

Minimally important difference of the fatigue severity scale and modified fatigue impact scale in people with multiple sclerosis

Rooney, Scott; McFadyen, Angus; Wood, Lesley; Moffat, Fiona; Paul, Lorna

Published in:
Multiple Sclerosis and Related Disorders

DOI:
[10.1016/j.msard.2019.07.028](https://doi.org/10.1016/j.msard.2019.07.028)

Publication date:
2019

Document Version
Author accepted manuscript

[Link to publication in ResearchOnline](#)

Citation for published version (Harvard):
Rooney, S, McFadyen, A, Wood, L, Moffat, F & Paul, L 2019, 'Minimally important difference of the fatigue severity scale and modified fatigue impact scale in people with multiple sclerosis', *Multiple Sclerosis and Related Disorders*, vol. 35, pp. 158-163. <https://doi.org/10.1016/j.msard.2019.07.028>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

If you believe that this document breaches copyright please view our takedown policy at <https://edshare.gcu.ac.uk/id/eprint/5179> for details of how to contact us.

Minimally important difference of the Fatigue Severity Scale and Modified Fatigue Impact Scale in people with Multiple Sclerosis

Scott Rooney,^a Dr Angus McFadyen,^b Dr Leslie Wood,^a Dr Fiona Moffat,^c Professor Lorna Paul,^a

^aSchool of Health and Life Sciences, Glasgow Caledonian University, Glasgow, Scotland, UK; ^bAKM-Stats, Statistical Consultant, Glasgow, Scotland; ^cNHS Forth Valley, Scotland, UK.

Corresponding Author: Scott Rooney, School of Health and Life Sciences, Glasgow Caledonian University, Cowcaddens Road, Glasgow, G4 0BA. Email address: scott.rooney@gcu.ac.uk

Word count: 2892

No. of tables: 3

No. of figures: 1

Supplementary tables: 1

Abstract

Background: Fatigue is a common and debilitating symptom of Multiple Sclerosis (MS); however, it is unknown what constitutes a clinically significant change in fatigue.

Establishing the minimally important difference (MID) of fatigue outcome measures can inform the interpretation of changes in fatigue by estimating the level of change that is considered clinically relevant.

Aim: Determine the MID for the Fatigue Severity Scale (FSS) and Modified Fatigue Impact Scale (MFIS) in people with MS.

Methods: This cross-sectional study collected information on self-reported fatigue (FSS and MFIS) and quality of life (EQ-5D and MS Impact Scale 29) through an online survey. Anchor-based methods were used to estimate MID, and ordinal logistic regression models were used to determine the difference in fatigue that would predict a significant effect on quality of life.

Results: 365 people with MS (81.9% female, 69.3% relapsing-remitting MS, mean age 46.2±11.6 years, mean time since diagnosis 9.6±8.7 years) responded to the survey. MID estimates for the FSS and MFIS ranged from 0.45-0.88 and 3.86-8.11 respectively, accounting for 6.4-12.6% of maximum FSS score and 4.6-9.7% of maximum MFIS score.

Conclusions: MID estimates derived from this study indicate that a difference of at least 0.45 points on the FSS or 4 points on the MFIS constitutes a clinically significant difference in fatigue. Therefore, these estimates represent a threshold value which can be used to interpret changes in the FSS and MFIS over time or in response to an intervention.

Key words: Multiple Sclerosis; Fatigue; Minimally important difference; Fatigue Severity Scale; Modified Fatigue Impact Scale

1 Background

Fatigue is a complex symptom of Multiple Sclerosis (MS) that is reported in 70% of the population (Lerdal et al., 2007; Hadjimichael et al., 2008; Rooney et al., 2019), and is often perceived as the most debilitating symptom which significantly impacts upon quality of life (QoL) (Bakshi, 2003). Fatigue may be described as exhaustion, a lack of energy, or overwhelming tiredness which can occur at rest (Mills & Young, 2008), and is commonly defined as “a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities” (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998). Due to the subjective nature of fatigue, patient reported outcome measures (PROMs) are commonly used to assess the severity and impact of fatigue, and two of the most frequently used in studies involving people with MS are the Fatigue Severity Scale (FSS) and the Modified Fatigue Impact Scale (MFIS) (Blikman et al., 2013; Heine et al., 2015; van den Akker et al., 2016).

Interpreting changes in PROMs is important when evaluating the effectiveness of interventions, and it is recognised that conventional statistical analysis provides little information regarding the clinical significance of changes observed following an intervention (Goodman, 1999). However, the interpretation of meaningful changes in fatigue can be enhanced by establishing the minimally important difference (MID) for fatigue PROMs (Revicki et al., 2006). MID, which is defined as “the smallest difference in the outcome of interest which patients perceive as beneficial” (Jaeschke et al., 1989), is a threshold value used to interpret whether a change in an outcome is important from the patient’s perspective (Guyatt et al., 2002). MID can be determined using anchor-based or distribution-based methods – the details of which are reported elsewhere (Beaton et al., 2002; Guyatt et al., 2002; Copay et al., 2007; Revicki et al., 2008). Briefly, distribution-based methods make use of the statistical characteristics of the distribution of scores – standard deviation and standard error of measurement – to determine the MID, but are criticised for failing to convey the patient’s perspective when determining what constitutes a meaningful difference (Revicki et al., 2008). Alternatively, anchor-based methods use external indicators that are often patient-reported to determine the level of change in the PROM of interest that results in a significant difference in the anchor measurement (Revicki et al., 2008). As anchor-based methods usually use the patient’s perspective when interpreting change in PROMs, this method is

thought to generate more meaningful estimates of MID in comparison to distribution-based methods.

