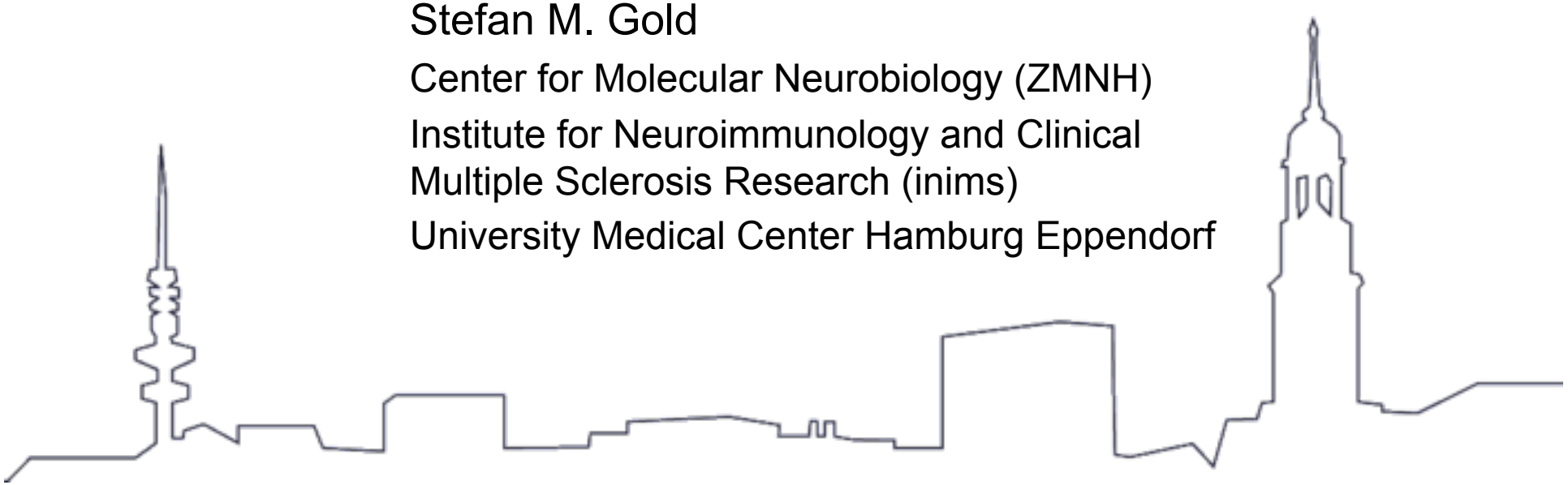
ZMNH Center for Molecular Neurobiology Hamburg

Rehabilitation in Multiple Sclerosis, Hamburg 2012
Session:

Quality of life in clinical trials:

From tertiary endpoint to labeling claim

Stefan M. Gold
Center for Molecular Neurobiology (ZMNH)
Institute for Neuroimmunology and Clinical Multiple Sclerosis Research (inims)
University Medical Center Hamburg Eppendorf



Overview

- Quality of life in multiple sclerosis
- FDA recommendations for labeling claims
  - Reliability
  - Validity
- Detecting changes in clinical trials
  - Ability to detect change
  - Interpretability
- Special issues
  - Specific populations (cognitive impairments)
  - Translations and cross-cultural validity

ZMNH Center for Molecular Neurobiology Hamburg

Quality of life in multiple sclerosis

- Quality of life is strongly associated with psychosocial factors
- QoL is therefore often investigated in behavioral interventions
- Quality of life has increasingly been included as an additional endpoint in MS clinical trials

Panel 3: Predictors of reduced HRQoL[33]

Strong predictors
Depression
Demoralisation or hopelessness
Cognitive impairment
Lack of autonomy
Lack of support
Pain

Moderate
Fatigue
Anxiety
Communication difficulties
Rapidly progressive disease
Low self esteem

Weak
Long duration of disease
Neurological symptoms
Subtypes of disease
Forced unemployment
MRI disease burden

Mitchell et al., Lancet Neurol 2005

ZMNH Center for Molecular Neurobiology Hamburg

QoL measures in multiple sclerosis

Scale	Number of Items	Time to Complete (min)	Physical				Neuropsychiatric				Psychosocial		
			Physical	Mobility	Bladder/Bowel	Sensory	Communication	Sexual	Cognitive	Fatigue	Emotional	Social	Self-efficacy
MS QoL[103]	54	11–18	y	y	n	y	n	y	y	y	y	y	n
Disability and Impact Profile[104]	39	25	y	y	y	y	y	y	n	n	y	y	y
Functional assessment of MS (FAMS)[105]	59	20	y	y	y	y	y	y	y	y	y	y	y
Hamburg QoL questionnaire in MS[106]	38	25	y	y	y	y	y	y	y	y	y	y	n
Leeds MS QoL[107]	8	5	n	n	n	n	n	n	n	y	n	y	n
MS impact scale-29[108]	29	15	y	y	y	n	n	n	y	y	y	y	y
MS QoL inventory[109]	30	45	y	y	y	y	n	y	y	y	y	y	y
RAYS[110]	50	30	y	y	y	y	y	y	y	y	y	y	n
Pfennings HRQoL instrument[111]	40	10	y	y	y	n	n	n	y	y	y	n	n
QoL index MS Version[112]	18	45	y	n	n	n	y	y	y	y	y	n	y
Performance scales[113]	21	10	y	y	y	y	n	n	y	y	n	n	n

