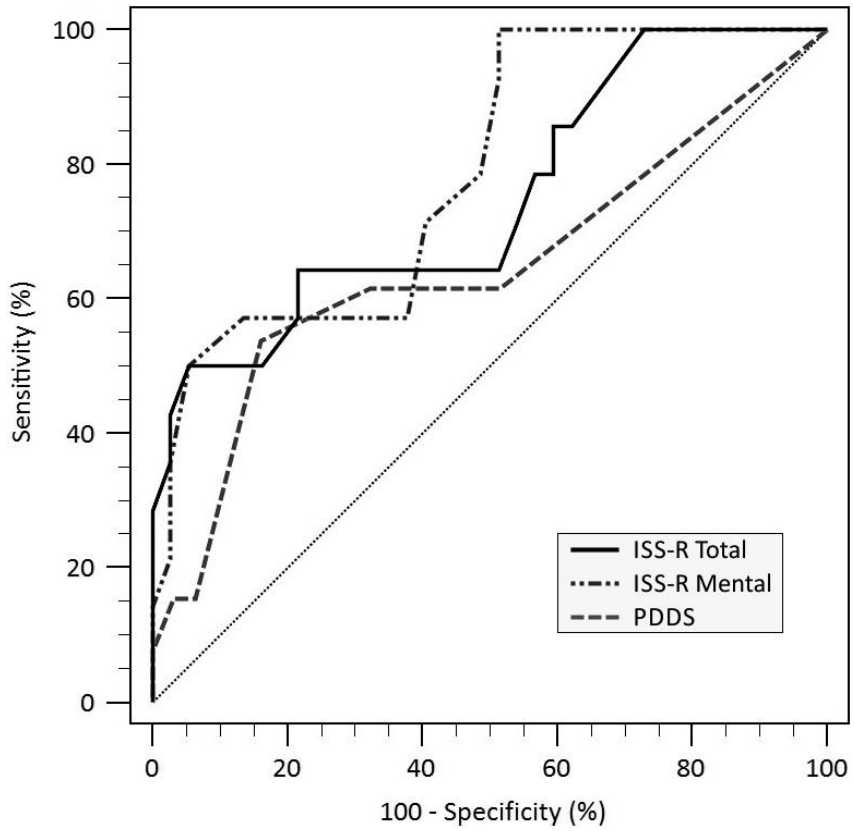
ISS-R = Incapacity Status Scale–Revised; PDDS = Patient Determined Disease Steps; AUC = Area under curve; *J* = Youden index; RR = Relative risk.
Threshold criteria were evaluated for coordinates yielding the maximum Youden index, and the coordinate producing the highest-specificity value at sensitivity greater than or equal to 80.00%.
*Relative risk was statistically significant at the .05 α-level.

PDDS did not produce a significant model of anxiety disorder diagnosis (AUC = .645, $p = .159$). These results are summarized in Table 17. The ROC curves are plotted in Figure 6.

ISS-R total score produced a moderately strong overall model of cognitive impairment (AUC = .736, $p < .001$). Maximum *J* yielded a criterion of score greater than or equal to 15, corresponding to a significantly elevated risk of cognitive impairment (RR =

7.000, $p = .001$). Maximum specificity at sensitivity greater than or equal to 80.0% yielded the same criterion.

