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Health-Related Quality of Life Instruments Used in Multiple Sclerosis Clinical Trials: A Systematic Review

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INTRODUCTION

- Health-related quality of life (HRQoL) measurements provide a comprehensive view of health status from patient perspective and provide valuable information for clinical trials. HRQoL measurements are increasingly incorporated into clinical trials, suggesting the need to include patient perspectives about evaluations of new drugs.[1]
- Patients with multiple sclerosis (MS) commonly experience a range of debilitating symptoms. The progressive nature of the disease leads to increasing disability, with both physical and mental impairment concomitant with increasing impact on patients' general QoL. Patients with MS rank their QoL to be lower than not only that of the general population but also lower than that of patients with other chronic diseases.[2]
- Disease-modifying therapies (DMTs) for MS aim to reduce the relapse rate, delay disease progression, and manage the symptoms of the disease. In addition to clinical benefits, some of them have also demonstrated effect on improving HRQoL.[3–7]
- The objective of this study was to systematically review and identify HRQoL instruments used in clinical trials for the approved and late-phase DMTs for MS.

METHODS

- A systematic review was conducted to understand the use of HRQoL instruments in MS clinical trials.
- The review was prespecified to focus on MS phase 2, 3, and 4 randomized controlled trials (RCTs) that are conducted on currently approved or late-phase DMTs (Table 1).

Table 1: List of MS DMTs included in the systematic review

Generic name	Product	Administration	Dosing frequency	Approval status*
IFNβa-1a	Avonex®	IM	30 µg QW	Approved for relapsing forms of MS in the US
	Rebif®	SC	22 µg or 44 µg TIW	Approved for relapsing forms of MS in the US
IFNβa-1b	Betaferon®/ Betaseron®	SC	250 µg EOD	Approved for relapsing forms of MS in the US
	Extavia®	SC	250 µg EOD	Approved for relapsing forms of MS in US
Glatiramer acetate	Copaxone®	SC	20 mg QD or 40 mg TIW	Approved for RRMS and CIS with MRI features that are consistent with MS in US
Natalizumab	Tysabri®	IV infusion	300 mg Q4W	Approved for relapsing forms of MS in US
Fingolimod	Gilenya®	Oral	0.5 mg QD	Approved for relapsing forms of MS in the US, with restrictions on pre-existing medical conditions, and additional testing and heart monitoring requirements
Teriflunomide	Aubagio®	Oral	7 mg or 14 mg QD	Approved for relapsing forms of MS in the US
Dimethyl fumarate	Tecfidera®	Oral	240 mg BID	Approved for relapsing forms of MS in the US
Alemtuzumab	Lemtrada®	IV infusion	12 mg/day administered by IV infusion for 2 treatment courses Initial treatment course: 12 mg/day for 5 consecutive days (60-mg total dose) Second treatment course: 12 mg/day for 3 consecutive days (36-mg total dose) administered 12 months after the initial treatment course	Not yet approved in the US Approved by the EMA for RRMS with active disease defined by clinical or imaging features
Laquinimod	Nerventra®	Oral	0.6 mg QD	Not yet approved
PEGylated IFNβa-1a	Plegridy®	SC	125 µg Q2W or 125 µg Q4W	Not yet approved
Daclizumab		SC	300 mg or 150 mg Q4W	Not yet approved

BID, twice a week; CIS, clinically isolated syndrome; DMTs, disease-modifying therapies; EMA, European Medicines Agency; EOD, every other day; IFNβ, interferon beta; IM, intramuscular; IV, intravenous; MRI, magnetic resonance imaging; MS, multiple sclerosis; Q2W, every 2 weeks; Q4W, every 4 weeks; QD, once daily; QW, once weekly; RRMS, relapsing-remitting multiple sclerosis; SC, subcutaneous; TIW, 3 times a week.
*Assessed as of April 2014.

- The sources of data were from ClinicalTrials.gov, PubMed, and relevant conferences (Table 2). The eligibility criteria for trials included are listed in Table 3. Independent screening of citations was conducted by 2 reviewers and any discrepancies between reviewers were reconciled by further discussion to reach consensus.
- The ClinicalTrials.gov search was conducted using "multiple sclerosis" as search terms and restricted to phase 2, 3, and 4. Retrieved trials were then independently assessed by 2 reviewers to include RCTs that were conducted in patients with MS and were using 1 of the listed DMTs.
- The PubMed search was conducted using the key words: (multiple sclerosis) and ((quality of life) or QoL) and ((clinical trial) or trial). Titles and abstracts of retrieved studies were then assessed by 2 reviewers independently to include phase 2, 3, and 4 RCTs that were conducted in patients with MS and were using 1 of the listed DMTs.
- Conference titles and abstracts were manually screened by 2 reviewers independently to identify phase 2, 3, and 4 RCTs that were conducted in patients with MS and were using 1 of the listed DMTs.
- The outcomes of all these identified trials were validated through the PROQOLID database or additional literature search to be indeed measuring HRQoL.[8] Non-HRQoL measurements were removed.

