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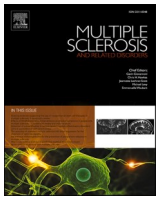

Review article

The effect of disease modifying therapies on fatigue in multiple sclerosis

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ABSTRACT

Introduction: Fatigue is one of the most common and debilitating symptoms in people with multiple sclerosis (PwMS). Disease-modifying therapies (DMTs) are currently the gold standard in the treatment of MS and their effectiveness has been assessed through randomized clinical trials (RCTs). However, there is limited evidence on the impact of DMTs on fatigue in (PwMS). We conducted a systematic review to 1) understand whether fatigue is included as an outcome in MS trials of DMTs; 2) determine the effects on fatigue of treating MS with DMTs and 3) assess the quality of MS trials including fatigue as an outcome.

Methods: Two independent researchers systematically searched MEDLINE, EMBASE and ClinicalTrials.gov from 1993 to January 2023 for RCTs that measured fatigue as an outcome. Adherence to reporting standards was assessed with the Consolidated Standards of Reporting Trials (CONSORT)-Patient-Reported Outcomes (PRO), while the risk of bias (RoB) was assessed with the RoB 2 tool by the Cochrane Handbook for Systematic Reviews of Interventions. The systematic review protocol was registered in PROSPERO (CRD42022383321).

Results: The search strategy identified 130 RCTs of DMTs of which 7 (5%) assessed fatigue as an outcome. Of the 7 trials, only two presented statistically significant results. In addition, the reporting of fatigue among RCTs was suboptimal with a mean adherence to the CONSORT-PRO Statement of 36% across all trials. Of the 7 trials included, four were assessed as 'high' RoB..

Conclusions: Fatigue has a major impact on PwMS yet there is limited trial-based evidence on the impact of DMTs on fatigue. Assessment of fatigue as an outcome is underrepresented in trials of DMTs and the reporting of PRO trial data is suboptimal. Thus, it is imperative that MS researchers conduct RCTs that include fatigue as an outcome, to support clinicians and people with MS (PwMS) to consider the impact of the different DMTs on fatigue.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system. In 2020, there were 2.8 million MS cases globally, equating to a prevalence of 35.9 cases per 100,000 people (Walton et al., 2020). In the UK, there are 130,000 estimated cases, affecting 1 in every 500 people (MSSociety, 2020). MS is more common in White individuals; however, the incidence of MS among African Americans and Hispanics is increasing in the US (Amezcua and McCauley, 2020).

Typical MS symptoms include physical disability, cognitive

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impairment, changes in mood, pain, fatigue, bladder dysfunction, among others (Compston and Coles, 2008). Fatigue and changes in cognition are regarded as two of the most common symptoms of MS. Fatigue prevalence range between 52% and 88%, while cognition affects approximately 60% of people with MS (PwMS) (Landmeyer et al., 2020; Rooney et al., 2019).

Fatigue is commonly accompanied by depression, which are recognized as serious and debilitating symptoms that has a profound impact on individuals' quality of life, employment and productivity (Braley and Chervin, 2010).

The burden of fatigue on PwMS can be systematically assessed using patient-reported outcome measures (PROMs). PROMs are questionnaires used to determine the impact of disease and treatment from the patient's perspective on their symptom burden, functional status and health-related quality of life (Black, 2013). A systematic review appraising, comparing and summarizing PROMs to assess fatigue in MS, Parkinson's disease and stroke outlines different self-reported measures such as the Modified Fatigue Impact Scale and Fatigue Severity Scale (Elbers et al., 2012). In addition, the review demonstrates the availability of a wide number of PROMs, each accompanied by methodological advantages and disadvantages, making the standardization of fatigue PRO assessment challenging.

Disease-modifying therapies (DMTs) are the gold standard in the treatment of MS. Currently there are 19 DMTs approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) (Chen et al., 2023). In 1993, interferon beta-1b (IFNβ−1b) became the first DMT approved by the FDA (FDA, 1993). The aim of DMTs is to reduce early clinical disease activity that eventually leads to long-term disability (Robertson and Moreo, 2016). To date, the effectiveness of DMTs in randomized controlled trials (RCTs) has been evaluated primarily on clinical outcomes such annualized relapse rate, neurological disability, or MRI measures of disease burden (e.g., brain lesions) (Landmeyer et al., 2020), with relatively little emphasis on quality of life measures as reported by PwMS. A recent systematic review and meta-analysis determined that the assessment of cognition as an outcome is largely underrepresented in RCTs of DMTs and the available evidence does not support the treatment escalation to improve cognition (Landmeyer et al., 2020).

Furthermore, there is limited evidence on the benefits on fatigue of treating PwMS with DMTs. Determining the impact on fatigue has the potential to inform clinicians and PwMS in the selection of MS treatment. Therefore, we conducted a systematic review to 1) understand whether fatigue is included as an outcome in MS trials of DMTs; 2) determine the effects on fatigue of treating MS with DMTs and 3) assess the quality of MS trials including fatigue as an outcome. The secondary aim of the review is to understand what ethnicities are recruited and whether mental health is assessed in MS trials of DMTs that include fatigue as an outcome.

2. Methods

2.1. Search strategy and eligibility criteria

The systematic review protocol was registered in PROSPERO (CRD42022383321). Initially, a search strategy was developed to identify available trials regarding the impact of DMTs on fatigue in patients treated for MS. The following keywords: 'multiple sclerosis", "fatigue", "disease-modif* therap*" and their synonyms in combination with the Cochrane search filters for identifying trials (Lefebvre et al., 2022), were used to search the Medical Literature Analysis and Retrieval System Online MEDLINE (Ovid) and the Excerpta Medica Database (EMBASE) databases (from 1993 to January 2023). The search strategy is included in Appendix A.

Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance (Moher et al., 2009), two independent investigators systematically screened for MS RCTs that assessed the effectiveness or efficacy of DMTs. For those trials that fulfilled the inclusion criteria assessing fatigue, we evaluated the impact of DMT treatment on mental health, whether the PRO data informed labeling claims and aspects of equity, diversity, and inclusivity (EDI). To determine the impact of PRO data on labeling claims, the database PROLABELS (Mapi, 2023b)' was searched (March 2023) with the different DMTs.

Clinical trials were deemed eligible if they defined fatigue as a primary, secondary or exploratory outcome. Trial protocols, follow-up studies and re-randomized trials were excluded. In addition, trials including clinician-reported fatigue as adverse event only without any PRO data and RCTs targeting children or adolescents (<18 years) were excluded. There were no language restrictions.

To identify additional trials that may have been missed due to poor database indexing, ClinicalTrials.gov was searched. The keywords "multiple sclerosis" AND "fatigue" were searched from 1996 to Feb 9th, 2023. The search strategy was limited to phase III and IV clinical trials (interventional studies). Trials were excluded if they did not have results or included fatigue as an adverse event only.