Figure 6. *Receiver operating characteristic curves for anxiety disorders.*



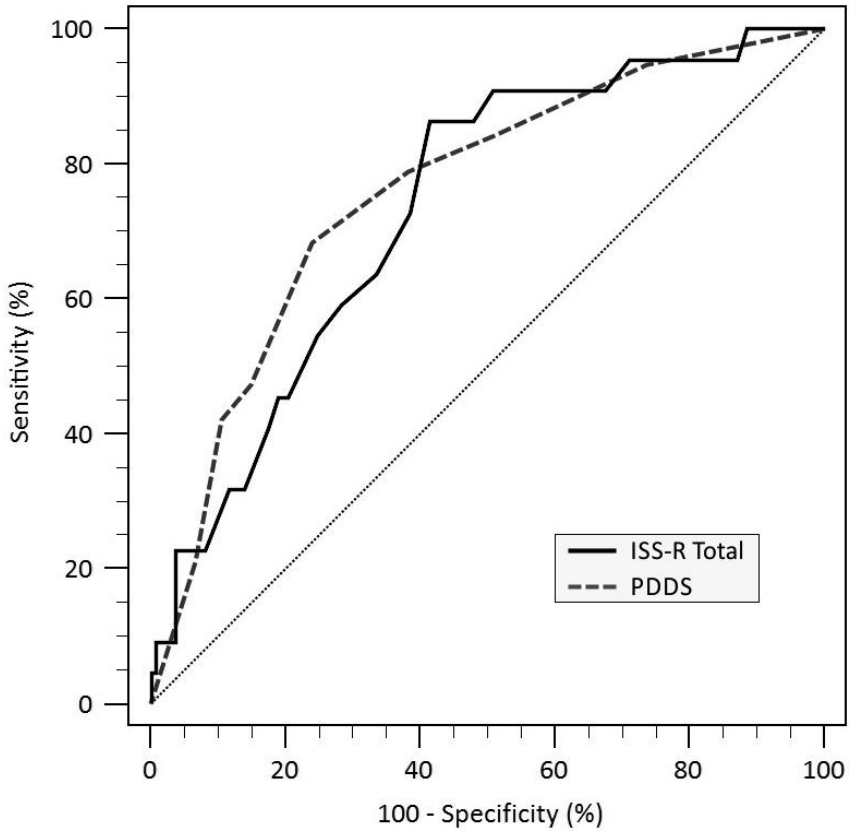
PDDS produced a moderately strong overall model of cognitive impairment (AUC = .759, $p < .001$). Maximum *J* yielded a criterion of score greater than or equal to 4, corresponding to a significantly elevated risk of cognitive impairment (RR = 5.152, $p < .001$). Maximum specificity at sensitivity greater than or equal to 80.0% yielded a criterion of score greater than or equal to 1, corresponding to a significantly elevated risk of cognitive impairment (RR = 4.318, $p = .016$). These results are summarized in Table 18. The ROC curves are plotted in Figure 7.

Table 18. *Receiver operating characteristic analysis for dichotomous cognitive impairment.*

	AUC	95% CI	*p*		
ISS-R Total	.736	[.632, .841]	< .001		
Criterion	Sensitivity	Specificity	*J*	RR	95% CI
≥ 15	86.4	58.7	.451	7.000*	[2.156, 22.723]
	AUC	95% CI	*p*		
PDDS	.759	[.644, .874]	< .001		
Criterion	Sensitivity	Specificity	*J*	RR	95% CI
≥ 4	68.4	75.9	.444	5.152*	[2.090, 12.703]
≥ 2	84.2	48.9	.331	4.318*	[1.312, 14.206]

ISS-R = Incapacity Status Scale–Revised; PDDS = Patient Determined Disease Steps; AUC = Area under curve; *J* = Youden index; RR = Relative risk.
Threshold criteria were evaluated for coordinates yielding the maximum Youden index, and the coordinate producing the highest-specificity value at sensitivity greater than or equal to 80.00%.
*Relative risk was statistically significant at the .05 α-level.

Figure 7. *Receiver operating characteristic curves for cognitive impairment.*



Chapter IV

Interpretation

Preliminary analyses supported the suitability of the data for the primary analyses conducted in this study. Subsamples were demographically homogeneous, showing no significant difference in age, length of education, sex, race, marital status, or employment status, and a modestly significant difference in length of diagnosis. Participants across subsamples provided similar responses to the ISS-R and similar performances in other primary outcomes. Time required to complete the scale was significantly shorter for the digital version. Statistical metrics also demonstrated that the sample was appropriate for principal component analysis, which was used to assess the components underlying patients' ISS-R responses.