Despite the prevalence and impact of fatigue in people with MS, few studies have estimated MID values for fatigue outcome measures in this population (Nordin et al., 2016), with only one study estimating MID for the FSS in a relapsing-remitting MS population (Robinson et al., 2009) and another estimating MID of the Fatigue Impact Scale (Rendas-Baum et al., 2010). Consequently, it is currently unclear what constitutes a meaningful change in fatigue in people with MS. This limits the interpretation of treatment effectiveness when evaluating fatigue management interventions, as it is not possible to determine whether interventions have a clinically significant effect on fatigue. In addition to evaluating changes in fatigue, MID estimates are important for the planning of clinical trials that are adequately powered to detect changes in fatigue through informing sample sizes calculations. Therefore, this study aims to determine the MID for the FSS and MFIS in a MS population using anchor-based methods.

2 Methods

2.1 Design and participant recruitment

This study used cross-sectional data collected through an online survey that was designed using RedCap software v6.15. The survey was open-access and made available for one month between 30 May-30 June 2018, and potential participants were recruited through information shared online by international MS charities and organisations based in the UK, USA, and Australia. Eligible participants were required to confirm that they had a medical diagnosis of MS, were aged 18 years or older, and were asked to provide consent before accessing the main survey questions. Data collected through the survey included self-reported demographic information, and a series of PROMs which included measures of fatigue (FSS and MFIS), MS impact, and QoL. Both MS impact and QoL were chosen as anchors in this study due to their association with fatigue (Janardhan et al., 2002; Lerdal et al., 2007; Mills & Young, 2011), and both measures represent multidimensional global ratings of health and function that would enable quantification of meaningful differences in fatigue. In addition, participants

were required to complete the Patient Determined Disease Steps (PDDS), which is a valid and reliable self-reported measure of disability in MS populations (Hohol et al., 1995; Schwartz et al., 1999). The survey took approximately 30-40 minutes to complete, and participants were allowed to save responses and return to the survey at a later time. Ethical approval for this study was obtained from Glasgow Caledonian University School of Health and Life Sciences Ethics Committee.

2.2 Outcome measures

2.2.1 Fatigue

Fatigue was assessed using the FSS and MFIS. The FSS is a nine-item unidimensional questionnaire which measures the severity of fatigue symptoms on a seven-point ordinal scale (maximum score of seven) (Krupp et al., 1989), whereas the MFIS is a 21-item multidimensional questionnaire that measures the physical, cognitive, and psychosocial impact of fatigue using a five-point ordinal scale (maximum total score of 84) (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998). Higher scores recorded on both scales indicate greater impact/severity of fatigue symptoms. The FSS and MFIS are reliable measures of fatigue, and both scales have strong internal consistency and high precision in MS populations (Flachenecker et al., 2002; Amtmann et al., 2012; Learmonth et al., 2013).

2.2.2 Quality of life

The EQ-5D-3L was used to measure QoL. The EQ-5D-3L requires participants to rate their health over five domains – mobility, self-care, usual activities, pain/discomfort, and anxiety/depression – using a 3 point ordinal scale. Participant response over the five health domains generates a health index with a maximum score of 1 indicating ‘full health’ (EuroQol Group, 1990). The UK value set was used to generate the weighted health index (Dolan et al., 1997).

2.2.3 MS impact

The MS Impact Scale-29 (MSIS-29) version one was used to measure MS impact. The MSIS-29 assesses the physical and psychological impact of MS in response to 29 items, producing physical and psychological subscale scores which range between 20-100 and 9-45 respectively (Hobart et al., 2001). The MSIS-29 demonstrates strong validity and reliability in MS populations (Hobart et al., 2001; McGuigan et al., 2004; Gray et al., 2009).

2.3 Data analysis

All participants who provided complete questionnaire responses were included in the data analysis. Demographic characteristics and questionnaire responses of study participants were reported as mean values as data were normally distributed according to the Shapiro-Wilk statistic. In order to derive MID values for the FSS and MFIS, ordinal logistic regression models (specifically proportional odds models) were used to predict the difference in fatigue PROM scores that would result in a change in each MSIS-29 and EQ-5D-3L response item. Therefore, 34 response items (29 from MSIS-29 and 5 from EQ-5D-3L) were considered as potential anchor variables for each analysis. All data analysis was performed using IBM SPSS v23 (IBM Corporation, Armonk, NY, USA).

2.3.1 Anchor variable selection

To assess the viability of each anchor variable, Spearman correlation coefficients were calculated to determine the strength of association between potential anchors and fatigue (FSS and MFIS scores), with correlation coefficients ≥ 0.3 being used to select anchor variables (Revicki et al., 2008). In addition, the proportional odds assumption was assessed using the probability values derived from the test of parallel lines to determine whether the cumulative odds ratio was consistent between each response category of the anchor variable. Anchor variables that violated the proportional odds assumption were excluded from the analysis.

2.3.2 Determining minimally important difference

MID scores were derived using ordinal logistic regression methods recommended by Angst et al. (2017) and previously used by Rendas-Baum et al. (2010) in a similar cross-sectional study of people with MS. Initially, proportional odds models were used to predict the effects of the independent variables – FSS and MFIS – on each dependent anchor variable that fulfilled the selection criteria (Supplementary Table 1). According to the proportional odds model, the odds ratio associated with moving between ordinal response categories on the dependent anchor variable (that is either worsened or improved QoL/MS impact), is proportional to change in the independent variable. Therefore, using the coefficients (β) generated from each proportional odds model, MID was estimated based on the smallest difference in FSS/MFIS scores that predicted a 1.5 odds of moving between response categories for each anchor variable using the following formula: $x = \ln(1.5) / \beta$ (where x is the difference in FSS/MFIS scores, thus representing the MID). In line with the methods described by Rendas-Baum et al. (2010), an odds ratio of 1.5 was selected as this corresponds to a standardised difference of 2.54 and a small effect size (Cohen, 1992; Tritchler, 1995). Therefore, MID scores translate to the difference in fatigue outcome that would predict at least a small effect on QoL and MS impact.