2.2. Data screening

Database records were downloaded into Excel and imported into the online review software COVIDENCE. Two independent investigators (SCR and OLA) conducted all the screening. The records were screened by title and abstract followed by full-text screening. The full-text screening stage identified the trial publications included for data extraction. Discrepancies were resolved through discussion, with the involvement of a third reviewer (MJC) when necessary.

2.3. Data extraction and quality analysis

Data extraction occurred after the final selection of included trials from databases and ClinicalTrials.gov. SCR and OLA independently extracted the following data from the trial publications: year of publication, study design, country of recruitment, MS type, participants demographics, time since first symptom or time from MS diagnosis or disease duration, baseline expanded disability status scale (EDSS), DMT being evaluated (intervention), comparator and primary outcome. Additional data extracted included whether fatigue was a primary or secondary outcome, details of the PROM used to assess fatigue. (Appendix B).

Completeness of the PRO reporting of included trials was assessed using the 2013 CONSORT (Consolidated Standards of Reporting Trials)-PRO Extension for PRO-specific data (Calvert et al., 2013). The CONSORT-PRO Statement aims to improve the transparent reporting of RCTs in which PROs are primary or secondary outcomes. For each publication, individual items were given a 1-point score if elements were present, resulting in a cumulative score (Kyte et al., 2019).

In addition, two authors independently assessed (SCR and OLA) the risk of bias (RoB) of the trials with the RoB 2 tool (Higgins et al., 2011). The tool is designed to score bias from the randomization, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result. Within each domain, a number of questions (signaling questions) seek specific information about the included trial characteristics that could potentially introduce bias (Higgins et al., 2011). The risk of bias arising from each domain is generated by an algorithm, based on the signaling questions answers (yes, probably yes, no, probably not and no information). Each domain was classified according to the risk of bias judgement as 'low', 'high' or 'some concern'. Furthermore, the Drugs@FDA: FDA-Approved Drugs (FDA, 2023) was searched to identify the clinical review(s) of each FDA-approved DMT included to support the PRO trials methodology appraisal.

3. Results

3.1. Fatigue as an outcome in MS trials of DMTs

Of the 264 records identified from databases and 165 records from ClinicalTrials.gov, we identified 130 RCTs of DMTs of which 7 (5%) assessed fatigue as an outcome. Five trials were identified through database searching and two additional trials were included following the search of ClinicalTrials.gov (Fig. 1). Of the seven trials, two (Confavreux et al., 2014; O'Connor et al., 2011) assessed fatigue as an outcome and included fatigue as an adverse event as reported by the clinician.

3.2. Studies characteristics

The characteristics of the 7 included trials are summarized in Table 1. Six trials were classified as phase 3 and one as phase 4. The number of participants included ranged from $n = 334$ to $n = 1169$ (mean $n = 869$). Five trials focused on relapsing-remitting MS, one on secondary progressive MS and one on clinically isolated syndrome. Four different approved DMTs were included, four trials assessed teriflunomide 7 mg and 14 mg, one IFNβ−1a, one trial ponesimod 20 mg and one glatiramer acetate (GA) 40 mg/mL. A total of 5629 participants were included, of which 3863 (69%) were female. The mean baseline EDSS of the participants ranged from 1.5 to 5.2.

3.3. Impact on fatigue

The assessment of fatigue was measured with three different PROMs. Of the seven trials included, four (57%) assessed fatigue with the Fatigue Impact Scale (FIS) (Fisk et al., 1994). Two (28%) trials with the Modified Fatigue Impact Scale (MFIS) subscale, a component of the MS Quality of Life Inventory (MSQLI) (Fischer et al., 1999) and one (14%) trial with the Fatigue Symptoms and Impacts Questionnaires – Relapsing-Remitting MS (FSIQ-RRMS) (Hudgens et al., 2019; Ritvo et al., 1997).

In the OPTIMUM trial (Kappos et al., 2021), PwMS receiving ponesimod 20 mg showed a stable fatigue score from baseline to week 108, measured with the FSIQ-RMS. By contrast PwMS receiving teriflunomide had an increase in fatigue score over the same period. The difference between the two treatments was significant in favor of ponesimod.

The TENERE trial (Vermersch et al., 2014), reported an increase from baseline to week 48 in FIS score for IFNβ−1a, compared to teriflunomide 7 mg and teriflunomide 14 mg. This indicates the largest increase in fatigue for patients receiving IFNβ−1a. The difference in LSM was only significant for teriflunomide 7 mg vs IFNβ−1a. The fatigue increase in the teriflunomide 7 mg group was smaller than that of the IFNβ−1a group but was not significantly different. The fatigue PRO data from both trials did not inform labeling claims, according to the information available in the PROLABELS database. Further details on the impact of DMTs on fatigue are presented in Table 2.

3.4. Reporting of PRO trial results

The 7 trials included measured fatigue as a secondary outcome. Publications included a mean of 0.26 (SD = 0.13) (range = 0.14 to 0.64) of the CONSORT-PRO Extension checklist items. Commonly omitted CONSORT-PRO items included: 1) rationale of PRO assessment, 2) PRO hypothesis and relevant domains, 3) plans to minimize avoidable missing data, 4) PRO estimated effect size and 5) PRO-specific limitations and generalizability (Fig. 2). Trials included an adjusted mean for denominator variability of 36% of CONSORT-PRO items. Items including PRO-specific criteria, sample size determination and results of any other PRO analyses performed were excluded from this analysis since they were not relevant to any of the trials included. The trials did not report minimum clinically important difference for fatigue.

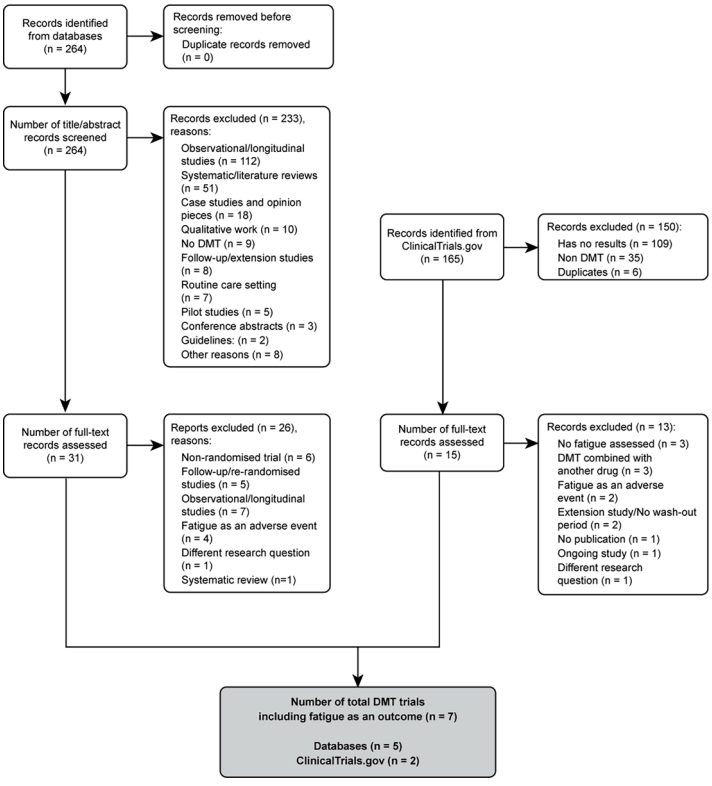

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.
Abbreviations: DMT, Disease-modifying therapy

Table 1
Trials characteristics and demographics.