Table 2: Databases and conferences examined for the systematic review

Data source	Service provider	Date
PubMed	www.ncbi.nih.gov	All*
ClinicalTrials.gov	www.clinicaltrials.gov	All†
Conference	**Website**	**Date**
AAN	www.aan.com	2009–2013
ACTRIMS	www.actrims.org	2009–2013
CMSC	www.cmsc.org	2009–2013
ECTRIMS	www.ectrims.eu	2009–2013
EFNS	www.efns.org	2009–2013
ISPOR	www.ispor.org	2009–2013

AAN, American Academy of Neurology; ACTRIMS, Americas Committee for Treatment and Research in Multiple Sclerosis; CMSC, Consortium of Multiple Sclerosis Centers; ECTRIMS, European Committee for Treatment and Research in Multiple Sclerosis; EFNS, European Federation of Neurological Societies; ISPOR, International Society of Pharmacoeconomics and Outcomes Research.
*Search conducted on November 15, 2013.
†Search conducted on November 7, 2013.

Table 3: Eligibility criteria for trials to be included in the systematic review

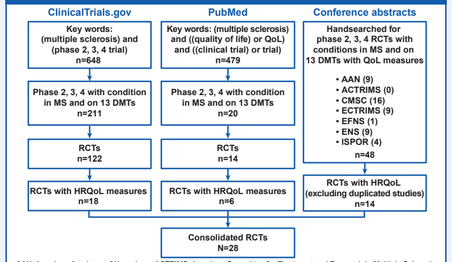
Inclusion criteria	Rationale
Population • Age: any • Sex: any • Race: any • Disease: any type of MS (including RRMS, PRMS, PPMS, SPMS, or CIS) • Line of therapy: any	The review included clinical trials conducted on patients of any type of MS or CIS
Either intervention or comparator arm contains one of the following: • IFNβ-1a • IFNβ-1b • Glatiramer acetate • Fingolimod • Natalizumab • Teriflunomide • Dimethyl fumarate • Alemtuzumab • Laquinimod • PEGylated IFNβ-1a • Daclizumab	The review included DMTs which are used in clinical practices or are being assessed for treatment of MS in clinical trials
Study design • RCTs	RCTs are the gold standard of clinical evidence, minimizing the risk of confounding and allowing the comparison of the relative efficacy of interventions. Studies with double-blind, single-blind, and open-label design were included
Study status • Completed • Ongoing • Terminated trials were excluded	All studies except those that have already been terminated
Language restrictions • English only	The restriction would not limit results substantially due to data availability in English
Publication timeframe • All available publications through November 15, 2013 for literature searches • All available registered trials through November 7, 2013 for ClinicalTrials.gov search • 2009–2013 for conference abstract search	Studies which are presented at conferences are usually published in journals within 3 years

CIS, clinically isolated syndrome; DMTs, disease-modifying therapies; IFNβ, interferon beta; MS, multiple sclerosis; PPMS, primary-progressive multiple sclerosis; PRMS, progressive-relapsing multiple sclerosis; RCTs, randomized controlled trials; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary-progressive multiple sclerosis.

RESULTS

- QoL is a broad multidimensional concept that usually includes subjective evaluations of both positive and negative aspects of life.[8] HRQoL is a multidimensional concept that includes domains related to physical, mental, emotional, and social functioning.
- The search conducted on November 7, 2013 identified 648 phase 2, 3, and 4 trials registered on ClinicalTrials.gov by using the key word search. Of these, 211 trials were conducted using 1 of the listed 13 DMTs, with 122 were being RCTs. The numbers of phase 2, 3, and 4 RCTs were 35, 59, and 28, respectively. Among these, 3 trials were reported as phase 2/3. A total of 18 RCTs included HRQoL measures as primary or secondary endpoints (Figure 1). ClinicalTrials.gov does not report tertiary endpoints.
- 6 additional published clinical trials, which either only included HRQoL measures as tertiary endpoints (n=5), or were not registered on ClinicalTrials.gov (n=1), were identified from a PubMed search conducted on November 15, 2013.
- Another 14 trials that used an HRQoL measure as one of the outcomes were identified from the recent 5 years (2009–2013) of abstracts from relevant conferences (Figure 1).