Aim 1: Domains underlying dysfunction. The retention of two components allowed for explanation of almost half of the variance in patients' responses. The assignment of items to subscales resulted in a first subscale, composed of nine items (Stair Climbing, Grooming, Bowel Function, Bladder Function, Ambulation, Dressing, Transfers, Bathing, and Feeding); and a second subscale, composed of seven items (Sensation, Fatigue, Speech/Hearing, Mood, Cognition, Vision, Sexual Function). Based on the content of these items, the subscales appeared to represent physical incapacity and mental/sensory incapacity.

Accordingly, physical and non-physical complaints seem to represent distinct areas of MS symptomatology, although they are by no means mutually exclusive, and patients may experience deficits in both domains, indicated by the moderate-to-strong interrelation of the

two subscales. Physical incapacities, such as: difficulty with lower motor function affecting walking and movement; upper limb functions affecting manual activities and self-care; eating and food preparation; and bowel and bladder dysfunction appear most likely to occur alongside each other and impair functioning, collectively representing one primary area of disability. Similarly, non-physical incapacities, including: altered tactile, visual, or auditory sensation; fatigue; emotional dysfunction; cognitive difficulties; and impairments in sexual functioning occur together, and constitute a second major disability domain.

The ISS-R and its subscales were all significantly related to the performance-based MSFC. The MSFC is weighted toward motor functions, with two of its subtests measuring motor functions explicitly, and the third measuring cognitive processing speed tested via oral response, requiring intact motor functions for speech. Not surprisingly, the ISS-R Physical subscale was strongly associated with the MSFC total and with measures of manual dexterity and walking speed, while the Mental subscale did not significantly relate to either motor subtest, though it was associated with cognitive processing. This reinforces the dichotomy between physical and non-physical symptomatology among MS patients.

Consistent with past studies indicating that non-physical symptoms have the largest influence on subjective illness burden, the Mental subscale was related most strongly to illness intrusiveness. In particular, the Mental subscale was associated strongly with intrusiveness on relationships and intimacy, while the Physical subscale was related moderately and non-significantly to those types of illness intrusiveness, respectively. Both Mental and Physical disability were strongly associated with perceived intrusiveness on the performance of instrumental activities, suggesting a prominent role for each type of disability in day-to-day functioning.

Aim 2: Psychometric properties and validity of the ISS-R. The ISS-R demonstrated reliability and consistency for the total scale and two subscales. Each of the 16 items was retained for the final scale, having contributed value to the scale from both quantitative and qualitative perspectives. Item analyses further suggested that the scale and subscales showed strong item consistency and discrimination, indicating that while the items all contribute to the same broader construct of incapacity, there is not an excess of overlap, and they measure distinct symptoms.

The ISS-R total score was strongly associated with overall functional ability on the MSFC, and moderately-to-strongly associated with ambulation, upper limb function, and cognitive processing speed. It was very strongly associated with each of the two subscales, indicating capable reflection of both physical and mental disability constructs. As described previously, the Physical and Mental subscales were significantly associated with corresponding MSFC subtests, and the Mental subscale was not significantly related to subtests exclusively measuring physical functions.

The ISS-R total and Physical subscale scores were very strongly associated with self-reported walking on the PDDS. The Mental subscale also showed a moderate relationship with PDDS score. The ISS-R total score was significantly associated with self-reports measuring each of anxiety, depression, cognitive symptoms, pain and sensory disturbance, fatigue, bladder control, bowel control, visual impairment, and sexual dysfunction. The Physical subscale was strongly related to pain, generalized and motor fatigue, bladder problems, bowel problems, and sexual dysfunction, and moderately related to visual impairment. It was not significantly related to anxiety, depression, cognitive fatigue, or other cognitive complaints. The Mental subscale was strongly related to anxiety, depression,

cognitive symptoms, pain, fatigue, bowel and bladder problems, and sexual dysfunction. It was moderately related to visual impairment. None of the three subscales related significantly to the EAT, a dysphagia scale. Items within the ISS-R were also significantly associated with the corresponding symptom self-report measures used in validity analysis for the scales.