Table 3: **MS-specific HRQoL instruments**

Mitchell et al., Lancet Neurol 2005

ZMNH Center for Molecular Neurobiology Hamburg

COSMIN taxonomy

Mokkink et al., Qual Life Res 2010

ZMNH Center for Molecular Neurobiology Hamburg

FDA guidelines for supporting labeling claims

Health and Quality of Life Outcomes

BioMed Central

Guidelines

Open Access

Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance

U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research*[1], U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research*[2] and U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health*[3]

Address: [1]U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 2085, USA, [2]U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, USA and [3]U.S. Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiological Health, Food and Drug Administration, 1350 Piccard Drive, Rockville, MD 20850-430, USA

Email: U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research* - laurie.burke@fda.hhs.gov; U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research* - toni.stifano@fda.hhs.gov ; U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health* - SXD@cdrh.fda.gov

* Corresponding authors

Published: 11 October 2006

Health and Quality of Life Outcomes 2006, 4:79 doi:10.1186/1477-7525-4-79

Received: 21 April 2006
Accepted: 11 October 2006

FDA guidance for instrument development

- Instrument development
  - Conceptual framework
  - Generation of items
  - Recall period and recall options
  - Evaluation of patient understanding
  - Confirmation of conceptual framework and instrument finalization

FDA, Health and Quality of Life Outcomes 2006

FDA guidance on measurement properties

- Reliabilty
  - Test-retest
  - Internal consistency
  - (Interrater reliability)
- Validity
  - Content-related
  - Construct-related (discriminant, convergent, known-groups)
  - Ability to predict future outcomes

FDA, Health and Quality of Life Outcomes 2006

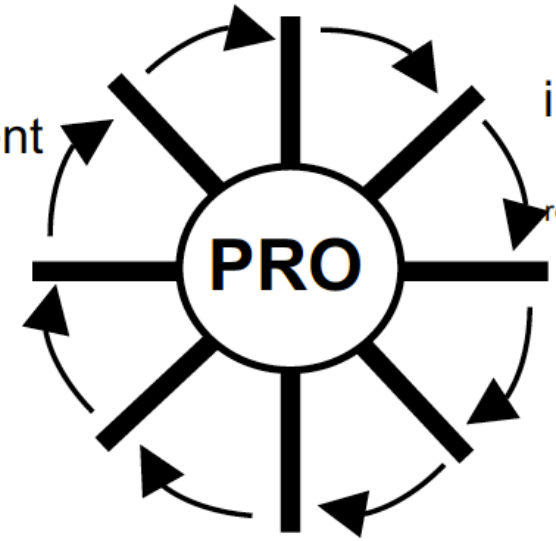
Instrument development

i. Identify Concepts and Develop Conceptual Framework

Identify concepts and domains that are important to patients.
Determine intended population and research application.
Hypothesize expected relationships among concepts.

ii. Create Instrument

Generate items.
Choose administration method, recall period, and response scales.
Draft instructions.
Format instrument.
Draft procedures for scoring and administration. Pilot test draft instrument. Refine instrument and procedures.



iii. Assess Measurement Properties

Assess score reliability, validity, and ability to detect change.
Evaluate administrative and respondent burden. Add, delete, or revise items.
Identify meaningful differences in scores. Finalize instrument formats, scoring, procedures, and training materials.

iv. Modify Instrument

Change concepts measured,
populations studied,
research application,
instrumentation,
or method of administration.

FDA, Health and Quality of Life Outcomes 2006

ZMNH Center for Molecular Neurobiology Hamburg

COSMIN taxonomy

Mokkink et al., Qual Life Res 2010

ZMNH Center for Molecular Neurobiology Hamburg

FDA guidance on ability to detect change

Measurement Property	Test	What is Assessed	FDA Review Considerations
Ability to detect change	Includes calculations of effect size and standard error of measurement among others	Whether PRO scores are stable when there is no change in the patient, and the scores change in the predicted direction when there has been a notable change in the patient as evidenced by some effect size statistic. Ability to detect change is always specific to a time interval.	Has ability to detect change been demonstrated in a comparative trial setting, comparing mean group scores or proportion of patients who experienced a response to the treatment? Has ability to detect change been assessed for the time interval appropriate to study?