Trial	ClinicalTrials.gov identifier	Trial phase	Sample size n	Type of MS	Intervention	Comparator	Female *n*= (%)	Time since first diagnosis years, (SD)	Baseline EDSS mean, (SD)
OPTIMUM (Kappos et al., 2021)	NCT02425644	III	1133	Relapsing-remitting	Ponesimod 20mg	Teriflunomide 14mg	363 (64) 372 (65)	7.63 (6.78) 7.65 (6.78)	2.57 (1.17) 2.56 (1.23)
TENERE (Vermersch et al., 2014)	NCT00883337	III	324	Relapsing-remitting	Teriflunomide 7 mg and 14mg	IFNβ−1a	71 (68.3) 70 (64.2) 78 (70.3)	7.7 (7.6) 7.0 (6.9) 6.6 (7.6)	2.0 (1.2) 2.0 (1.2) 2.3 (1.4)
CONFIDENCE (Cutter et al., 2019)	NCT02499900	IV	861	Relapsing-remitting	Glatiramer acetate 40 mg/mL	Glatiramer acetate 20 mg/mL	288 (66.8) 307 (71.4)	5.7 (6.5) 5.6 (6.3)	2.2 (1.3) 2.1 (1.3)
TEMSO (O'Connor et al., 2011)	NCT00134563	III	1088	Relapsing-remitting	Teriflunomide 7 mg and 14mg	Placebo	255 (69.7) 255 (71.0) 275 (75.8)	8.6 (7.1) 8.8 (6.8) 8.7 (6.7)	2.68 (1.34) 2.67 (1.24) 2.68 (1.34)
TOWER (Confavreux et al., 2014)	NCT00751881	III	1169	Relapsing-remitting	Teriflunomide 7 mg and 14mg	Placebo	300 (74) 258 (69) 273 (70)	8·18 (6·75) 8·18 (6·73) 7·64 (6·70)	2.71 (1·39) 2·71 (1·35) 2·69 (1·36)
IMPACT (Cohen et al., 2002)	–	III	436	Secondary progressive	IFNβ−1a	Placebo	138 (64) 141 (64)	**Disease duration*** 16.2 (9.0) 16.7 (9.0)	5.2 (1.1) 5.2 (1.1)
TOPIC (Miller et al., 2014)	NCT00622700	III	618	Clinically isolated syndrome	Teriflunomide 7 mg and 14mg	Placebo	130 (63) 154 (71) 135 (69)	**Time since neurological event (months, (SD)):** 1·89 (0·56) 1·80 (0·56) 1·88 (0·52)	1.50 (1·02) 1.80 (0·97) 1.71 (1·00)

ESDD, Equivalent Single Degree of Freedom; IFNβ−1a, interferon β−1a; MS, Multiple Sclerosis; SD, standard deviation.
* Time since first diagnosis and disease duration refer to the duration that has passed since an individual has been diagnosed with MS.

3.5. Risk of bias analysis

The five elements of the RoB 2 tool were assessed according to the Cochrane Handbook for Systematic Reviews of Interventions. Fig. 3 provides a summary of the RoB analysis, specifically for fatigue as an outcome. Of the seven trials included, three (42%) presented an overall score of 'some concern' (Cohen et al., 2002; Cutter et al., 2019; O'Connor et al., 2011), whereas four trials (57%) presented 'high concern' (Confavreux et al., 2014; Kappos et al., 2021; Miller et al., 2014; Vermersch et al., 2014). Bias due to missing outcome data was scored as 'high' among four trials whereas three trials were scored as 'no information' as there was not enough information within the trial publication to assess the bias. In addition, four trials presented 'some concerns' in the domain 'bias in selection of the reported results.

To support the analysis of the fatigue element, the clinical review(s) of each FDA-approved DMT was appraised. However, the ponesimod clinical review(s) was the only appraisal identified (Table 3).

3.6. Mental health

Of the seven trials included, three assessed the impact of DMT treatment on mental health alongside fatigue (Cohen et al., 2002; Confavreux et al., 2014; Cutter et al., 2019). The Mental Health Inventory (Veit and Ware, 1983), short form 36 health survey (SF-36) (Brazier et al., 1992) and the Beck Depression Inventory (Beck et al., 1988), were used to assess mental health (Table 4).

3.7. Equity, diversity, and inclusion analysis

Of the seven studies included, four recruited more than 90% of individuals from White or Caucasian ethnicity despite recruiting participants from different countries (Kappos et al., 2021; Miller et al., 2014; O'Connor et al., 2011; Vermersch et al., 2014). One trial recruited approximately 20% participants from Asian, Black, and other ethnicities (Confavreux et al., 2014). An additional trial recruited over 15% of participants from a different ethnicity, which was not specified (Cutter et al., 2019). Participants recruited among the included trials was predominantly women. The mean age of the participants included was 38 years old (range 32 to 48). Participants socioeconomic status was not reported by any of the trials included (Table 5).

4. Discussion

This review evaluated whether fatigue is assessed in MS RCTs of DMTs and the effect of MS DMT treatment on fatigue. The assessment of fatigue as an outcome is underrepresented in trials of DMTs even though fatigue is one of the most common and detrimental symptoms of MS, with only 5% of RCTs of DMTs assessing this outcome using PROMs. As fatigue has a profound effect on the quality of life of individuals with MS further consideration should be given to inclusion of fatigue as a secondary outcome in future MS trials.

Symptom management is a crucial element of the care of PwMS, which can the potential to improve patients' quality of life and general wellbeing (Ziemssen, 2011). A previous randomized clinical trial has shown that remote symptom monitoring through PROs can lead to reduced emergency departments attendances, lower hospitalization rates, prompt earlier interventions and improve patients' quality of life (Basch et al., 2022). Thus, the inclusion of PROs in remote symptom monitoring among PwMS has the potential to tailor care among those in greatest need.

Currently, there is limited evidence on the effect on fatigue of treating MS with DMTs. Of the 7 trials included, only 2 (28%) trials presented statistically significant results (Kappos et al., 2021; Vermersch et al., 2014). Ponesimod 20 mg showed a significantly better stabilization of fatigue than teriflunomide 14 mg in the OPTIMUM trial, consistent with reductions in brain volume loss and annualized relapse rate and improved magnetic resonance imaging activity. In contrast, in the TENERE trial, teriflunomide 7 mg showed significantly better fatigue

Table 2
Impact of DMTs on fatigue.