Figure 1: Search strategy and results flow chart



AAN, American Academy of Neurology; ACTRIMS, Americas Committee for Treatment and Research in Multiple Sclerosis; CMSC, Consortium of Multiple Sclerosis Centers; DMTs, disease-modifying therapies; ECTRIMS, European Committee for Treatment and Research in Multiple Sclerosis; EFNS, European Federation of Neurological Societies; HRQoL, health-related quality of life; ISPOR, International Society of Pharmacoeconomics and Outcomes Research; MS, multiple sclerosis; QoL, quality of life; RCTs, randomized controlled trials.

- 10 RCTs were identified from a PubMed or conference abstract search, but not from ClinicalTrials.gov, although most of these trials also were registered on the site. This is because ClinicalTrials.gov only lists primary and secondary outcomes. To identify trials that included HRQoL measurements as tertiary outcomes, we relied on published studies.

Table 4: List of identified RCTs that used HRQoL measures as 1 of the endpoints

Phase 2	Phase 3			Phase 4
NCT00228163 Teriflunomide	NCT00027300 (AFFIRM) Natalizumab	NCT00451451 (CONFIRM) Dimethyl fumarate	NCT00883337 (TENERE) Teriflunomide	NCT00179478 (CHAMPIONS10) IFNβ-1a 30 µg
NCT00324506 Mycophenolate mofetil (comparator: IFNβ-1a 30 µg)	NCT00030966 (SENTINEL) Natalizumab	NCT00530348 (CARE-MSI) Alemtuzumab	NCT00906399 (ADVANCE) PEGylated IFNβ-1a	NCT01144052 Natalizumab
NCT00390221 (SELECT) Daclizumab	NCT00134563 (TEMSO) Teriflunomide	NCT00548405 (CARE-MSII) Alemtuzumab	NCT01064401 (DECIDE) Daclizumab	NCT01216072 (EPOC) Fingolimod
NCT00333138 Fingolimod	NCT00340834 (TRANSFORM) IFNβ-1a 30 µg	NCT00622700 (TOPIC) Teriflunomide	NCT01332019 (ATTAIN) PEGylated IFNβ-1a	NCT01333501 (Cognition) Fingolimod
	NCT00355134 (FREEDOMS 2) Oral fingolimod	NCT00751881 (TOWER) Teriflunomide	NCT01416181 (ASCEND) Natalizumab	NCT01490840 (PACE) Fingolimod
	NCT00420212 (DEFINE) Dimethyl fumarate	NCT00835770 Dimethyl fumarate	MSCRG IFNβ-1a 30 ug	NCT01791244 (RebiQoL) IFNβ-1a

HRQoL, health-related quality of life; IFNβ, interferon beta; RCTs, randomized controlled trials.

- In total, we identified 28 RCTs conducted on ≥1 of the listed DMTs in MS populations that included HRQoL measurements. Of these, 4 were phase 2, 18 were phase 3, and 6 were phase 4 (Table 4).

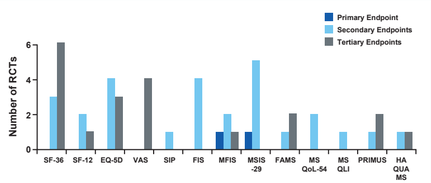
Table 5: List of identified HRQoL measures and number of RCTs using these measures

Generic HRQoL measures		Disease-specific HRQoL measures	
Instrument	**No. of RCTs (%)**	**Instrument**	**No. of RCTs (%)**
36-item Short Form 36 Health Survey (SF-36) and SF-36v2	9 (27)	MS Impact Scale (MSIS-29)	6 (18)
EuroQol 5-dimension instrument (EQ-5D)	7 (21)	Modified Fatigue Impact Scale (MFIS)	4 (12)
Fatigue Impact Scale (FIS)	4 (12)	Functional Assessment in MS (FAMS)	3 (9)
Visual analog scale (VAS)*	4 (12)	Patient-Reported Outcome Indices in MS (PRIMUS)	3 (9)
12-item Short-Form Health Survey (SF-12) and SF-12v2	3 (9)	Hamburg Quality of Life Questionnaire Multiple Sclerosis (HAQUAMS)	2 (6)
Sickness Impact Profile (SIP)	1 (3)	MS Quality of Life Questionnaire-54 (MSQoL-54)	2 (6)
		MS Quality of Life Inventory (MSQLI)	1 (3)

HRQoL, health-related quality of life; MS, multiple sclerosis; RCTs, randomized controlled trials.
Note: the percentages are derived from dividing number of RCTs using HRQoL instruments by the total of 28 RCTs identified. >1 quality of life instruments may have been used for 1 RCT; thus, the sum of all instruments used exceeds 100%.
*VAS includes both EQ-5D VAS and global assessment of well-being VAS.