3 Results

3.1 Demographic data

Of the 498 people who agreed to take part in the survey, 365 (73%) provided sufficient data to be included in this analysis. Participants were mostly female (81.9%), had a relapsing-remitting form of MS (69.3%), and had a mean age of 46.2 ± 11.6 years and time since diagnosis of 9.6 ± 8.7 years (Table 1). In addition, the mean PDDS score was 3.1 ± 2.3 indicating that participants mostly reported mild-moderate levels of disability. Descriptive statistics for each of the possible 34 anchor variables are provided in Table 2.

Table 1 near here

Table 2 near here

3.2 Anchor variable selection

Overall, 26 and 28 variables met the selection criteria and were regarded as eligible anchor variables for determining the MID of the FSS and MFIS respectively. Of the eight variables excluded from the FSS analysis, three were excluded as Spearman correlation coefficients were found to be <0.3 (EQ-5D item 4 = 0.296; EQ-5D item 5 = 0.230; MSIS-29 item 24 = 0.293) (Table 3). The remaining variables were excluded following the test of parallel lines, as odds ratios were not consistent between ordinal response categories for the 2nd ($\chi^2 = 8.989$, $p = 0.029$), 7th ($\chi^2 = 12.376$, $p = 0.006$), 10th ($\chi^2 = 8.013$, $p = 0.046$), 25th ($\chi^2 = 9.860$, $p = 0.020$), and 26th ($\chi^2 = 17.825$, $p < 0.001$) items of the MSIS-29. For the MFIS analysis, all 34 potential anchor variables demonstrated an association with MFIS scores ($r_s \geq 0.3$); however, six variables were excluded due to violation of the proportional odds assumption including the 5th item of the EQ-5D ($\chi^2 = 4.992$, $p = 0.025$), and the 19th ($\chi^2 = 9.408$, $p = 0.024$), 21st ($\chi^2 = 11.657$, $p = 0.009$), 26th ($\chi^2 = 10.151$, $p = 0.017$), 27th ($\chi^2 = 8.429$, $p = 0.038$), and 28th ($\chi^2 = 12.244$, $p = 0.007$) items of the MSIS-29.

Table 3 near here

3.3 Minimally important difference of the Fatigue Severity Scale and Modified Fatigue Impact Scale

Estimates of MID for the FSS ranged between 0.45-0.88 (6.4-12.6% of maximum FSS score), and the mean MID estimate from the 26 anchor variables was 0.68 ± 0.12 (Figure 1). The anchor variable with the smallest MID estimate (0.45) was MSIS-29 item 13 which asked participants: “how much has your MS limited your social and leisure activities at home”. Similarly, items 14 and 19 of the MSIS-29, which related to activity limitations, were also sensitive to differences in fatigue, with MID estimates of 0.52 and 0.50 respectively. The least sensitive anchor variables were MSIS-29 items 9 (MID = 0.88) and 22 (MID = 0.87), which asked participants how much they have been affected by “tremor of your arms and legs” and “problems sleeping”.

For the MFIS, estimates of MID ranged from 3.86-8.11 (4.6-9.7% of maximum MFIS score), and the mean MID estimate from the 28 anchor variables was 6.25 ± 1.13 (Figure 1). Similar to the FSS, smaller MID estimates were derived from anchor variables that were related to activity limitations such as MSIS-29 items 13 “how much has your MS limited your social and leisure activities at home” (MID = 4.94) and 14 “how much has your MS resulted in you being stuck at home more than you would like to be” (MID = 4.94) and 18 “how much has your MS resulted in you taking longer to do things?” (MID = 4.77). However, the smallest MID estimate for the MFIS was derived from MSIS-29 item 23: “how much have you been bothered by feeling mentally fatigued” (MID = 3.86). The least sensitive anchor variables were EQ-5D item 1 (mobility) and item 2 (self-care) with MID estimates of 8.11 and 7.80 respectively.

Figure 1 near here

4 Discussion

This study estimated that the MID of the FSS ranged between 0.45-0.88, meaning that a difference of 6.4-12.6% in the maximum FSS score would predict at least a small effect on QoL and MS impact. In addition, the MID of the MFIS was estimated to range from 3.86-8.11, accounting for 4.6-9.7% of the maximum MFIS score. Therefore, these findings suggest that a threshold value of at least 0.45 points for the FSS and 4 points for the MFIS constitutes a clinically significant difference in outcome measure scores. Accordingly, the MID estimates reported in this study can be used to interpret changes in the FSS and MFIS, and evaluate the effectiveness of interventions in managing fatigue.

Importantly, this is the first study to estimate MID for the MFIS in a MS population, and although another study has estimated MID for the FSS in people with relapsing-remitting MS (Robinson et al., 2009), the present study has a larger sample size ($n= 365$ vs. 249), includes both progressive and relapsing-remitting MS types, and used a greater number of anchor variables. The findings of the present study are similar to those of Robinson et al. (2009) as

MID for the FSS was reported to range between 0.5 and 1.1, accounting for 7.1-15.7% of maximum FSS score. In addition, although Rendas-Baum et al. (2010) calculated MID for the Fatigue Impact Scale (FIS), the MID estimate of 5.6-15.0% of maximum FIS score is similar to the results of the present study for the FSS, but is larger than the estimated value for the MFIS. While another study by Learmonth et al. (2013) reported that significantly larger differences in FSS (38%) and MFIS (49%) scores constitute a clinically significant change, these estimates refer to the minimal detectable change, which describes the change in scores that are above the level of measurement error as opposed to the MID (the change that is perceived important from the participants' perspective) (Copay et al., 2007); therefore, these estimates do not necessarily reflect a clinically significant difference as concluded.