Trial	PROM	Intervention	Comparator	Impact on fatigue	Statical significant changes in PRO scores
OPTIMUM (Kappos et al., 2021)	FSIQ-RMS[1]	Ponesimod 20mg	Teriflunomide 14mg	The LSM score change: ponesimod 20 mg −0.01 (absolute score change from 32.8 to 36.36) vs teriflunomide 14mg: 3.56 from baseline to week 108 (mean difference, −3.57 [95% CLs, −5.83 to −1.32]; *p*-value: 0.002	Yes
TENERE (Vermersch et al., 2014)	FIS[2]	Teriflunomide 7 mg and 14mg	IFNβ−1a	LSM (SE) score change from baseline to week 48, IFNβ−1a: 9.10 (3.21) (absolute score change from 34.2 to 43.3); teriflunomide 7mg: 0.97 (2.96) (absolute score change from 39.2 to 40.47); teriflunomide 14mg: 4.10 (3.03). LSM difference from IFNβ−1a, teriflunomide 7 mg −8.13 (3.67) and teriflunomide 14 mg −5.00(3.71). *p*-value vs IFNβ−1a: teriflunomide 7 mg 0.03; teriflunomide 14 mg 0.18	Yes, (only for teriflunomide 7 mg)
CONFIDENCE (Cutter et al., 2019)	MSQL – MFIS subscale[3]	Glatiramer acetate 40 mg/mL	Glatiramer acetate 20 mg/mL	LSM scores change from baseline to month 6 in the GA40 group: –3.6 vs GA20 group: –2.8. Difference between GA40 and GA20, LSM difference −0.8, [95% CI, −2.1, 0.4], *p*-value: 0.208	No
TEMSO (O'Connor et al., 2011)	FIS[2]	Teriflunomide 7 mg and 14mg	Placebo	Changes in FIS scores from baseline: placebo 4.3 ± 1.7; teriflunomide 7 mg 2.3 ± 1.6; teriflunomide 14 mg 3.8 ± 1.7. *p-value*: 7 mg 0.39; 14 mg 0.83	No
TOWER (Confavreux et al., 2014)	FIS[2]	Teriflunomide 7 mg and 14mg	Placebo	There were no statistically significant differences from baseline to week 48 for teriflunomide 7 mg and 14 mg. LSM (SE): teriflunomide 7mg: 2.51 *p-value*: 0.3090 and teriflunomide 14mg: 1.92, *p-value*: 0.2083. However, changes in FIS score from baseline to last visit were statistically significant for teriflunomide 14 mg. LSM (SE): teriflunomide 7mg: 2·51, *p*-value: 0.3686 and teriflunomide 14mg: 2.04, *p*-value 0.0429	No
IMPACT (Cohen et al., 2002)	MSQLI – MFIS subscale[3]	IFNβ−1a	Placebo	The IFNβ−1a group improved from baseline to month 24 on 10 of 11 subscales (all except the Bladder Control Scale). In contrast, the placebo group worsened from baseline to month 24 on 10 of 11 subscales, the MFIS being the only subscale showing improvement – **no data provided**.	No
TOPIC (Miller et al., 2014)	FIS[2]	Teriflunomide 7 mg and 14mg	Placebo	The change in FIS did not differ significantly between the treatment groups at week 108. Mean change from baseline at week 108 (SD) teriflunomide 14 mg –4·487 (32·519); teriflunomide 7 mg –2·730 (30·410); Placebo –3·535 (29·298). LSM difference vs placebo (SE): teriflunomide 14mg: 0·710 (3·731), teriflunomide 7mg: 0·012 (3·842); *p*-value vs placebo: Teriflunomide 14 mg 0·8492, teriflunomide 7 mg 0·9974	No

[1] Fatigue Symptoms and Impacts Questionnaires – Relapsing-Remitting MS (FSIQ-RRMS): 20-item scale, scores range between 0 and 100. Higher scores indicate higher fatigue.
[2] Fatigue Impact Scale: 40-item scale, scores range between 0 and 160. Higher scores indicate worsen fatigue.
[3] MS Quality of Life Inventory: consists of 10 individual scales (fatigue is measured with the MFIS) with a total of 138 items. Each of the individual scales generates a separate score. There is no global composite combining all the scales into a single score. MFIS: 21-item scale, scores range between 0 and 84. Higher scores indicate increased fatigue.

CI, Confidence interval; FSIQ-RMS, Fatigue Symptom and Impact Questionnaire–Relapsing Multiple Sclerosis; FIS, Fatigue Impact Scale; GA, glatiramer acetate; IFNβ−1a, interferon β−1a; MSQL – MFIS, Multiple Sclerosis Quality of Life- Modified Fatigue Impact Scale; PROM, patient reported outcome measure; PRO, patient reported outcome; LSM, least-squares mean; p value, probability value; SE, standard error.

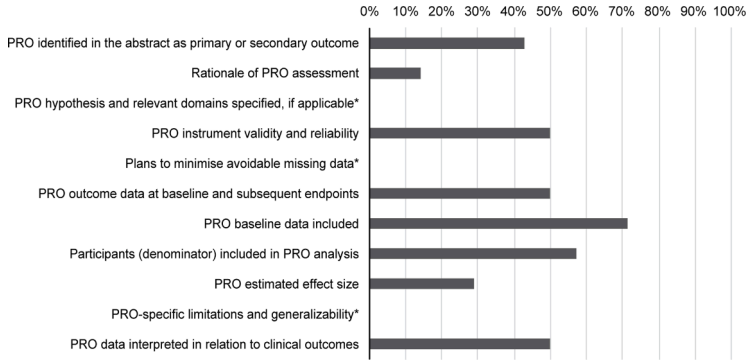

Fig. 2. Percentage of trials including each CONSORT PRO checklist item
*These items are not PRO specific extensions and are included as per the CONSORT Statement
Abbreviations: PRO, Patient-Reported Outcomes.

results than IFNβ−1a but this was not the case for teriflunomide 14 mg (the approved dose). There was also no difference between either dose of teriflunomide and IFNβ−1a with respect to time to failure and annualized relapse rate.

It is important to highlight that both trials presented concerning levels of PRO missing data, thus, careful consideration should be given when interpreting the PRO results. Furthermore, the interpretation of the PRO data was limited due to the lack of discussion around the

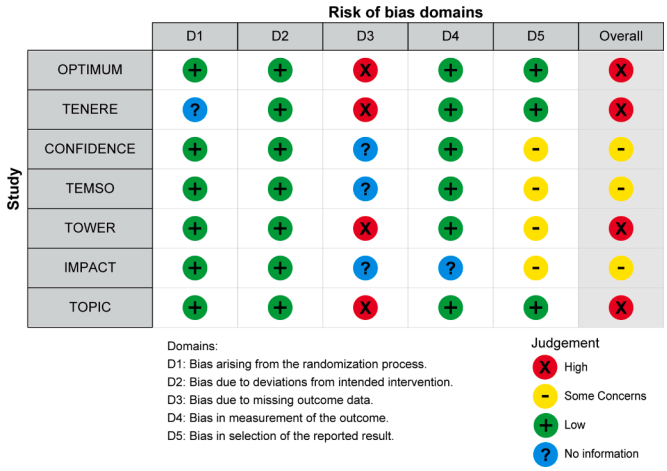

Fig. 3. Risk of bias (RoB) summary in the context of fatigue.