- We identified 13 different HRQoL measures in the trials, including both generic and MS-specific HRQoL instruments.
- The most frequently used generic instruments included the 36-Item Short-Form Health Survey (SF-36®), EuroQol (EQ-5D™), and Fatigue Impact Scale (FIS).
- The most frequently used MS-specific instruments included the Multiple Sclerosis Impact Scale (MSIS-29), Modified Fatigue Impact Scale (MFIS), Functional Assessment in Multiple Sclerosis (FAMS), and Hamburg Quality of Life Questionnaire Multiple Sclerosis (HAQUAMS; Table 5).
- In general, generic HRQoL measures (28 times) were used slightly more frequently in clinical trials than MS-specific measures (21 times).
- Most of the trials included HRQoL as secondary or tertiary endpoints. Only 2 identified trials used HRQoL as primary endpoints (MSIS-29 and MFIS); both are MS-specific HRQoL instruments (Figure 2).

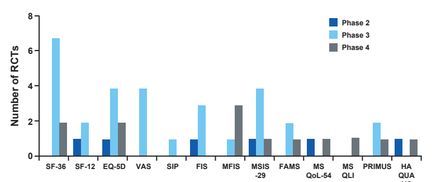
Figure 2: Number of RCTs using HRQoL measures as primary, secondary, or tertiary endpoints



EQ-5D, EuroQol 5-dimension instrument; FAMS, Functional Assessment in Multiple Sclerosis; FIS, Fatigue Impact Scale; HAQUAMS, Hamburg Quality of Life Questionnaire Multiple Sclerosis; MFIS, Modified Fatigue Impact Scale; MSIS-29, Multiple Sclerosis Impact Scale; MSQLI, Multiple Sclerosis Quality of Life Inventory; MSQoL-54, Multiple Sclerosis Quality of Life Questionnaire-54; PRIMUS, Patient-Reported Outcome Indices in Multiple Sclerosis; RCTs, randomized controlled trials; SF-36, 36-Item Short-Form Health Survey, SF-12, 12-Item Short-Form Health Survey; SIP, Sickness Impact Profile; VAS, visual analog scale.

- Among the identified RCTs (N=28) that included HRQoL measures as one of the endpoints, most of these trials were phase 3 (n=18), followed by phase 4 (n=6) and then phase 2 (n=4). When this is divided by all RCTs that were conducted in patients with MS and also included ≥1 of the 13 listed DMTs, 11.4% of the phase 2 trials, 30.5% of the phase 3 trials, and 21.4% of the phase 4 trials included HRQoL as one of the outcome measures. In general, generic instruments were more frequently used in phase 3 trials, compared with MS-specific instruments (21 times vs 9 times; Figure 3).

Figure 3: Number of RCTs using HRQoL measures by clinical trial phases



EQ-5D, EuroQol 5-dimension instrument; FAMS, Functional Assessment in Multiple Sclerosis; FIS, Fatigue Impact Scale; HAQUAMS, Hamburg Quality of Life Questionnaire Multiple Sclerosis; MFIS, Modified Fatigue Impact Scale; MSIS-29, Multiple Sclerosis Impact Scale; MSQLI, Multiple Sclerosis Quality of Life Inventory; MSQoL-54, Multiple Sclerosis Quality of Life Questionnaire-54; PRIMUS, Patient-Reported Outcome Indices in Multiple Sclerosis; RCTs, randomized controlled trials.

DISCUSSION

- This systematic review aimed to identify HRQoL instruments used in MS RCTs based on information that is published or in the public domain. As ClinicalTrial.gov only reports primary and secondary endpoints, we conducted additional PubMed and conference abstract searches and to identify trials that used HRQoL instruments as tertiary endpoints. However, the numbers reported in this study may underestimate the real rate of HRQoL instruments being used because we may have missed unpublished trials.
- This review did not include nonrandomized clinical trials that also included HRQoL measures in the study design. This is particularly common for single-arm phase 4 studies. For future studies, we will expand the review criteria to all phase 2, 3, and 4 studies.
- Inclusion of HRQoL measures will significantly improve the understanding of health status of individuals from the patient's perspective and provide valuable information on the interventions being tested.

CONCLUSIONS

- Both generic and MS-specific HRQoL instruments are used in MS clinical trials. The most frequently used instruments were the SF-36, EQ-5D, and MSIS-29. More phase 3 studies included HRQoL measurements compared with phase 2 or 4 studies. Most of the time, HRQoL measurements were used as secondary or tertiary endpoints.
- In phase 3 MS clinical trials conducted using 1 of the listed DMTs, less than 1/3 (30.5%) reported using HRQoL measurements. The rate was even lower with phase 4 (21.4%) and phase 2 (11.4%) RCTs. While it is likely that the rates are underestimated as some trials may not report the design or results of their HRQoL measures, there seems to be an overall trend of MS RCTs that lack HRQoL measures.

References

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Disclosures

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