As the estimated MID values reported in the present study accounted for a small proportion of both maximum FSS and MFIS scores, these findings suggest that a small difference in fatigue severity/impact is clinically significant in relation to QoL/MS impact. While the estimated values for MID accounted for a similar proportion of maximum FSS and MFIS scores (6.4-12.6% vs. 4.6-9.7% respectively), MID estimates for the MFIS covered a smaller range in scores and values for each individual anchor variable were comparatively lower. Therefore, the MFIS may be more responsive to clinically significant changes in fatigue when compared to the FSS – perhaps due to the multidimensional nature of the measurement scale. However, the MFIS has limited content validity and limited ability to distinguish between overall levels of function (e.g. physical, cognitive, and psychosocial function) and the impact of fatigue on these domains (Hobart et al., 2013); thus, the smaller MID estimate for the MFIS may reflect the stronger association between MFIS and outcome measures of global function (e.g. MSIS-29 and EQ-5D) (Flachenecker et al., 2002).

Importantly, the estimates of MID reported in the present study were derived using anchor-based methods as the participants' own subjective evaluation of QoL and MS impact were used to determine MID. Therefore, these MID estimates reflect the difference in fatigue severity/impact that could be interpreted as clinically significant by participants. While several cross-sectional studies have reported anchor-based MID estimates for fatigue outcome measures in various clinical populations (Nordin et al., 2016), only Rendas-Baum et al. (2010) have used the logistic regression methods followed in this study. These methods

avoid the need to dichotomise outcomes using arbitrary cut-points in order to determine MID by comparing fatigue scores between groups; instead, the transition between categories on response items of the EQ-5D/MSIS-29 was used to represent either improving or worsening QoL/MS impact. However, due to the cross-sectional study design, the logistic regression models used in this study can only predict the changes in fatigue that constitute MID. Therefore, future studies should determine whether these MID estimates reflect the level of change that participants perceived as meaningful when measuring longitudinal differences in fatigue.

As the choice of anchor variable can influence the responsiveness of MID estimates, this study used multiple anchor variables from the EQ-5D and MSIS-29 to estimate MID scores (Revicki et al., 2008). Therefore, the range of MID scores reported in this study reflect the likely effect that differences in fatigue severity/impact would have on the various factors that constitute QoL and MS impact. Within this study there was varying responsiveness of different anchor variables, as anchor variables related to activity limitations were more responsive to changes in FSS and produced lower MID scores in comparison to variables related to specific impairments (such as upper/lower limb tremor). Similarly restrictions in activities of daily living were most responsive to changes in MFIS, suggesting that a small change in fatigue is likely to impact activity limitations in people with MS.

4.1 Limitations

Due to the cross-sectional design, the MID estimates reported in this study are derived from predictive regression models and not from longitudinal differences in fatigue. Therefore, there is a need for longitudinal studies to confirm whether the findings of this present study can be applied when evaluating differences in fatigue over time. In addition, this study reports only anchor-based estimates of MID which limits the ability to compare the results to other studies that have used distribution based methods to estimate MID. Importantly, although MS diagnosis and type were self-reported, the participant demographics of this study sample were representative of a typical MS population (Compston & Coles, 2008; Mackenzie et al., 2014), suggesting that the results of this study are generalizable to those with MS. However, due to the open online nature of the survey used in this study, all

outcomes were self-reported and it was not possible to screen for cognitive impairment which may have influenced participant questionnaire responses. Lastly, as this study estimated MID using a MS population, these results are not generalizable to other clinical populations in which the FSS and MFIS have been validated.

5 Conclusions

This study provided novel data on the MID of the FSS and MFIS in a large sample of people with MS and indicated that a small difference in fatigue severity (FSS = 0.45) and impact (MFIS = 4) predicted a significant effect on quality of life. As these estimates were derived using the participant's self-reported MS impact and QoL, the MID values reported in this study can be used to inform researchers and clinicians of the clinical significance of differences in FSS and MFIS scores. Furthermore, the estimated MID can be used to plan adequately powered clinical trials that use the FSS or MFIS as the primary outcome measure through informing sample size calculation. However, to confirm the findings of this study, future studies should consider using longitudinal designs to provide more precise anchor-based estimates of MID.

Conflicts of interest: All authors declare no conflicts of interest

Funding sources: The first author was funded by a Glasgow Caledonian University PhD studentship.

References

- (1) Lerdal A, Celius EG, Krupp L, Dahl AA. A prospective study of patterns of fatigue in multiple sclerosis. *Eur J Neurol* 2007 Dec;14(12):1338-1343.
- (2) Hadjimichael O, Vollmer T, Oleen-Burkey M, North American Research Committee on Multiple Sclerosis. Fatigue characteristics in multiple sclerosis: the North American Research Committee on Multiple Sclerosis (NARCOMS) survey. *Health Qual Life Outcomes* 2008 Nov 14;6:100-7525-6-100.
- (3) Rooney S, Wood L, Moffat F, Paul L. Prevalence of fatigue and its association with clinical features in progressive and non-progressive forms of Multiple Sclerosis. *Multiple Sclerosis and Related Disorders* 2019 February 2019;28:276-282.
- (4) Bakshi R. Fatigue associated with multiple sclerosis: diagnosis, impact and management. *Multiple Sclerosis* 2003;9(3):219-27.
- (5) Mills RJ, Young CA. A medical definition of fatigue in multiple sclerosis. *QJM* 2008 Jan;101(1):49-60.
- (6) Multiple Sclerosis Council for Clinical Practice Guidelines. Fatigue and multiple sclerosis: Evidence-based management strategies for fatigue in multiple sclerosis. 1998.
- (7) Blikman LJ, Huisstede BM, Kooijmans H, Stam HJ, Bussmann JB, van Meeteren J. Effectiveness of energy conservation treatment in reducing fatigue in multiple sclerosis: a systematic review and meta-analysis. *Arch Phys Med Rehabil* 2013 Jul;94(7):1360-1376.
- (8) Heine M, van dP, Rietberg MB, van Wegen E,E.H., Kwakkel G. Exercise therapy for fatigue in multiple sclerosis. *The Cochrane database of systematic reviews* 2015;9:CD009956.
- (9) van den Akker LE, Beckerman H, Collette EH, Eijssen IC, Dekker J, de Groot V. Effectiveness of cognitive behavioral therapy for the treatment of fatigue in patients with multiple sclerosis: A systematic review and meta-analysis. *J Psychosom Res* 2016 Nov;90:33-42.
- (10) Goodman SN. Toward evidence-based medical statistics. 1: The P value fallacy. *Ann Intern Med* 1999 Jun 15;130(12):995-1004.
- (11) Revicki DA, Cella D, Hays RD, Sloan JA, Lenderking WR, Aaronson NK. Responsiveness and minimal important differences for patient reported outcomes. *Health Qual Life Outcomes* 2006 Sep 27;4:70-7525-4-70.
- (12) Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials* 1989 Dec;10(4):407-415.
- (13) Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR, Clinical Significance Consensus Meeting Group. Methods to explain the clinical significance of health status measures. *Mayo Clin Proc* 2002 Apr;77(4):371-383.