Objectively measured cognitive ability with no motor component on the WCST was significantly related to ISS-R total and Mental subscale scores and the cognition item. It was not related to the Physical subscale score.

Length of education was used to further evaluate discriminant validity, as it was believed to be conceptually unrelated to the constructs measured by the ISS-R. Education was weakly associated with the ISS-R total scale and Physical subscale, and with ISS-R items assessing fatigue ambulation, and speech/hearing. It was not significantly associated with the Mental subscale or any other items.

Taken in summary, these findings, using both objective and subjective measures, provide strong support for the convergent and discriminant validity of the ISS-R total scale, subscales, and individual items.

Aim 3: Self-rated impairment and comprehensive representation of disability. The ISS-R total score was strongly related to each of the above-described symptom inventories, with the exception of the dysphagia scale; this may have related to some of the known psychometric and structural weaknesses of the EAT. The PDDS, by contrast, was limited to significant associations with only pain, generalized and motor fatigue, bladder control, and sexual function; that is, it failed to adequately represent anxiety, depression, cognitive symptoms (including cognitive fatigue), visual difficulties, or problems with bowel

control. Even where the PDDS did demonstrate significant findings, those relationships were weaker than for the ISS-R in all but one case (bladder control symptoms).

Furthermore, while the PDDS was significantly associated with illness intrusiveness, this relationship was again considerably weaker than for the ISS-R; in particular, the PDDS did not reflect the intrusive effects of illness on intimacy, and was less strongly associated with the effects of illness on relationships. Similarly, the PDDS was not significantly associated with objective cognitive performance on the WCST. The strong relationship between the ISS-R and illness intrusiveness indicates that it properly assesses the elements of disability important to patients' perceptions of their health while still accurately reflecting their objectively measured capacities.

The ISS-R, its subscales, and the PDDS each showed significantly higher scores among: unemployed patients compared to their employed counterparts; patients who had fallen in the prior two months compared to those who had not; and patients who were cognitively impaired, per SDMT performance. As noted previously, the latter finding appears to relate to the oromotor demands of the test. By contrast, only the ISS-R total score and Mental subscale showed a significant difference between patients who met criteria for each of depressive and anxiety disorders. There was no significant difference across these two groups in ISS-R Physical or PDDS score. In addition to supporting the criterion and discriminant validity of the ISS-R, this demonstrates a significant limitation of the PDDS in ability to assess disability comprehensively, as it does not detect emotional dysfunction. This follows logically, given that the single item of the PDDS inquires only about lower motor functioning, and further supports the idea that neuropsychiatric disability in MS is distinct from physical disability.

The ISS-R total score produced strong predictive models of employment status and history of falls, and moderately strong models of depression, anxiety, and cognitive impairment. The ISS-R Mental subscale produced stronger models of the two mood disorder types. The PDDS produced moderately strong models of employment status, history of falls, and cognitive impairment. However, it produced non-significant predictive models of depressive and anxiety disorders, again demonstrating its inadequate representation of mood as a form of disability in MS.

Classification analyses provided cutoffs for practical use of the ISS-R in clinical settings, with some flexibility provided to the clinician depending on their desire to maximize classification accuracy or to prioritize sensitivity for the purposes of screening patients. Relative risk at each cutoff was also calculated. The suggested interpretive cutoffs are as follows.

To assess risk of unemployment, a total ISS-R score of at least 16 optimizes classification, while a total score of at least 10 should be used to screen patients. At either cutoff, patients are at approximately three times the risk of being unemployed. To assess falls risk, a total score of at least 22 optimizes classification, and is associated with a five-times risk, while a score of at least 15 is recommended for screening. Patients scoring at least 15 on the ISS-R were at a seven-times risk of performing below normal limits on the oral SDMT. This cutoff can be used for both optimal classification and screening purposes.