FDA, Health and Quality of Life Outcomes 2006

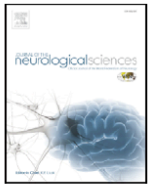
ZMNH Center for Molecular Neurobiology Hamburg

Ability to detect change: Responsiveness

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns



Responsiveness of patient-based and external rating scales in multiple sclerosis: Head-to-head comparison in three clinical settings

Stefan M. Gold [d,*], Holger Schulz [b], Heike Stein [a], Katrin Solf [a], Karl-Heinz Schulz [b,c], Christoph Heesen [a]

[a] Institute of Neuroimmunology and Clinical MS-Research (INiMS), University Hospital Eppendorf, Martinistrasse 52, Hamburg, Germany
[b] Institute of Medical Psychology, Center for Psychosocial Medicine, University Hospital Eppendorf, Martinistrasse 52, Hamburg, Germany
[c] Department of Hepatobiliary Surgery, Center for Transplantation Medicine, University Hospital Eppendorf, Martinistrasse 52, Hamburg, Germany
[d] Department of Neurology, UCLA School of Medicine, 635 Charles Young Dr S, Los Angeles, CA, USA

Clinical and demographic data of the studies.

	Rehabilitation study (approx 20 sessions)	Fitness training (8 weeks)	Observational study (1 year)
n	40	15	53
Age	43.9 + 9.5	39.0 + 9.0	42.1 + 2.1
Gender (male/female)	14/26	4/11	17/36
Disease course (RRMS/SPMS/PPMS/UK)	17/18/5/0	11/1/1/2	13/15/19/6
EDSS at study entry	4.0 + 1.3	2.0 + 1.4	4.6 + 1.8

ZMNH Center for Molecular Neurobiology Hamburg

Responsiveness to worsening

Responsiveness of external rating scale (EDSS) and patient-rated outcome scores (HAQUAMS) in 53 MS patients with overall health status worsening over a 6–18 month period according to 'subjective global impression' (SGI) and 'clinical global impression' (CGI).

	Measure	Baseline	Follow-up	ES	SRM	RE
	EDSS	4.48 + 1.81	5.17 + 1.60	**−0.38**	**−0.58**	
HAQUAMS	Total score	2.48 + 0.74	2.70 + 0.70	**−0.30**	**−0.55**	1.00
	Fatigue	2.33 + 0.98	2.69 + 1.05	**−0.37**	**−0.54**	0.98
	Lower limb	3.43 + 1.07	3.59 + 0.94	−0.15	**−0.30**	0.26
	Upper limb	2.29 + 1.07	2.57 + 1.07	**−0.26**	**−0.49**	0.91
	Social	1.88 + 0.70	2.01 + 0.83	−0.19	**−0.25**	0.28
	Mood	2.49 + 0.92	2.64 + 0.88	−0.16	**−0.24**	0.16

Gold et al., J Neurol Sci 2010

ZMNH Center for Molecular Neurobiology Hamburg

Responsiveness to rehabilitation

	Measure	Baseline	Follow-up	ES	SRM	RE
5×/wk, 1 m	EDSS	3.73 + 1.36	3.73 + 1.48	0.00	0.00	
	RMI	14.00 + 1.08	14.15 + 0.99	−0.14	**−0.25**	
	FIM	116.95 + 6.67	118.20 + 7.27	−0.19	**−0.29**	
HAQUAMS	Total score	2.30 + 0.62	2.12 + 0.52	**0.29**	**0.51**	1.00
	Fatigue	2.67 + 1.19	2.26 + 0.94	**0.34**	**0.54**	1.12
	Lower limb	2.79 + 0.93	2.62 + 0.97	0.17	**0.39**	0.59
	Upper limb	1.76 + 0.75	1.67 + 0.75	0.12	**0.24**	0.22
	Social	1.96 + 0.66	1.84 + 0.60	0.18	**0.27**	0.28
	Mood	2.35 + 0.78	2.21 + 0.64	0.17	**0.22**	0.18

Gold et al., J Neurol Sci 2010

ZMNH Center for Molecular Neurobiology Hamburg

Responsiveness to MBSR

MS quality of life, depression, and fatigue improve after mindfulness training

A randomized trial

P. Grossman, PhD
L. Kappos, MD
H. Gensicke, MD
M. D'Souza, MD
D.C. Mohr, PhD
I.K. Penner, PhD
C. Steiner, MS

Address correspondence and reprint requests to Dr. Paul Grossman, Department of Psychosomatic Medicine, Division of Internal Medicine, University Hospital Basel, Hebelstrasse 2, CH-3041 Basel, Switzerland
PGrossman@uhbs.ch

ABSTRACT

Objective: Health-related quality of life (HRQOL) is often much reduced among individuals with multiple sclerosis (MS), and incidences of depression, fatigue, and anxiety are high. We examined effects of a mindfulness-based intervention (MBI) compared to usual care (UC) upon HRQOL, depression, and fatigue among adults with relapsing-remitting or secondary progressive MS.