- (14) Beaton DE, Boers M, Wells GA. Many faces of the minimal clinically important difference (MCID): a literature review and directions for future research. *Curr Opin Rheumatol* 2002 Mar;14(2):109-114.
- (15) Copay AG, Subach BR, Glassman SD, Polly DW, Jr, Schuler TC. Understanding the minimum clinically important difference: a review of concepts and methods. *Spine J* 2007 Sep-Oct;7(5):541-546.
- (16) Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. *J Clin Epidemiol* 2008 Feb;61(2):102-109.
- (17) Nordin A, Taft C, Lundgren-Nilsson A, Dencker A. Minimal important differences for fatigue patient reported outcome measures-a systematic review. *BMC Med Res Methodol* 2016 May 26;16:62-016-0167-6.
- (18) Robinson D, Jr, Zhao N, Gathany T, Kim LL, Cella D, Revicki D. Health perceptions and clinical characteristics of relapsing-remitting multiple sclerosis patients: baseline data from an international clinical trial. *Curr Med Res Opin* 2009 May;25(5):1121-1130.
- (19) Rendas-Baum R, Yang M, Cattelin F, Wallenstein GV, Fisk JD. A novel approach to estimate the minimally important difference for the Fatigue Impact Scale in multiple sclerosis patients. *Qual Life Res* 2010 Nov;19(9):1349-1358.
- (20) Janardhan V, Bakshi R. Quality of life in patients with multiple sclerosis: The impact of fatigue and depression. *J Neurol Sci* 2002;205(1):51-58.
- (21) Mills RJ, Young CA. The relationship between fatigue and other clinical features of multiple sclerosis. *Mult Scler* 2011 May;17(5):604-612.
- (22) Hohol MJ, Orav EJ, Weiner HL. Disease steps in multiple sclerosis: a simple approach to evaluate disease progression. *Neurology* 1995;45(2):251-255.
- (23) Schwartz CE, Vollmer T, Lee H. Reliability and validity of two self-report measures of impairment and disability for MS. North American Research Consortium on Multiple Sclerosis Outcomes Study Group. *Neurology* 1999;52(1):63-70.
- (24) Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989 Oct;46(10):1121-1123.
- (25) Flachenecker P, Kümpfel T, Kallmann B, Gottschalk M, Grauer O, Rieckmann P, et al. Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters. *Multiple Sclerosis* 2002;8(6):523-526.
- (26) Amtmann D, Bamer AM, Noonan V, Lang N, Kim J, Cook KF. Comparison of the Psychometric Properties of Two Fatigue Scales in Multiple Sclerosis. *Rehabilitation Psychology* 2012;57(2):159-166.

- (27) Learmonth YC, Dlugonski D, Pilutti LA, Sandroff BM, Klaren R, Motl RW. Psychometric properties of the Fatigue Severity Scale and the Modified Fatigue Impact Scale. *J Neurol Sci* 2013;331(1-2):102-107.
- (28) EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990 Dec;16(3):199-208.
- (29) Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997 Nov;35(11):1095-1108.
- (30) Hobart J, Lamping D, Fitzpatrick R, Riazi A, Thompson A. The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. *Brain* 2001 May;124(Pt 5):962-973.
- (31) McGuigan C, Hutchinson M. The multiple sclerosis impact scale (MSIS-29) is a reliable and sensitive measure. *J Neurol Neurosurg Psychiatry* 2004 Feb;75(2):266-269.
- (32) Gray O, McDonnell G, Hawkins S. Tried and tested: the psychometric properties of the multiple sclerosis impact scale (MSIS-29) in a population-based study. *Mult Scler* 2009 Jan;15(1):75-80.
- (33) Angst F, Aeschlimann A, Angst J. The minimal clinically important difference raised the significance of outcome effects above the statistical level, with methodological implications for future studies. *J Clin Epidemiol* 2017 Feb;82:128-136.
- (34) Cohen J. A power primer. *Psychol Bull* 1992;112:155-159.
- (35) Titchler D. Interpreting the standardized difference. *Biometrics* 1995 Mar;51(1):351-353.
- (36) Hobart J, Cano S, Baron R, Thompson A, Schwid S, Zajicek J, et al. Achieving valid patient-reported outcomes measurement: a lesson from fatigue in multiple sclerosis. *Mult Scler* 2013;19(13):1773-1783.
- (37) Compston A, Coles A. Multiple sclerosis. *The Lancet* 2008;372(9648):1502-1517.
- (38) Mackenzie IS, Morant SV, Bloomfield GA, Macdonald TM, O'Riordan J. Incidence and prevalence of multiple sclerosis in the UK 1990–2010: a descriptive study in the General Practice Research Database. *J Neurol Neurosurg Psychiatry* 2014;85(1):76.