Interpretation of the ISS-R Mental subscale score is recommended to assess risk of having a depressive or anxiety disorder. For depressive disorders, a score of at least 14 optimizes classification, and a score of at least 9 should be used for screening purposes. For

anxiety disorders, a score of at least 7 is recommended for both optimal classification and screening.

Clinical and Research Implications

The primary goal of this research was to develop an instrument that reflected patients' beliefs about their illness while using ecological anchor points to avoid self-report biases and the effects of catastrophizing. This study provides a strong base of evidence supporting the accuracy of the ISS-R in representing patients' level of function, and in reflecting their capacities through a comprehensive, multi-dimensional framework.

In addition to its use as a PRO producing a single score of overall incapacity, the ISS-R provides subscales, allowing clinicians and researchers to independently examine physical and mental/sensory disability. By providing 16 distinct item scores and these two subscale scores, patients can better convey the specific deficits they have noticed in daily functioning. Researchers can measure each of these areas using a single inventory, while clinicians can target further assessment and treatment to patients' complaints. Clinicians can also easily screen patients who may be at risk for poor functional outcomes, such as losing employment or falling. These virtues of the scale are especially valuable for measuring neuropsychiatric disability, which is insufficiently reported, evaluated, and treated in MS.

Although no formal inquiry was conducted into patient satisfaction with the computerized adaptive version of the ISS-R, the use of a digital format reduced administration time by approximately one minute, and was conducive to faster scoring and recording of data. In general, digital PROs are preferred by MS patients, who demonstrate the requisite enthusiasm and technological literacy to benefit from such forms of measurement (Haase, Schultheiss, Kempcke, Thomas, & Ziemssen, 2013, 2012), and who

experience reduced questionnaire burden through the use of adaptive measures like the ISS-R. Digital measures are also preferred by clinicians, for whom the use of electronic data collection allows for off-site or more efficient on-site surveying of patients, and immediate access to scored, interpretable PRO instruments during the patient's office visit (Coons et al., 2015; Jensen et al., 2015).

Integration of PROs with the rest of the patient's electronic health records promotes improvements in personalized medicine, a primary focus for a disease as idiosyncratic as MS where patients benefit profoundly from individualized assessment and treatment (Ziemssen, Kern, & Thomas, 2016). The digital version of the ISS-R therefore appears to be an especially valuable alternative to traditional pen-and-paper PROs.

Limitations and Future Directions

As this study involved data collection only at a single time point, the ISS-R's longitudinal sensitivity to changes could not be measured. Subsequent research could work to validate the test-retest reliability of the scale. It would also be beneficial to assess the scale's ability to predict symptom worsening or risk of experiencing an MS relapse. If it were to demonstrate such predictive value, regularly updated ISS-R scores could easily be obtained at each office visit (or more frequently through remote administration) in order to identify patients at risk of decline in functional or health status.

Another limitation of this study is that data were collected only from an MS population, and not from healthy controls for comparative purposes. Items were written to reflect levels of increased incapacity, difficulty with activities, or need for mechanical or personal assistance compared to normal, independent functioning. A healthy individual would therefore be expected to endorse few or no symptoms as phrased on the ISS-R, and

accordingly score at or near zero for the entire scale. Regardless, the scale was not administered to healthy controls, and this analysis could not be conducted. Future studies should evaluate scale responses from healthy controls to allow a point of comparison between normal functioning and the varying levels of incapacity among MS patients. Other disease populations with heterogeneous forms of disability could then also be evaluated using the ISS-R, possibly expanding its utility.