Table 3
FDA clinical review(s) appraisal of the trials' fatigue element, where review is available.

Trial	ClinicalTrials.gov identifier	FDA clinical review(s)
OPTIMUM (Kappos et al., 2021)	NCT02425644	"This review notes that the confidence intervals for the change from baseline in the FSIQ-RMS-S appear to overlap at every time point except week 108 and that a large number of subjects appear to be missing data, even at baseline. Fatigue, as measured by the FSIQ-RMS-S stabilized (but did not improve) in individuals randomized to ponesimod." (CDER, 2017)
TENERE (Vermersch et al., 2014)	NCT00883337	No clinical review available
CONFIDENCE (Cutter et al., 2019)	NCT02499900	No clinical review available
TEMSO (O'Connor et al., 2011)	NCT00134563	No clinical review available
TOWER (Confavreux et al., 2014)	NCT00751881	No clinical review available
IMPACT (Cohen et al., 2002)	–	No clinical review available
TOPIC (Miller et al., 2014)	NCT00622700	No clinical review available

CDER, Center for Drug Evaluation and Research; FDA, Food and Drug Administration; FSIQ-RMS, Fatigue Symptom and Impact Questionnaire–Relapsing Multiple Sclerosis.

clinically meaningfulness of the PRO data. Currently, there is limited research to support the clinical relevance interpretation of the FSQI-RMS and FIS scores (i.e., significant change of, reduction and increase in scores), limiting the objective interpretation of the PROM scores (Larson, 2013). Furthermore, it was not possible to compare the changes in fatigue as both trials used different PROMs. Standardizing the use of PROMs to measure fatigue would help to facilitate comparison of PRO trial data.

The reporting of PRO data is suboptimal among the trials included, indicating low adherence to CONSORT-PRO guidelines (Calvert et al., 2013). The 7 (100%) trials included failed to report a PRO hypothesis, plans to minimize avoidable PRO missing data and discuss PRO-specific limitations and generalizability. Pre-specification of PRO objectives and hypotheses at study design would promote identification of key PRO domains and timepoints since PRO data are multidimensional, resulting in reduced multiple statistical testing and selective reporting (Calvert et al., 2021). Missing trial data is common; however, it is essential the reasons for missing data and statistical methods to deal with it are reported. Failure to report these can threaten the interpretation and validity of the PRO findings (Moher et al., 2010).The discussion of PRO-specific limitations and generalizability of PRO results at patient- and center-level is essential to interpret PRO findings and their relation to clinical outcomes (Calvert et al., 2013). In addition, high quality PRO methods and availability of PRO data are needed to inform labeling claims (Patrick et al., 2007).

Table 4
Impact of DMTs on mental health.

Trial	PROM	Impact on mental health
CONFIDENCE	Mental Health Inventory	There was no statistically significant difference between the groups in MHI total score. GA40 group (LSM=3.8) and GA20 group (LSM=3.1). LSM difference 0.7, 95% CI (−1.5, 1.8) *p-value* 0.8.
TOWER	SF-36	Based on ANCOVA change from baseline to week 108, teriflunomide 14 mg compared to placebo showed statistically significant change (LSM = −1.70) *p-value* 0.02. Baseline SF-36 mental health data was not reported. There was no statistically significant difference between teriflunomide 7 mg (LSM –2·79) *p-value* 0.12, and placebo (−1.09)
IMPACT	Beck Depression scale	No PRO data reported

ANCOVA, analysis of covariance; GA, glatiramer acetate; LSM, least-squares mean; MHI, Mental Health Inventory; p value, probability value; PRO, patient related outcome; SF-36, Short Form 36-Item Health Survey.

The RoB analysis showed that 'bias due to missing outcome data' was predominant among the trials included. A systematic review of meta-epidemiological studies concluded that missing data is linked to over-estimation of effect estimates among some studies (Page et al., 2016). In addition, the RoB analysis presented some concerns in the domain 'bias in selection of the reported results'. Selective reporting can lead to bias if result selection is based on the direction, magnitude or statistical significance of the effect estimate (Higgins et al., 2011). It is important to mention that the RoB tool does not assess bias due to selective reporting. Assessment of selective reporting is essential to ensure that trial results are not excluded based on their direction, magnitude or statistical significance. An additional tool to assess the RoB due to missing data is the Risk Of Bias due to Missing Evidence in a synthesis (RoB-ME) tool, currently being piloted by the CBMG (CochraneMethods, 2023).

The use of translated and culturally validated PROMs is widely omitted by the studies. Although the included trials recruited participants from different countries, only one trial (Cohen et al., 2002) specified the administration of the PROM selected, MSQLI (Braley and Chervin, 2010), to English-speaking participants only. However, there are not translated versions available for this measure according to the ePROVIDE database, which provides a summary of measures, evidence of validity and their available translations (Mapi, 2023a). An additional trial stated in its protocol that the FSIQ-MRS will be completed only in countries for which validated translations are available; however, the validated translated versions are not available according to ePROVIDE. Furthermore, the four trials that administrated the FIS (Fisk et al., 1994) did not specify the use of a culturally validated or translated version, despite the PROM being available in different languages. Failure to use translated and culturally validated PROMs may lead to sample attrition and missing data due to misinterpretation of items or culturally irrelevant items, while threatening the validity of the research and generalizability of PRO data (Slade et al., 2021; Wild et al., 2005).

The number of RCTs assessing fatigue and mental health were limited (3%). The low rate is accompanied by suboptimal PRO data, hindering the interpretation of PRO results. The included trials recruited a larger number of women than men, which was expected as MS is more

Table 5
EDI characteristics of MS trials assessing fatigue.