Figure legend

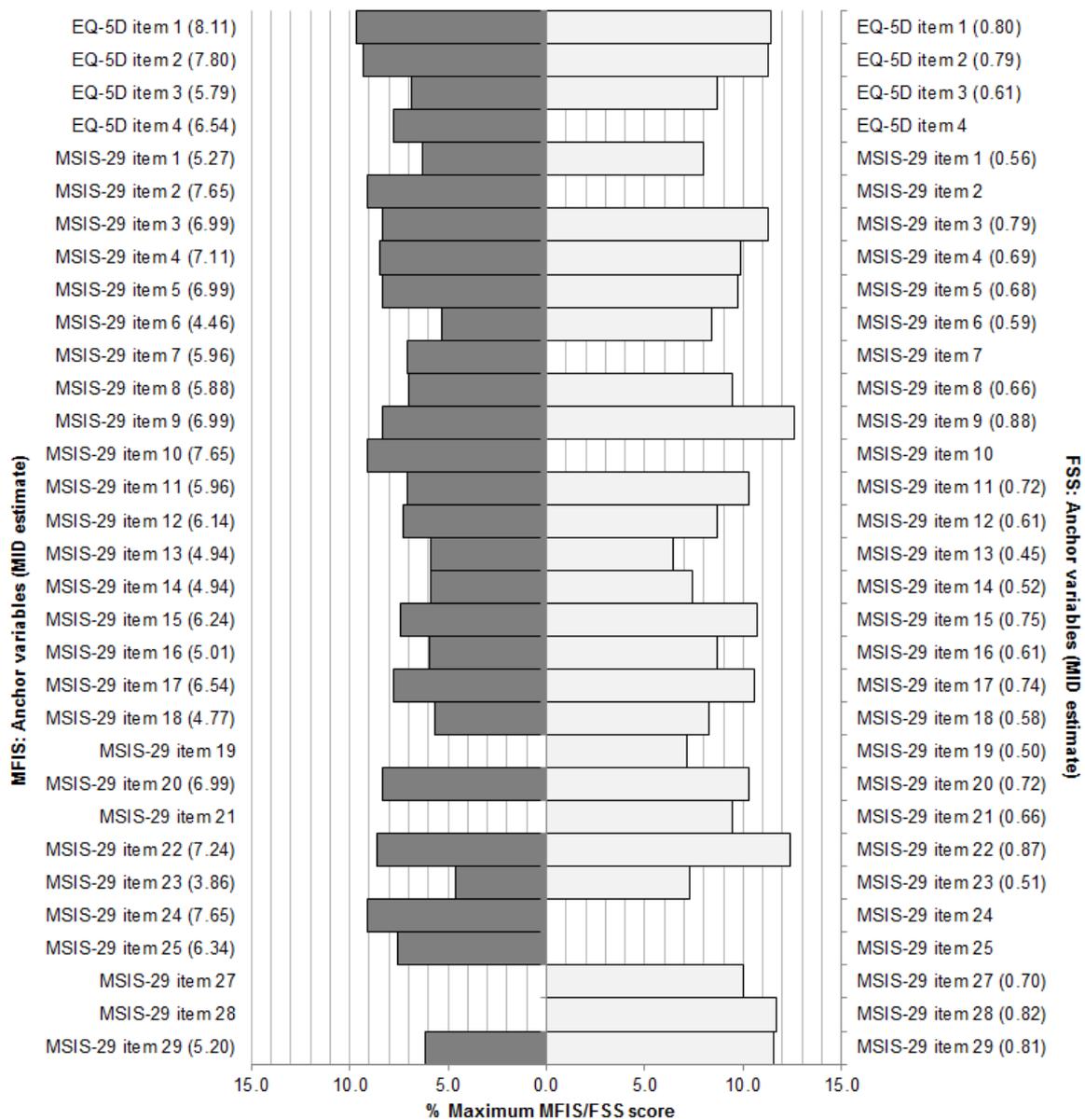


Figure 1 MID estimates for the Fatigue Severity Scale and Modified Fatigue Impact Scale, and the proportion of maximum FSS/MFIS scores these estimates account for (missing values indicate excluded variables)

Table 1 Participant demographics

Participants, n	365
Age (years), mean \pm SD (range)	46.2 \pm 11.6 (22-79)
Time since diagnosis (years), mean \pm SD (range)	9.6 \pm 8.7 (0-44)
MS type, % (n)	
RRMS	69.3% (253)
SPMS	18.6% (68)
PPMS	9.3% (34)
Benign	0.5% (2)
Unknown	2.2% (8)
PDDS , mean \pm SD (range)	3.1 \pm 2.3 (0-8)
Sex, % (n)	
Female	81.9% (299)
Male	18.1% (66)
Work status, % (n)	
Working	46.8% (171)
Not working	53.2% (194)
Highest level of education, % (n)	
University or college	70.4% (257)
Trade/vocational training	9.9% (36)
High school	19.5% (71)
Did not complete high school	0.3% (1)
FSS , mean \pm SD	5.38 \pm 1.39
MFIS (total) , mean \pm SD	54.5 \pm 16
MFIS (physical), mean \pm SD	25.3 \pm 7.3
MFIS (cognitive), mean \pm SD	23.6 \pm 9.2
MFIS (psychological), mean \pm SD	5.4 \pm 2
EQ-5Dindex , mean \pm SD	0.51 \pm 0.34
MSIS-29 (physical) , mean \pm SD	61.5 \pm 20.1

MSIS-29 (psychological), mean \pm SD

27.8 \pm 8.9

Abbreviations : FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; MS, Multiple Sclerosis; MSIS-29, Multiple Sclerosis Impact Scale-29; PDDS, Patient Determined Disease Steps; PPMS, Primary Progressive Multiple Sclerosis; RRMS, Relapsing Remitting Multiple Sclerosis; SPMS, Secondary Progressive Multiple Sclerosis