The broader representativeness of a sample collected from a single site must also be considered. Although the demographic features of this sample were very much in line with published epidemiological statistics for the United States and Europe (see Wallin et al., 2019; Howard et al., 2016; Langer-Gould, Brara, Beaber, & Zhang, 2013), the fact remains that the patients in this study were drawn exclusively from a single clinic in the northeastern United States. It cannot be determined from this study alone whether other unmeasured factors, including cultural or socioeconomic variables, may have influenced the behaviors of this group. Because of this uncertainty, and because of the potential difference in diagnostic and functional outcome rates between patients at a tertiary care center and the MS population at large, it was not appropriate to conduct Bayesian classification analyses in this study. A larger sample drawn from multiple sites would be better suited to these forms of analysis. Future data collection efforts might focus on different regions and clinic types in an effort to replicate the findings of this study, and provide additional support to the external validity of the ISS-R.

There remain opportunities to investigate comparisons between the ISS-R and other measurements of disability and disease. The performance of the ISS-R was evaluated against that of the PDDS, and through its predictive ability for a set of five functional outcomes.

Additional research could evaluate the ISS-R in direct comparison to EDSS data, as the EDSS remains the current gold standard for clinical trials. The ability of the ISS-R to predict activities of daily living would also have meaningful implication for the scale's use in clinical and research settings. Other potential areas of comparison include serological analyses and MRI parameters, including evidence of disease activity, diffusion tensor imaging, and parenchymal and lesion volumetric studies.

Conclusion

The ISS-R offers clinicians and researchers a new PRO capable of simultaneously measuring both mental and physical disability constructs in MS. Its style of inquiry differs considerably from existing patient-reported instruments to permit accurate reporting of symptom severity and influence, and to allow for appropriate reflection of both the MS patient experience and meaningful aspects of real-world functioning. The ISS-R is effective in minimizing the influence of typical PRO reporting biases, and demonstrates strong validity, reliability, and association with objective and subjective measures of dysfunction.

Given its ability to bridge the gap between patient complaints and functional status across multiple areas of disability, the ISS-R provides a valuable alternative to previously existing measures used with the MS population. Its availability in both paper and digital formats facilitates ease of administration, regardless of resources available to a particular clinic, and its straightforward scoring system enables integration with existing clinical data systems or research databases. Although further inquiry is needed to validate the ISS-R with a larger patient population and demonstrate predictive capacity for additional clinical outcomes, it represents a highly useful tool for MS providers and researchers to investigate and quantify their patients' symptoms and level of disability.

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Appendix: Incapacity Status Scale—Revised

The paper version of the ISS-R is reproduced beginning on the subsequent page. Formatting of items has been modified to fit the margins of this document.

ISS-R

Revised Status Scale

Name: _____ *Date:* _____

Sex: *Female* ○ *Male* ○ *Age:* _____ *ID:* _____

Read the following questions and answer choices carefully. If you choose an answer next to a down arrow (↓), continue reading and answer the follow-up question immediately below it. If you choose an answer next to a numbered circle, place a mark through that circle and skip ahead to the next set of questions. Be sure to mark **exactly one numbered circle** in each set of questions.

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1. Could you walk up and down a flight of about 12 stairs without any difficulty, and without holding onto anyone or anything?

⓪ Yes

↓ No

Which of the following best describes how you go up and down stairs?

① I have some difficulty, but I can do it /on my own without using any tools or devices.

② I can do it on my own, but I need to use my cane, braces, or prosthesis; or I need to hold onto a railing.

③ I need another person to help me, or I need to use a machine lift.

④ I cannot go up and down stairs.

2. Are you able to groom yourself, care for your teeth and hair, shave, and/or apply cosmetics without any difficulty and without special tools or help from another person?

⓪ Yes

↓ No

Which of the following best describes how you groom yourself?

① I have some difficulty, but I can do it on my own without using any special tools.

② I can do it on my own, but it takes longer than it did before, or I need to use special grooming tools (such as long-handled nail clippers, modified brushes for my hair or teeth).