Methods: A total of 150 patients were randomly assigned to the intervention (n = 76) or to UC (n = 74). MBI consisted of a structured 8-week program of mindfulness training. Assessments were made at baseline, postintervention, and 6 months follow-up. Primary outcomes included disease-specific and disease-aspecific HRQOL, depression, and fatigue. Anxiety, personal goal attainment, and adherence to homework were secondary outcomes.

Results: Attrition was low in the intervention group (5%) and attendance rate high (92%). Employing intention-to-treat analysis, MBI, compared with UC, improved nonphysical dimensions of primary outcomes at postintervention and follow-up ($p < 0.002$); effect sizes, 0.4–0.9 posttreatment and 0.3–0.5 at follow-up. When analyses were repeated among subgroups with clinically relevant levels of preintervention depression, fatigue, or anxiety, postintervention and follow-up effects remained significant and effect sizes were larger than for the total sample.

Conclusions: In addition to evidence of improved HRQOL and well-being, these findings demonstrate broad feasibility and acceptance of, as well as satisfaction and adherence with, a program of mindfulness training for patients with MS. The results may also have treatment implications for other chronic disorders that diminish HRQOL.

Classification of evidence: This trial provides Class III evidence that MBI compared with UC improved HRQOL, fatigue, and depression up to 6 months postintervention. *Neurology*® 2010;75:1141–1149

ZMNH Center for Molecular Neurobiology Hamburg

Responsiveness to MBSR

Table 2 Mean, SD, and 95% CI on outcome measures for all patients before and after receiving MBI or UC[a]

Outcome	Baseline level, mean (SD)	Direct postintervention, change (95% CI)	6-Month follow-up change (95% CI)	Postintervention effects (change from preintervention)			6-Month follow-up effects (change from preintervention)		
				F	*p* Value	ES (95% CI)	*F*	*p* Value	ES (95% CI)
PQOLC (range, 0–24)									
MBI (n = 76)	14.40 (3.74)	2.54 (1.91 to 3.17)	1.77 (0.97 to 2.58)	37.90	10^{-8}	0.86 (0.52 to 1.19)	8.82	0.003	0.51 (0.18 to 0.84)
UC (n = 74)	14.99 (3.48)	−0.57 (−1.29 to 0.15)	−0.10 (−0.83 to 0.64)						
HAQUAMS (range, 1–5)									
MBI (n = 76)	2.22 (0.67)	0.18 (0.09 to 0.27)	0.13 (0.00 to 0.25)	14.91	0.0002	0.43 (0.10 to 0.75)	4.23	0.04	0.28 (−0.05 to 0.61)
UC (n = 74)	2.13 (0.60)	−0.09 (−0.20 to 0.01)	−0.05 (−0.16 to 0.07)						
CES-D (range, 0–60)									
MBI (n = 76)	16.33 (10.46)	5.29 (3.50 to 7.07)	4.63 (2.51 to 6.75)	23.36	10^{-5}	0.65 (0.31 to 0.97)	4.63	0.03	0.36 (0.03 to 0.69)
UC (n = 74)	15.62 (10.36)	−1.43 (−3.47 to 0.61)	0.86 (−1.07 to 2.78)						
MFIS (range, 0–84)									
MBI (n = 76)	35.15 (16.68)	6.65 (4.14 to 9.16)	6.58 (3.63 to 9.53)						
		6.19 (3.96 to 8.41)[b]	5.94 (3.01 to 8.87)[b]	16.48	0.0001	0.41 (0.09 to 0.73)	11.29	0.001	0.38 (0.05 to 0.71)
UC (n = 74)	30.28 (14.98)	−0.10 (−2.26 to 2.05)	−0.71 (−3.80 to 2.37)						
		0.36 (−1.90 to 2.61)[b]	−0.09 (−2.98 to 2.79)[b]						
STAI (range, 20–80)									
MBI (n = 76)	42.54 (10.67)	3.95 (2.31 to 5.59)	3.68 (1.84 to 5.52)	12.56	0.0006	0.39 (0.06 to 0.71)	5.97	0.02	0.33 (0.00 to 0.66)
UC (n = 74)	41.04 (10.84)	−0.22 (−1.89 to 1.46)	0.13 (−1.62 to 1.88)						