Table 2 Descriptive summary of the 34 potential anchors variables

EQ-5D/MSIS-29 response items	Response categories frequency (%)					Item mean \pm SD
	1	2	3	4	5	
EQ-5D						
1) Mobility	30.7	67.4	1.9			1.7 \pm 0.5
2) Self-care	62.5	32.6	4.9			1.4 \pm 0.6
3) Usual activities	20.0	67.9	12.1			1.9 \pm 0.6
4) Pain/discomfort	24.1	60.0	15.9			1.9 \pm 0.6
5) Anxiety/depression	36.2	52.6	11.2			1.7 \pm 0.6
MSIS-29	1	2	3	4	5	
How much has MS limited your ability to...						
1) ...do physically demanding tasks	5.5	15.6	18.9	33.7	26.3	3.6 \pm 1.2
2) ...grip things tightly	19.5	23.0	22.2	23.6	11.8	2.9 \pm 1.3
3) ...carry things	15.9	22.5	26.0	21.1	14.5	3.0 \pm 1.3
How much have you been bothered by...						
4) ...problems with your balance	8.8	17.0	22.2	31.8	20.3	3.4 \pm 1.2
5) ...difficulties moving about indoors	20.0	22.2	20.8	23.8	13.2	2.9 \pm 1.3
6) ... being clumsy	7.4	24.1	23.3	29.6	15.6	3.2 \pm 1.2
7) ...stiffness	11.2	16.7	20.5	30.7	20.8	3.3 \pm 1.3
8) ...heavy arms and/or legs	12.1	15.9	21.6	26.6	23.8	3.3 \pm 1.3
9) ...tremor of your arms or legs	35.1	24.7	17.5	13.4	9.3	2.4 \pm 1.3
10) ...spasms in your limbs	28.8	24.1	18.4	16.2	12.6	2.6 \pm 1.4
11) ...your body not doing what you want it to	18.1	22.5	21.9	20.8	16.7	3.0 \pm 1.4
12) ...having to depend on others to do things for you	21.1	19.7	18.4	24.1	16.7	3.0 \pm 1.4
13) ...limitations in your social and leisure activities at home	10.7	22.5	21.1	25.2	20.5	3.2 \pm 1.3
14) ...being stuck at home more than you would like to be	20.0	18.9	12.1	22.2	26.8	3.2 \pm 1.5
15) ...difficulties using your hands in everyday tasks	25.8	21.4	21.4	18.1	13.4	2.7 \pm 1.4
16) ...having to cut down the amount of time you spend on work or other daily activities	14.0	18.1	20.0	23.6	24.4	3.2 \pm 1.4
17) ...problems using transport	34.8	17.8	18.6	14.2	14.5	2.6 \pm 1.5

18) ...taking longer to do things	10.4	15.6	23.0	27.4	23.6	3.4 ± 1.3
19) ...difficulty doing things spontaneously	13.7	14.0	19.5	24.1	28.8	3.4 ± 1.4
20) ...needing to go to the toilet urgently	15.6	15.1	14.0	29.3	26.0	3.4 ± 1.4
21) ...feeling unwell	15.9	23.6	28.5	20.5	11.5	2.9 ± 1.2
22) ...problems sleeping	17.0	15.9	23.3	24.4	19.5	3.1 ± 1.4
23) ...feeling mentally fatigued	5.5	13.4	18.1	37.0	26.0	3.7 ± 1.2
24) ...worries related to your MS	17.0	20.3	25.5	20.3	17.0	3.0 ± 1.3
25) ...feeling anxious or tense	17.5	20.5	21.6	25.2	15.1	3.0 ± 1.3
26) ...feeling irritable, impatient or short tempered	13.4	18.1	23.6	28.2	16.7	3.2 ± 1.3
27) ...problems concentrating	11.8	15.9	27.7	29.9	14.8	3.2 ± 1.2
28) ...lack of confidence	12.6	25.5	21.1	22.2	18.6	3.1 ± 1.3
29) ...feeling depressed	27.4	24.1	19.2	15.1	14.2	2.7 ± 1.4

Abbreviations : FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; MS, Multiple Sclerosis; MSIS-29, Multiple Sclerosis Impact Scale-29

Table 3 Variables excluded from MID analysis

Excluded variables	Justification
(a)	
EQ-5D item 4	Correlation coefficient <0.3 ($r_s = 0.296$, $p < 0.001$)*
EQ-5D item 5	Correlation coefficient <0.3 ($r_s = 0.230$, $p < 0.001$)*
MSIS-29 item 2	Violation of proportional odds assumption ($\chi^2 = 8.989$, $p = 0.029$)†
MSIS-29 item 7	Violation of proportional odds assumption ($\chi^2 = 12.376$, $p = 0.006$)†
MSIS-29 item 10	Violation of proportional odds assumption ($\chi^2 = 8.013$, $p = 0.046$)†
MSIS-29 item 24	Correlation coefficient <0.3 ($r_s = 0.293$, $p < 0.001$)*
MSIS-29 item 25	Violation of proportional odds assumption ($\chi^2 = 9.86$, $p = 0.020$)†
MSIS-29 item 26	Violation of proportional odds assumption ($\chi^2 = 17.825$, $p < 0.001$)†
(b)	
EQ-5D item 5	Violation of proportional odds assumption ($\chi^2 = 4.992$, $p = 0.025$)†
MSIS-29 item 19	Violation of proportional odds assumption ($\chi^2 = 9.408$, $p = 0.024$)†
MSIS-29 item 21	Violation of proportional odds assumption ($\chi^2 = 11.657$, $p = 0.009$)†
MSIS-29 item 26	Violation of proportional odds assumption ($\chi^2 = 10.151$, $p = 0.017$)†
MSIS-29 item 27	Violation of proportional odds assumption ($\chi^2 = 8.429$, $p = 0.038$)†
MSIS-29 item 28	Violation of proportional odds assumption ($\chi^2 = 12.244$, $p = 0.007$)†

Abbreviations: MSIS-29, Multiple Sclerosis Impact Scale-29

(a) variables excluded from Fatigue Severity Scale analysis; (b) variables excluded from Modified Fatigue Impact Scale analysis