③ I can partly groom myself, but I need another person to help me.

④ I rely almost completely on another person to groom me.

3. Do you experience tingling, numbness, or pain?

⓪ No

↓ Yes

Which of the following best describes your experience of tingling, numbness, or pain?

① I experience some of these symptoms, but they do not interfere with my daily activities.

② I take medication or have made other changes (such as regularly using ice, heat, or compression), which almost completely manages these symptoms.

③ These symptoms sometimes interfere with my activities or relationships.

④ These symptoms very often interfere with my activities or relationships.

4. Have you had surgery, such as a colostomy or ileostomy, for bowel problems?

③ Yes, and I manage the surgical equipment (for example, ostomy bag) on my own.

④ Yes, and other people help me manage it.

↓ No

Do you lose control of your bowels at least once per month?

③ Yes, once a week or less.

④ Yes, twice a week or more.

↓ No

Which of the following best describes your experience of constipation?

⓪ I rarely or never feel constipated.

① I occasionally feel constipated, but I do not take any medications for this.

① I take a prescription medication, which almost completely relieves my constipation.

② I take a prescription medication, but I still sometimes feel constipated.

↓ I feel constipated, and use enemas, suppositories, or laxatives.

Which of the following best describes your use of enemas, suppositories, or laxatives?

① I use them once a week or less.

② I use them twice a week or more, but I can use them on my own.

③ I use them twice a week or more, and need help from another person to use them.

5. Have you had surgery, such as a urostomy, for bladder problems?

③ Yes, and I manage the surgical equipment (for example, ostomy bag) on my own.

④ Yes, and other people help me manage it.

↓ No

Do you lose control of your urine at least once per month?

③ Yes, once a week or less.

④ Yes, twice a week or more.

↓ No

Do you need to use a catheter or press with your hand to empty your bladder?

② Yes, I press with my hand.

② Yes, I have a catheter, which I manage on my own.

③ Yes, I have a catheter, which another person helps me manage.

↓ No

Do you ever have other bladder problems, such as having to go suddenly or not being able to start or maintain a urine stream?

⓪ No

① Yes, once a week or less.

② Yes, twice a week or more.

6. Do you easily become physically or mentally fatigued?

⓪ No

↓ Yes

Which of the following best describes your fatigue?

① I feel fatigued sometimes, but it does not interfere with my physical or mental activities.

② Due to my fatigue, I have some trouble with my physical or mental activities, but it is mild and passes quickly.

③ Due to my fatigue, I often have problems with my physical or mental activities, and must rest or take breaks frequently.

④ Due to my fatigue, I cannot function physically or mentally for any prolonged period of time.

7. Could you, without any difficulty, walk 50 meters (164 feet) on flat ground without stopping?

⓪ Yes

↓ No

Which of the following best describes how you would walk 50 meters (164 feet)?

① I would have some difficulty, but I could do it on my own without using any tools or devices.

② I could do it, but I would need to use my cane, walker, braces, or prosthesis.

③ I could go that distance on my own, but I would need to use my wheelchair.

④ I would not be able to walk that distance or use a wheelchair without help from someone else.

8. Do you have any difficulty speaking or hearing?

⓪ No

↓ Yes

Which best describes your experience speaking and hearing?

① I have some difficulty speaking or hearing, but it usually does not interfere with my ability to communicate.

② I use a hearing aid or voice amplifier, which is effective in helping me communicate.

③ I have great difficulty speaking or hearing, and I can almost only communicate using sign language, lip-reading, a keyboard, or other strategies.

④ I am almost completely unable to communicate because of my difficulty speaking or hearing.

9. Do you have difficulty with your mood, such as often feeling sad, anxious, or irritable?

⓪ No

↓ Yes

Which of the following best describes your difficulty with mood?

① I experience some difficulty with my mood, but it does not interfere with my daily activities or relationships.