Grossman et al., Neurology 2010

ZMNH Center for Molecular Neurobiology Hamburg

COSMIN taxonomy

Mokkink et al., Qual Life Res 2010

ZMNH Center for Molecular Neurobiology Hamburg

FDA guidance on interpretability

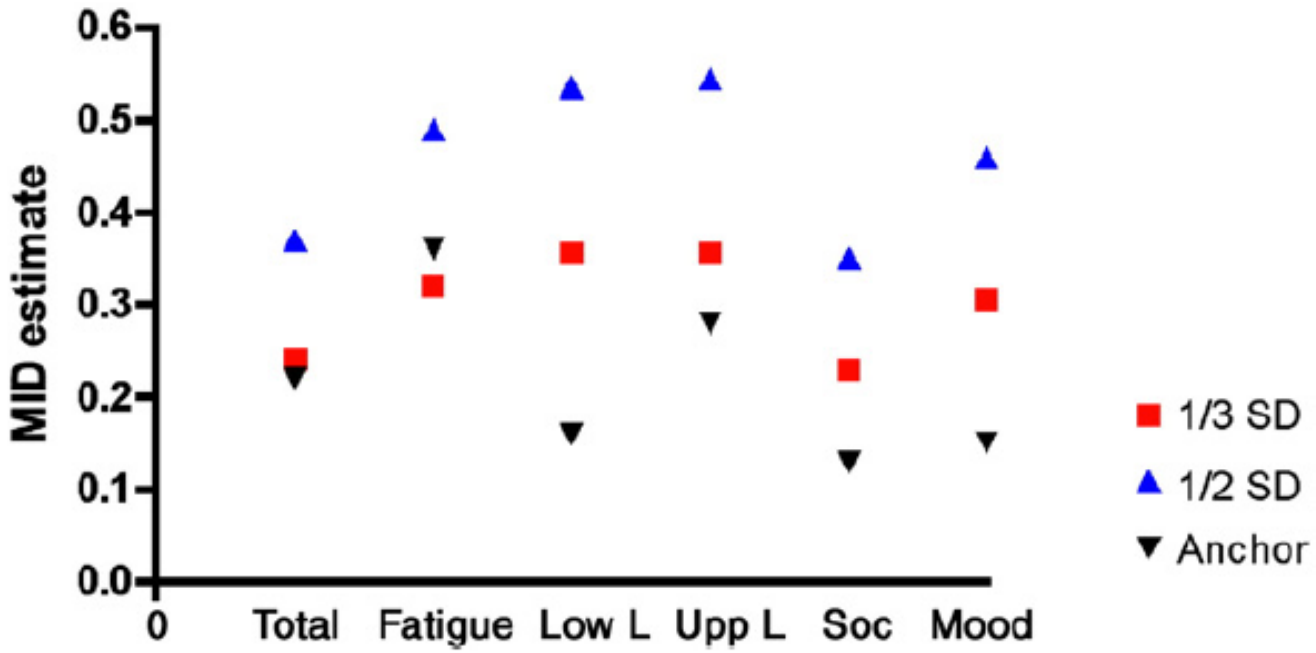
Measurement Property	Test	What is Assessed	FDA Review Considerations
Interpretability	Smallest difference that is considered clinically important; this can be a specified difference (the minimum important difference (MID)) or, in some cases, any detectable difference. The MID is used as a benchmark to interpret mean score differences between treatment arms in a clinical trial	Difference in mean score between treatment groups that provides convincing evidence of a treatment benefit. Can be based on experience with the measure using a distribution-based approach, a clinical or nonclinical anchor, an empirical rule, or a combination of approaches. The definition of an MID using a clinical anchor is sometimes called an MCID.	The FDA is specifically requesting comment on appropriate review of derivation and application of an MID in the clinical trial setting.

- Distribution-based MID
- Anchor-based MID (transition questions to clinician and/or patient)