* values derived from Spearman correlation analysis

† values derived from test of parallel lines

Supplementary Table 1 Results of the proportional odds models (n=54) which predict the odds of moving between ordinal response categories on the EQ-5D and MSIS-29 (dependent variables) for a 1-point difference in FSS/MFIS scores (independent variables)

	FSS				MFIS			
	OR (95% CI)	β (SE)	Wald χ^2	p	OR (95% CI)	β (SE)	Wald χ^2	p
EQ-5D item 1	1.657 (1.400-1.962)	0.505 (0.086)	34.4	<0.001	1.052 (1.035-1.068)	0.050 (0.008)	39.8	<0.001
EQ-5D item 2	1.671 (1.377-2.028)	0.513 (0.099)	27.0	<0.001	1.053 (1.036-1.070)	0.052 (0.008)	39.1	<0.001
EQ-5D item 3	1.950 (1.634-2.327)	0.668 (0.09)	54.8	<0.001	1.073 (1.055-1.091)	0.070 (0.008)	71.0	<0.001
EQ-5D item 4	1.064 (1.048-1.080)	0.062 (0.008)	65.5	<0.001
EQ-5D item 5
MSIS-29 item 1	2.073 (1.781-2.413)	0.729 (0.077)	88.6	<0.001	1.080 (1.065-1.095)	0.077 (0.007)	116	<0.001
MSIS-29 item 2	1.054 (1.041-1.068)	0.053 (0.007)	66.0	<0.001
MSIS-29 item 3	1.670 (1.448-1.926)	0.513 (0.073)	49.7	<0.001	1.060 (1.046-1.074)	0.058 (0.007)	78.1	<0.001
MSIS-29 item 4	1.804 (1.561-2.084)	0.590 (0.074)	64.0	<0.001	1.059 (1.045-1.073)	0.057 (0.007)	76.7	<0.001
MSIS-29 item 5	1.816 (1.565-2.107)	0.597 (0.076)	61.9	<0.001	1.060 (1.046-1.073)	0.058 (0.007)	75.6	<0.001
MSIS-29 item 6	1.995 (1.715-2.320)	0.690 (0.077)	80.3	<0.001	1.095 (1.079-1.112)	0.091 (0.008)	143.3	<0.001
MSIS-29 item 7	1.070 (1.056-1.085)	0.068 (0.007)	98.4	<0.001
MSIS-29 item 8	1.848 (1.597-2.138)	0.614 (0.074)	68.0	<0.001	1.072 (1.057-1.086)	0.069 (0.007)	100.9	<0.001
MSIS-29 item 9	1.589 (1.368-1.846)	0.463 (0.076)	36.8	<0.001	1.060 (1.045-1.074)	0.058 (0.007)	68.9	<0.001
MSIS-29 item 10	1.055 (1.041-1.069)	0.053 (0.007)	64.1	<0.001
MSIS-29 item 11	1.760 (1.522-2.036)	0.565 (0.074)	58.0	<0.001	1.070 (1.056-1.085)	0.068 (0.007)	96.0	<0.001
MSIS-29 item 12	1.934 (1.660-2.254)	0.660 (0.078)	71.4	<0.001	1.068 (1.053-1.082)	0.066 (0.007)	90.2	<0.001

MSIS-29 item 13	2.446 (2.077-2.881)	0.894 (0.083)	114.9	<0.001	1.086 (1.070-1.101)	0.082 (0.007)	126.9	<0.001
MSIS-29 item 14	2.170 (1.848-2.548)	0.775 (0.082)	89.5	<0.001	1.085 (1.069-1.101)	0.082 (0.008)	118.3	<0.001
MSIS-29 item 15	1.719 (1.482-1.993)	0.542 (0.076)	51.4	<0.001	1.068 (1.053-1.082)	0.065 (0.007)	87.7	<0.001
MSIS-29 item 16	1.946 (1.677-2.260)	0.666 (0.076)	76.5	<0.001	1.085 (1.069-1.100)	0.081 (0.007)	123.5	<0.001
MSIS-29 item 17	1.730 (1.481-2.020)	0.548 (0.079)	48.1	<0.001	1.064 (1.049-1.079)	0.062 (0.007)	75.9	<0.001
MSIS-29 item 18	2.011 (1.731-2.337)	0.699 (0.077)	83.3	<0.001	1.089 (1.073-1.104)	0.085 (0.007)	131.9	<0.001
MSIS-29 item 19	2.251 (1.921-2.638)	0.811 (0.081)	100.5	<0.001
MSIS-29 item 20	1.759 (1.522-2.032)	0.564 (0.074)	58.5	<0.001	1.060 (1.046-1.074)	0.058 (0.007)	76.3	<0.001
MSIS-29 item 21	1.855 (1.599-2.152)	0.618 (0.076)	66.7	<0.001
MSIS-29 item 22	1.596 (1.387-1.836)	0.468 (0.072)	42.8	<0.001	1.058 (1.044-1.072)	0.056 (0.007)	73.8	<0.001
MSIS-29 item 23	2.205 (1.887-2.576)	0.791 (0.079)	99.3	<0.001	1.111 (1.093-1.129)	0.105 (0.008)	164.8	<0.001
MSIS-29 item 24	1.054 (1.041-1.068)	0.053 (0.006)	67.0	<0.001
MSIS-29 item 25	1.067 (1.052-1.081)	0.064 (0.007)	89.7	<0.001
MSIS-29 item 26
MSIS-29 item 27	1.788 (1.547-2.067)	0.581 (0.074)	61.9	<0.001
MSIS-29 item 28	1.641 (1.424-1.889)	0.495 (0.072)	47.2	<0.001
MSIS-29 item 29	1.650 (1.424-1.911)	0.501 (0.075)	44.6	<0.001	1.081 (1.066-1.097)	0.078 (0.007)	109.8	<0.001

Abbreviations: FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; MSIS-29, Multiple Sclerosis Impact Scale-29

Missing values indicate excluded variables