Trial	Ethnicity *n* = (%)	Female *n* = (%)	Age - Years mean (SD)	Recruitment Countries *n*= (%)
OPTIMUM (Kappos et al., 2021)	**White race** Ponesimod 20mg: 551 (97.2) Teriflunomide 14mg: 553 (97.7)	363 (64) 372 (65)	36.1 (8.74) 36.8 (8.74)	North America, Europe, Mexico, Israel, and Turkey – no data
TENERE (Vermersch et al., 2014)	**Caucasian** IFNβ−1a: 104 (100) Teriflunomide 7mg: 109 (100) Teriflunomide 14mg: 111 (100)	71 (68.3) 70 (64.2) 78 (70.3)	37.0 (10.6) 35.2 (9.2) 36.8 (10.3)	Americas: 7 (6.7) 8 (7.3) 6 (5.4) Eastern Europe: 35 (33.7) 39 (35.8) 41 (36.9) Western Europe and Africa: 62 (59.6) 62 (56.9) 64 (57.7)
CONFIDENCE (Cutter et al., 2019)	**Caucasian** GA40: 359 (83.3) GA20: 363 (84.4) **Other ethnicity** GA40: 72 (16.7) GA20: 67 (15.6)	288 (66.8) 307 (71.4)	41.0 (11.2) 40.1 (10.7)	Russia, Poland, Italy, France, Croatia, USA (including Puerto Rico), Mexico, Spain, Austria, Turkey, Belgium, Argentina, Germany, and Finland – no data
TEMSO (O'Connor et al., 2011)	**White race** Teriflunomide 7mg: 355 (97.3) Teriflunomide 14mg: 347 (96.9) Placebo: 356 (98.3)	255 (69.7) 255 (71.0) 275 (75.8)	37.4 ± 9.0 37.8 ± 8.2. 38.4 ± 9.0	Czech Republic, Estonia, Poland, Russia, Ukraine, Austria, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Portugal, Sweden, Switzerland, Turkey, United Kingdom, Canada, Chile, and USA – no data
TOWER (Confavreux et al., 2014)	**White** Teriflunomide 7mg: 329 (81) Teriflunomide 14mg: 313 (84) Placebo: 318 (82), 329 **Asian** 60 (15), 49 (13), 60 (15) **Black** 8 (2), 7 (2), 7 (2) **Other**: 11 (3), 3 (1), 4 (1)	300 (74) 258 (69) 273 (70)	37.4 (9.4) 38.2 (9.4) 38.1 (9.1)	Western Europe and Tunisia: 127 (31%), 120 (32%), 121 (31%) Eastern Europe: 124 (30%), 116 (31%), 117 (30%) America: 92 (23%), 81 (22%), 84 (22%) Asia and Australia: 65 (16%), 55 (15%), 67 (17%)
IMPACT (Cohen et al., 2002)	Placebo: no data IFNβ−1a: no data	138 (64) 141 (64)	47.9 ± 7.7 47.2 ± 8.2	North America, Europe, and Israel – no data
TOPIC (Miller et al., 2014)	**White race** Teriflunomide 7mg: 198 (97) Teriflunomide 14mg: 208 (96) Placebo: 188 (95)	130 (63) 154 (71) 135 (69)	32.8 (8.1) 31.6 (9.0) 32.0 (8.4)	Eastern Europe: 96 (47%), 101 (47%), 94 (48%) Western Europe: 74 (36%), 74 (34%), 76 (39%) Americas and Australia: 35 (17%), 41 (19%), 27 (14%)

IFNβ−1a, interferon β−1a; GA, glatiramer acetate.

prevalent among women. In addition, the mean age of the participants included was 38 years old (mean range 32 to 48), reflecting the usual disease onset age of 20 to 40 years old. Socioeconomic status information was not included by the trials; however, collection of this data is essential. A recent observational study demonstrated that socioeconomic deprived people with relapsing-remitting MS presented higher mortality rates from symptom onset (Wilson et al., 2023). While in primary-progressive MS there was no clear association between socioeconomic status and mortality. Inequalities in access to treatment might be associated with higher mortality since early access to treatment has the potential to delay disability onset. In addition, the socioeconomic and cultural composition of the included studies could have influenced the reporting of fatigue levels. Factors such as gender, level of education, employment and economic status, access to MS support facilities, among other factors, may influence the different levels of disability reported (Reilly et al., 2017)

Although the prevalence of MS is higher among White people (Albor et al., 2017), the inclusion of minority groups is underrepresented in MS trials of DMTs. A 2013 UK study evaluated the prevalence of MS in east London and determined that MS prevalence is considerably lower among Black and South Asian individuals, compared to White population (Albor et al., 2017). However, a 2020 cohort study identified that the odds of MS among young Black British is higher than in White British (Dobson et al., 2020). An additional US retrospective cohort study of medical records demonstrated that the prevalence of MS in African Americans is 47% higher than in white American people (Langer-Gould et al., 2013). In addition, MS in African American people follow a more severe course, leading to earlier disability compared to white Americans (Avasarala, 2014). Evaluation of the safety and efficacy of DMTs in minority groups is essential to reduce disparities and promote equity The FDA guidance on 'Collection of Race and Ethnicity Data in Clinical Trials' outlines the expectations and recommendations for collecting and reporting race and ethnicity data in FDA medical submissions (FDA, 2016). Detailed reporting of ethnicity data is essential to understand the proportion of ethnic groups included from a particular country and accurate interpretation of safety and effectiveness of treatments in different ethnic groups. Several considerations for the assessment of fatigue as an outcome in DMT trials of MS are proposed in Box 1.

4.1. Limitations

A limitation of this systematic review was the potential exclusion of relevant studies. It was noticed that some studies failed to clearly report their study design. To ensure that we identified all the relevant studies, the two reviewers discussed articles with the research team when it was unclear whether an RCT was conducted. Furthermore, databases indexing errors could have led to the exclusion of relevant studies. However, we attempted to mitigate this by searching ClinicalTrials.gov.

5. Conclusion

In conclusion, the current available body of evidence is limited to determine the impact of treating fatigue in MS trials of DMTs. Notably, fatigue as a trial outcome is considerably underrepresented in RCTs assessing DMTs and the reporting of PRO trial data is suboptimal. Therefore, it is imperative that the MS researchers and trialists conduct RCTs that include fatigue as an outcome, especially among established DMTs, to support clinicians and PwMS considering the impact of the different DMTs on fatigue.

CRediT authorship contribution statement

SCR, MJC and **PK**: Conceptualization, Methodology. **OLA**: Validation, **SCR**: Data curation, Writing- Original draft preparation. **MJC, OLA, PK, DPM, AD, DH** and **CH**: Investigation, Formal analysis, Writing

Box 1
Considerations for the assessment of fatigue in DMT trials treating multiple sclerosis

- At the design stage carefully consider the inclusion of fatigue as a primary or secondary endpoint
- Carefully select PRO measures, considering measurement properties, interpretation guidelines and the measures ability to determine clinical meaningful changes.
- Consider the availability of translations and cultural validation of the PRO measure selected for the target population.
- Ensure inclusive and diverse enrollment of participants as recommended by the US Food and Drug Administration
- Inclusion of patient-focused drug development (PFDD) methodological strategies to collect meaningful patient data to better inform drug development and regulatory decision-making (FDA, 2018).
- Report studies transparently by adhering to international standards for patient-reported outcomes (CONSORT-PRO)

- Review & Editing. **MJC** and **PK**: Supervision.

PK and **MJC** contributed equally to the study.

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Supplementary materials

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References

Albor, C., du Sautoy, T., Kali Vanan, N., Turner, B.P., Boomla, K., Schmierer, K., 2017. Ethnicity and prevalence of multiple sclerosis in east London. Mult. Scler. J. 23 (1), 36–42.

Amezcua, L., McCauley, J.L., 2020. Race and ethnicity on MS presentation and disease course. Mult. Scler. 26 (5), 561–567.

Avasarala, J., 2014. Inadequacy of clinical trial designs and data to control for the confounding impact of race/ethnicity in response to treatment in multiple sclerosis. JAMA Neurol. 71 (8), 943–944.