② I take medication, see a therapist, or have made other changes, which mostly manages my difficulty with mood.

③ My difficulty with mood sometimes interferes with my daily activities or relationships.

④ My difficulty with mood very often interferes with my daily activities or relationships.

10. Can you dress yourself without any difficulty, and without tools, special clothing, or help from another person?

⓪ Yes

↓ No

Which of the following best describes how you get dressed?

① I have some difficulty, but I can do it on my own without using any tools or special clothing.

② I can do it on my own, but I need to use tools or special clothing.

③ I can partially dress myself, but I need another person to help me.

④ I rely almost completely on another person to dress me.

11. Can you enter and leave a chair, get on and off a toilet, and get into and out of bed without any difficulty, and without any tools, devices, or help from another person?

⓪ Yes

↓ No

Which of the following best describes how you do these activities?

① I have some difficulty, but I can do them on my own without using any tools or devices.

② I do them on my own, but I need to use tools, like a trapeze, sling, bars, or lift.

③ I can partly do these activities, but I need another person to help me.

④ I rely almost completely on another person to help me do these things.

12. Which of the following best describes your ability to think, remember, and focus when performing everyday activities, such as those at home or work?

⓪ I can complete everyday activities with no difficulty.

① I can complete everyday activities, but I have needed to make changes, such as making lists to help me organize, setting reminders, or giving myself extra time.

② It is hard for me to complete everyday activities, even when I make changes to help me think, remember, and focus, but I can eventually do them by myself.

③ It is very hard for me to complete everyday activities; or I need help from another person to complete them because it is hard for me to think, remember, and focus.

④ I am unable to complete many everyday activities because it is so hard for me to think, remember, and focus.

13. Can you bathe without any difficulty, and without tools, devices, or help from another person?

⓪ Yes

↓ No

Which of the following best describes how you bathe?

① I have some difficulty, but I can do it on my own without using any tools or devices.

② I can do it on my own, but I need to use tools, like a sling, bars, lift, chair, or special tub.

③ I can partially bathe myself, but I need another person to help with parts of my body.

④ I cannot bathe any part of my body, besides my hands or face, unless another person helps me.

14. Do you have a feeding tube?

③ Yes, and I manage it on my own.

④ Yes, and other people help me manage it.

↓ No

Which of the following best describes how you eat and drink?

⓪ I have no difficulty eating or drinking.

① I have some difficulty, but I do not need to prepare my food or drink in any special way.

② I need to use special utensils or straws, or specially prepare my food; for example, I need to gel or thicken liquids, or cut food into smaller pieces.

③ I can partly feed myself, but I need another person to help feed me.

④ I rely almost completely on another person to feed me.

15. Do you have difficulty with your vision that is not corrected completely by glasses or contact lenses?

⓪ No

↓ Yes

Which of the following best describes your difficulty with vision?

① I sometimes have blurry vision, double vision, or things move when I look at them, but this does not interfere with my activities.

② I have blurry vision, double vision, or things move when I try to look at them, and it interferes with my activities. I have needed to make changes, such as using larger print, a magnifying device, text-to-voice software, or other equipment.

③ My problems with vision interfere with some of my daily activities (such as reading or driving) and I require some help from another person for these activities.

④ Due to problems with vision, I rely almost completely on another person to help me with many daily activities.

16. Do you have any difficulty with sexual activities, such as masturbation, intercourse, or other activities performed by yourself or with others? (This includes becoming or staying aroused, becoming lubricated, reaching orgasm, or pleasing a partner.)

⓪ No

↓ Yes

Which of the following best describes your difficulty with sexual activities?

① I have some difficulty, but I have not needed to significantly change the way I perform sexual activities.

② I have some difficulty, and I have needed to make changes to my sexual activities, such as using medication, lubricant, or other sexual aids.

③ I am sometimes unable to engage fully in sexual activities due to this difficulty.

④ I am almost completely unable to engage in sexual activities due to this difficulty.