FDA, Health and Quality of Life Outcomes 2006

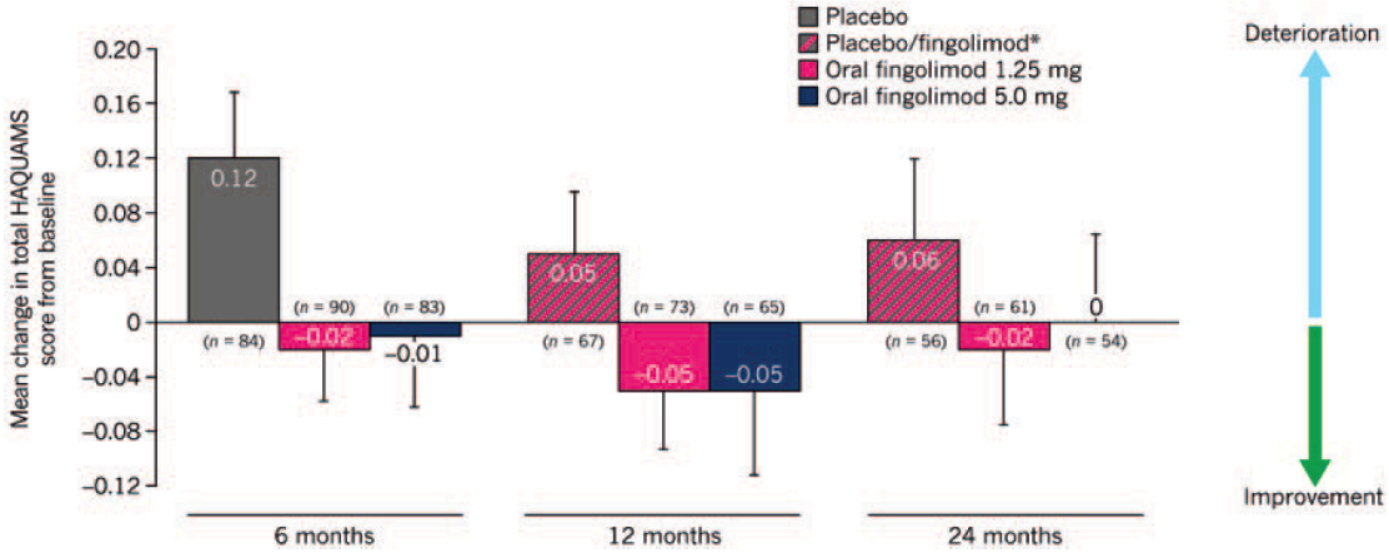
Interpretability

- Triangulation of minimally important difference



Gold et al., J Neurol Sci 2010

Interpretability: Application



Montalban et al., Mult Scler 2011

Interpretability: Application

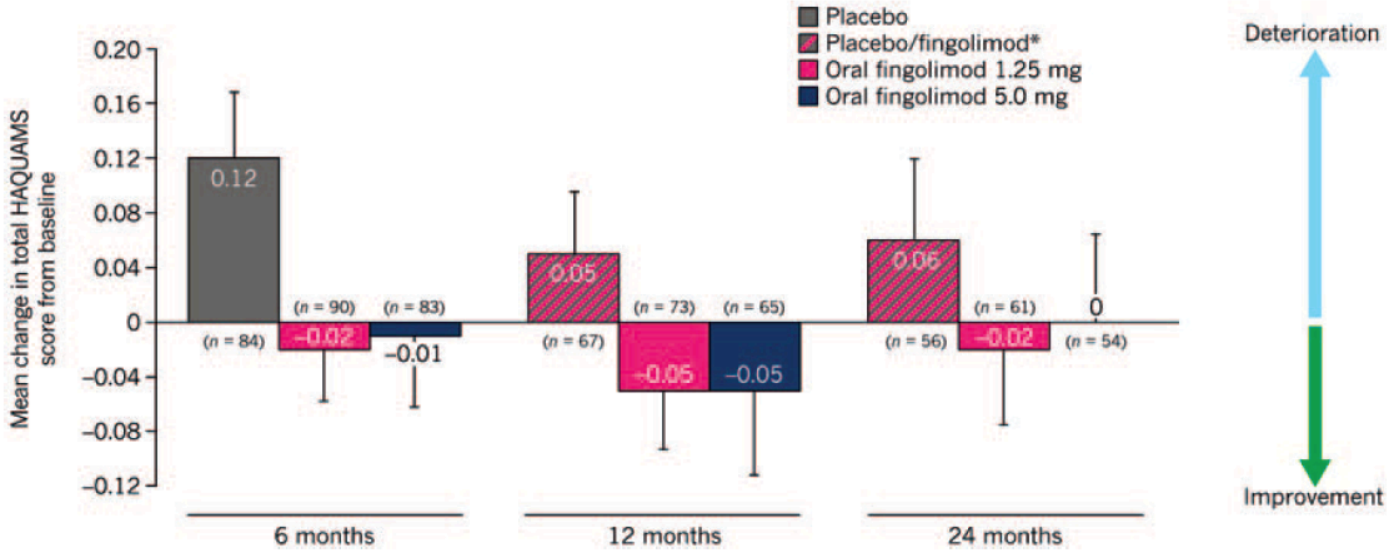


Table 4. Categorical change in Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS) scores from baseline to month six (intent-to-treat population)

	Placebo $n = 92$	Fingolimod 1.25 mg $n = 93$	Fingolimod 5.0 mg $n = 92$
Improvement, *n*/*N* (%)	12/88 (13.6)	17/93 (18.3)	21/89 (23.6)
Odds ratio (95% CI)*		1.35 (0.57 – 3.24)	2.26 (0.96 – 5.32)
p-value		0.496	0.062
No change, *n*/*N* (%)	47/88 (53.4)	60/93 (64.5)	51/89 (57.3)
Deterioration, *n*/*N* (%)	29/88 (33.0)	16/93 (17.2)	17/89 (19.1)
Odds ratio (95% CI)*		0.42 (0.21 – 0.84)	0.48 (0.24 – 0.96)
p-value		0.014	0.038