Basch, E., Schrag, D., Henson, S., Jansen, J., Ginos, B., Stover, A.M., Carr, P., Spears, P.A., Jonsson, M., Deal, A.M., Bennett, A.V., Thanarajasingam, G., Rogak, L.J., Reeve, B. B., Snyder, C., Bruner, D., Cella, D., Kottschade, L.A., Perlmutter, J., Geoghegan, C., Samuel-Ryals, C.A., Given, B., Mazza, G.L., Miller, R., Strasser, J.F., Zylla, D.M., Weiss, A., Blinder, V.S., Dueck, A.C., 2022. Effect of electronic symptom monitoring on patient-reported outcomes among patients with metastatic cancer: a randomized clinical trial. JAMA 327 (24), 2413–2422.

Beck, A.T., Steer, R.A., Carbin, M.G., 1988. Psychometric properties of the beck depression inventory: twenty-five years of evaluation. Clin. Psychol. Rev. 8 (1), 77–100.

Black, N., 2013. Patient reported outcome measures could help transform healthcare. BMJ 346, f167.

Braley, T.J., Chervin, R.D., 2010. Fatigue in multiple sclerosis: mechanisms, evaluation, and treatment. Sleep 33 (8), 1061–1067.

Brazier, J.E., Harper, R., Jones, N.M., O'Cathain, A., Thomas, K.J., Usherwood, T., Westlake, L., 1992. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ 305 (6846), 160–164.

Calvert, M., Blazeby, J., Altman, D.G., et al., 2013. Reporting of patient-reported outcomes in randomized trials: the CONSORT-PRO Extension. JAMA 309 (8), 814–822.

Calvert, M., King, M., Mercieca-Bebber, R., Aiyegbusi, O., Kyte, D., Slade, A., Chan, A.W., Basch, E., Bell, J., Bennett, A., Bhatnagar, V., Blazeby, J., Bottomley, A., Brown, J., Brundage, M., Campbell, L., Cappelleri, J.C., Draper, H., Dueck, A.C., Ells, C., Frank, L., Golub, R.M., Griebsch, I., Haywood, K., Hunn, A., King-Kallimanis, B., Martin, L., Mitchell, S., Morel, T., Nelson, L., Norquist, J., O'Connor, D., Palmer, M., Patrick, D., Price, G., Regnault, A., Retzer, A., Revicki, D., Scott, J., Stephens, R., Turner, G., Valakas, A., Velikova, G., von Hildebrand, M., Walker, A., Wenzel, L., 2021. SPIRIT-PRO Extension explanation and elaboration: guidelines for inclusion of patient-reported outcomes in protocols of clinical trials. BMJ Open 11 (6), e045105.

CDER, 2017. NDA 213498 - Ponvory (ponesimod) Clinical Review(S).

Chen, C., Zhang, E., Zhu, C., Wei, R., Ma, L., Dong, X., Li, R., Sun, F., Zhou, Y., Cui, Y., Liu, Z., 2023. Comparative efficacy and safety of disease-modifying therapies in patients with relapsing multiple sclerosis: a systematic review and network meta-analysis. J. Am. Pharm. Assoc. (Wash. DC) 63 (1), 8–22.e23.

CochraneMethods, 2023. A Tool For Assessing Risk Of Bias due to Missing Evidence in a Synthesis (ROB-ME). https://methods.cochrane.org/bias/resources/rob-me. (Accessed 23/03/2023.

Cohen, J.A., Cutter, G.R., Fischer, J.S., Goodman, A.D., Heidenreich, F.R., Kooijmans, M. F., Sandrock, A.W., Rudick, R.A., Simon, J.H., Simonian, N.A., Tsao, E.C., Whitaker, J.N., 2002. Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. Neurology 59 (5), 679–687.

Compston, A., Coles, A., 2008. Multiple sclerosis. Lancet North Am. Ed. 372 (9648), 1502–1517.

Confavreux, C., O'Connor, P., Comi, G., Freedman, M.S., Miller, A.E., Olsson, T.P., Wolinsky, J.S., Bagulho, T., Delhay, J.L., Dukovic, D., Truffinet, P., Kappos, L., 2014. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a

randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 13 (3), 247–256.
Cutter, G., Veneziano, A., Grinspan, A., Al-Banna, M., Boyko, A., Zakharova, M., Maida, E., Pasic, M.B., Gandhi, S.K., Everts, R., Cordioli, C., Rossi, S., 2019. Higher satisfaction and adherence with glatiramer acetate 40mg/mL TIW vs 20mg/mL QD in RRMS. Mult Scler Relat Disord 33, 13–21.
Dobson, R., Jitlal, M., Marshall, C.R., Noyce, A.J., Robson, J., Cuzick, J., Giovannoni, G., 2020. Ethnic and socioeconomic associations with multiple sclerosis risk. Ann. Neurol. 87 (4), 599–608.
Elbers, R.G., Rietberg, M.B., van Wegen, E.E.H., Verhoef, J., Kramer, S.F., Terwee, C.B., Kwakkel, G., 2012. Self-report fatigue questionnaires in multiple sclerosis, Parkinson's disease and stroke: a systematic review of measurement properties. Qual. Life Res. 21 (6), 925–944.
FDA, 1993. Betaseron Interferon BETA-1B Subcutaneous. https://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/103471s0000TOC.cfm#:~:text=Approval%20Date%3A%2007%2F23%2F1993. (Accessed 13/03/2023.
FDA, 2016. Collection of Race and Ethnicity Data in Clinical Trials.
FDA, 2023. Drugs@FDA: FDA-Approved Drugs. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. (Accessed May 2023.
Fischer, J.S., LaRocca, N.G., Miller, D.M., Ritvo, P.G., Andrews, H., Paty, D., 1999. Recent developments in the assessment of quality of life in multiple sclerosis (MS). Mult. Scler. 5 (4), 251–259.
Fisk, J.D., Ritvo, P.G., Ross, L., Haase, D.A., Thomas, M.J., Schlech, W.F., 1994. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. Clin. Infect. Dis. 18, S79–S83.
Higgins, J.P.T., Altman, D.G., Gøtzsche, P.C., Jüni, P., Moher, D., Oxman, A.D., Savović, J., Schulz, K.F., Weeks, L., Sterne, J.A.C., 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343, d5928.
Hudgens, S., Schüler, R., Stokes, J., Eremenco, S., Hunsche, E., Leist, T.P., 2019. Development and validation of the FSIQ-RMS: a new patient-reported questionnaire to assess symptoms and impacts of fatigue in relapsing multiple sclerosis. Value Health 22 (4), 453–466.
Kappos, L., Fox, R.J., Burcklen, M., Freedman, M.S., Havrdova, E.K., Hennessy, B., Hohlfeld, R., Lublin, F., Montalban, X., Pozzilli, C., Scherz, T., D'Ambrosio, D., Linscheid, P., Vaclavkova, A., Pirozek-Lawniczek, M., Kracker, H., Sprenger, T., 2021. Ponesimod compared with teriflunomide in patients with relapsing multiple sclerosis in the active-comparator phase 3 OPTIMUM study: a randomized clinical trial. JAMA Neurol. 78 (5), 558–567.
Kyte, D., Retzer, A., Ahmed, K., Keeley, T., Armes, J., Brown, J.M., Calman, L., Gavin, A., Glaser, A.W., Greenfield, D.M., Lanceley, A., Taylor, R.M., Velikova, G., Brundage, M., Efficace, F., Mercieca-Bebber, R., King, M.T., Turner, G., Calvert, M., 2019. Systematic evaluation of patient-reported outcome protocol content and reporting in cancer trials. J. Natl. Cancer Inst.
Landmeyer, N.C., Bürkner, P.C., Wiendl, H., Ruck, T., Hartung, H.P., Holling, H., Meuth, S.G., Johnen, A., 2020. Disease-modifying treatments and cognition in relapsing-remitting multiple sclerosis: a meta-analysis. Neurology 94 (22), e2373–e2383.
Langer-Gould, A., Brara, S.M., Beaber, B.E., Zhang, J.L., 2013. Incidence of multiple sclerosis in multiple racial and ethnic groups. Neurology 80 (19), 1734–1739.
Larson, R.D., 2013. Psychometric properties of the modified fatigue impact scale. Int. J. MS Care 15 (1), 15–20.
Lefebvre, C., G, J., Briscoe, S., Featherstone, R., Littlewood, A., Marshall, C., Metzendorf, M.I., Noel-Storr, A., Paynter, R., Rader, T., Thomas, J., Wieland, L.S., 2022. Technical supplement to chapter 4: searching for and selecting studies. Cochrane (Ed.). In: Higgins, JPT, Thomas, J, Chandler, J, Cumpston, MS, Li, T, Page, MJ, Welch, VA (Eds.), Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022).
Mapi, 2023a. ePROVIDE. https://eprovide.mapi-trust.org/(Accessed January 2023.
Mapi, 2023b. PROLABELS. https://eprovide.mapi-trust.org/about/about-prolabels. (Accessed May 2023.
Miller, A.E., Wolinsky, J.S., Kappos, L., Comi, G., Freedman, M.S., Olsson, T.P., Bauer, D., Benamor, M., Truffinet, P., O'Connor, P.W., 2014. Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 13 (10), 977–986.
Moher, D., Hopewell, S., Schulz, K.F., Montori, V., Gøtzsche, P.C., Devereaux, P.J., Elbourne, D., Egger, M., Altman, D.G., 2010. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ 340, c869.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., The, P.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6 (7), e1000097.
MSSociety, 2020. MS in the UK. https://www.mssociety.org.uk/sites/default/files/2020-08/MS-in-the-UK_2020.pdf. (Accessed 24/03/2023.
O'Connor, P., Wolinsky, J.S., Confavreux, C., Comi, G., Kappos, L., Olsson, T.P., Benzerdjeb, H., Truffinet, P., Wang, L., Miller, A., Freedman, M.S., Group, T.T., 2011. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N. Engl. J. Med. 365 (14), 1293–1303.
Page, M.J., Higgins, J.P., Clayton, G., Sterne, J.A., Hróbjartsson, A., Savović, J., 2016. Empirical evidence of study design biases in randomized trials: systematic review of meta-epidemiological studies. PLoS One 11 (7), e0159267.
Patrick, D.L., Burke, L.B., Powers, J.H., Scott, J.A., Rock, E.P., Dawisha, S., O'Neill, R., Kennedy, D.L., 2007. Patient-reported outcomes to support medical product labeling claims: FDA perspective. Value Health 10, S125–S137.
Reilly, G.D., Mahkawnghta, A.S., Jelinek, P.L., De Livera, A.M., Weiland, T.J., Brown, C. R., Taylor, K.L., Neate, S.L., Jelinek, G.A., Marck, C.H., 2017. International differences in multiple sclerosis health outcomes and associated factors in a cross-sectional survey. Front. Neurol. 8.
Ritvo, P., Fisher, J., Miller, D., Andrews, H., Paty, D., LaRocca, N., 1997. The consortium of multiple sclerosis centers health services research subcommittee. MSQLI Multiple Sclerosis Quality of Life Inventory: A User's Manual. National Multiple Sclerosis Society.
Robertson, D., Moreo, N., 2016. Disease-modifying therapies in multiple sclerosis: overview and treatment considerations. Fed. Pract. 33 (6), 28–34.
Rooney, S., Wood, L., Moffat, F., Paul, L., 2019. Prevalence of fatigue and its association with clinical features in progressive and non-progressive forms of Multiple Sclerosis. Mult. Scler. Relat. Disord. 28, 276–282.
Slade, A.L., Retzer, A., Ahmed, K., Kyte, D., Keeley, T., Armes, J., Brown, J.M., Calman, L., Gavin, A., Glaser, A.W., Greenfield, D.M., Lanceley, A., Taylor, R.M., Velikova, G., Turner, G., Calvert, M.J., 2021. Systematic review of the use of translated patient-reported outcome measures in cancer trials. Trials 22 (1), 306.
Veit, C.T., Ware Jr., J.E., 1983. The structure of psychological distress and well-being in general populations. J. Consult. Clin. Psychol. 51 (5), 730–742.
Vermersch, P., Czlonkowska, A., Grimaldi, L.M., Confavreux, C., Comi, G., Kappos, L., Olsson, T.P., Benamor, M., Bauer, D., Truffinet, P., Church, M., Miller, A.E., Wolinsky, J.S., Freedman, M.S., O'Connor, P., Group, T.T., 2014. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. Mult. Scler. 20 (6), 705–716.
Walton, C., King, R., Rechtman, L., Kaye, W., Leray, E., Marrie, R.A., Robertson, N., La Rocca, N., Uitdehaag, B., van Der Mei, I., 2020. Rising prevalence of multiple sclerosis worldwide: insights from the Atlas of MS. Mult. Scler. J. 26 (14), 1816–1821.
Wild, D., Grove, A., Martin, M., Eremenco, S., McElroy, S., Verjee-Lorenz, A., Erikson, P., 2005. Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: report of the ISPOR task force for translation and cultural adaptation. Value Health 8 (2), 94–104.
Wilson, S., Calocer, F., Rollot, F., Fauvernier, M., Remontet, L., Tron, L., Vukusic, S., Le Page, E., Debouverie, M., Ciron, J., Ruet, A., De Sèze, J., Zephir, H., Moreau, T., Lebrun-Frénay, C., Laplaud, D.A., Clavelou, P., Labauge, P., Berger, E., Pelletier, J., Heinzlef, O., Thouvenot, E., Camdessanché, J.P., Leray, E., Dejardin, O., Defer, G., 2023. Effects of socioeconomic status on excess mortality in patients with multiple sclerosis in France: a retrospective observational cohort study. Lancet Regional Health – Europe 24.
Ziemssen, T., 2011. Symptom management in patients with multiple sclerosis. J. Neurol. Sci. 311, S48–S52.