CI, confidence interval; *N*, the number of patients who had evaluable scores at baseline and 6 months (or 3 months if missing). Improvement was defined as a reduction in HAQUAMS scores from baseline of greater than the defined minimally important difference (>0.22); deterioration was defined as an increase in HAQUAMS scores from baseline of >0.22. Odds ratios and *p*-values were calculated using a logistic regression model, with baseline HAQUAMS scores as a covariate.

Montalban et al., Mult Scler 2011

Interpretability: Application

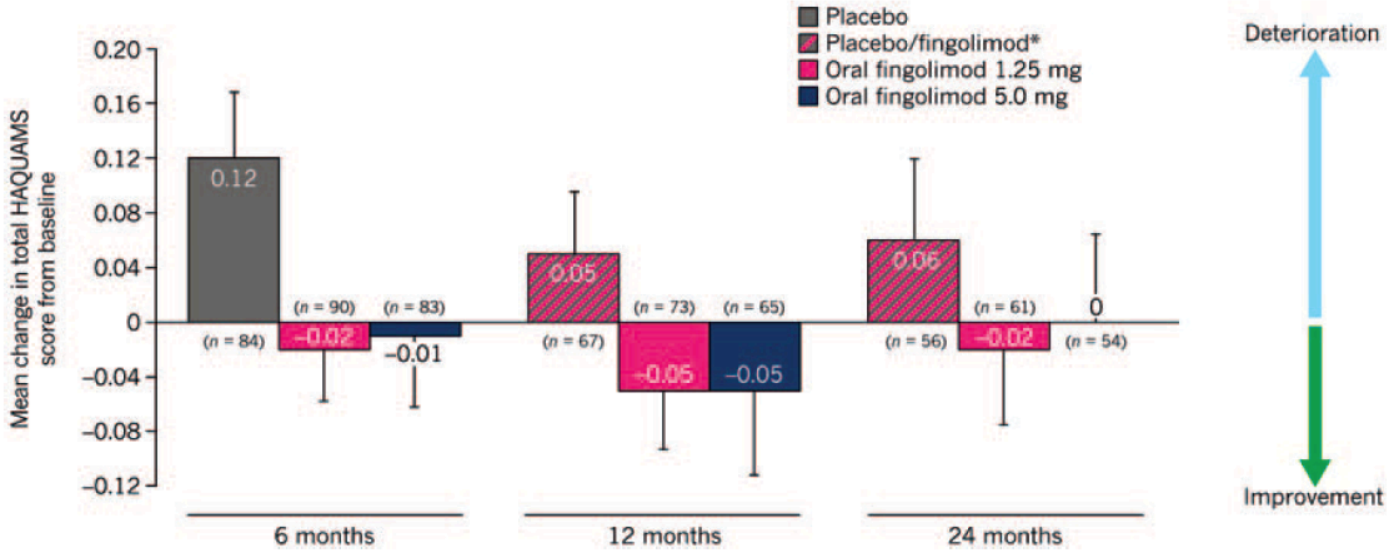


Table 4. Categorical change in Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS) scores from baseline to month six (intent-to-treat population)

	Placebo $n = 92$	Fingolimod 1.25 mg $n = 93$	Fingolimod 5.0 mg $n = 92$
Improvement, *n*/*N* (%)	12/88 (13.6)	17/93 (18.3)	21/89 (23.6)
Odds ratio (95% CI)*		1.35 (0.57 – 3.24)	2.26 (0.96 – 5.32)
p-value		0.496	0.062
No change, *n*/*N* (%)	47/88 (53.4)	60/93 (64.5)	51/89 (57.3)
Deterioration, *n*/*N* (%)	29/88 (33.0)	16/93 (17.2)	17/89 (19.1)
Odds ratio (95% CI)*		0.42 (0.21 – 0.84)	0.48 (0.24 – 0.96)
p-value		0.014	0.038

CI, confidence interval; *N*, the number of patients who had evaluable scores at baseline and 6 months (or 3 months if missing). Improvement was defined as a reduction in HAQUAMS scores from baseline of greater than the defined minimally important difference (>0.22); deterioration was defined as an increase in HAQUAMS scores from baseline of >0.22. Odds ratios and *p*-values were calculated using a logistic regression model, with baseline HAQUAMS scores as a covariate.

Montalban et al., Mult Scler 2011

FDA guidance on specific populations

- Cognitive impairment that occurs in some chronic diseases may affect measurement
  - Develop proxy-ratings

PAPER

Proxy measurements in multiple sclerosis: agreement between patients and their partners on the impact of multiple sclerosis in daily life

F A H van der Linden, J J Kragt, J C Hobart, M Klein, A J Thompson, H M van der Ploeg, C H Polman, B M J Uitdehaag

J Neurol Neurosurg Psychiatry 2006;77:1157–1162. doi: 10.1136/jnnp.2006.090795

  - Good agreement cross-sectionally, stronger for physical than for psychological domain

ZMNH Center for Molecular Neurobiology Hamburg

Low agreement longitudinally and in rehab settings

BMC Neurology

BioMed Central

Research article

Open Access

Longitudinal proxy measurements in multiple sclerosis: patient-proxy agreement on the impact of MS on daily life over a period of two years

Femke AH van der Linden*†[1,2], Jolijn J Kragt[1], Margarethe van Bon[1], Martin Klein[2], Alan J Thompson[4], Henk M van der Ploeg[2], Chris H Polman[1] and Bernard MJ Uitdehaag†[1,3]

Address: [1]Department of Neurology, VU University Medical Centre, Amsterdam, The Netherlands, [2]Medical Psychology, VU University Medical Centre, Amsterdam, The Netherlands, [3]Clinical Epidemiology and Biostatistics, VU University Medical Centre, Amsterdam, The Netherlands and [4]Neurological Outcome Measures Unit, Institute of Neurology, London, UK

Email: Femke AH van der Linden* - fah.vdlinden@vumc.nl; Jolijn J Kragt - jj.kragt@vumc.nl; Margarethe van Bon - msk700@student.vu.nl; Martin Klein - m.klein@vumc.nl; Alan J Thompson - a.thompson@ion.ucl.ac.uk; Henk M van der Ploeg - vanderploeg-stapert@planet.nl; Chris H Polman - ch.polman@vumc.nl; Bernard MJ Uitdehaag - bmj.uitdehaag@vumc.nl

* Corresponding author †Equal contributors

Published: 28 February 2008

BMC Neurology 2008, 8:2 doi:10.1186/1471-2377-8-2

Received: 22 August 2007
Accepted: 28 February 2008

European Journal of Neurology 2008, **15:** 933–939

doi:10.1111/j.1468-1331.2008.02224.x

Proxy ratings from multiple sources: disagreement on the impact of multiple sclerosis on daily life

F. A. H. van der Linden[a,b], M. B. D'hooghe[c], G. Nagels[c], A. Van Nunen[c], C. H. Polman[a] and B. M. J. Uitdehaag[a,d]

Departments of [a]Neurology, [b]Medical Psychology, VU University Medical Center, Amsterdam, The Netherlands; [c]National Multiple Sclerosis Center, Melsbroek, Belgium; and [d]Clinical Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands

Measuring QoL in cognitively impaired patients

Multiple Sclerosis 2003; **9:** 404–410
www.multiplesclerosisjournal.com

Cognitive impairment in multiple sclerosis does not affect reliability and validity of self-report health measures

Stefan M Gold[1,2,], Holger Schulz[2], Andrea Mönch[1], Karl-Heinz Schulz[2,3] and Christoph Heesen[1]*
[1]Department of Neurology, University Hospital Eppendorf, Hamburg, Germany; [2]Department of Medical Psychology, University Hospital Eppendorf, Hamburg, Germany; [3]Department of Hepatobiliary Surgery, University Hospital Eppendorf, Hamburg, Germany

		Cognitively preserved SDMT > 0.0 (n = 107)			*Definite cognitive impairment SDMT ≤ −2.5 (n = 80)*		
		M (SD)	*alpha*	*% low/high*	*M (SD)*	*alpha*	*% low/high*
HAQUAMS	Fatigue/Thinking	1.91 (0.84)	0.81	17/0	2.59 (1.02)	0.81	11/3
	Mobility (lower limb)	2.10 (1.16)	0.90	22/1	3.70 (1.11)	0.88	5/14
	Mobility (upper limb)	1.50 (0.71)	0.84	37/0	2.65 (1.20)	0.87	14/0
	Social function	1.73 (0.72)	0.73	18/0	2.28 (0.83)	0.65	5/0
	Mood	2.10 (0.80)	0.87	2/0	2.88 (0.96)	0.83	1/4
	HAQUAMS short form	1.90 (0.81)	0.74	17/0	2.78 (0.84)	0.61	0/0
	HAQUAMS total score	1.87 (0.60)	0.91	0/0	2.82 (0.74)	0.91	0/0
HADS	HADS depression	4.68 (3.53)	0.83	2/0	7.50 (4.03)	0.74	3/0
	HADS anxiety	6.95 (4.09)	0.84	3/0	7.38 (4.48)	0.81	8/0

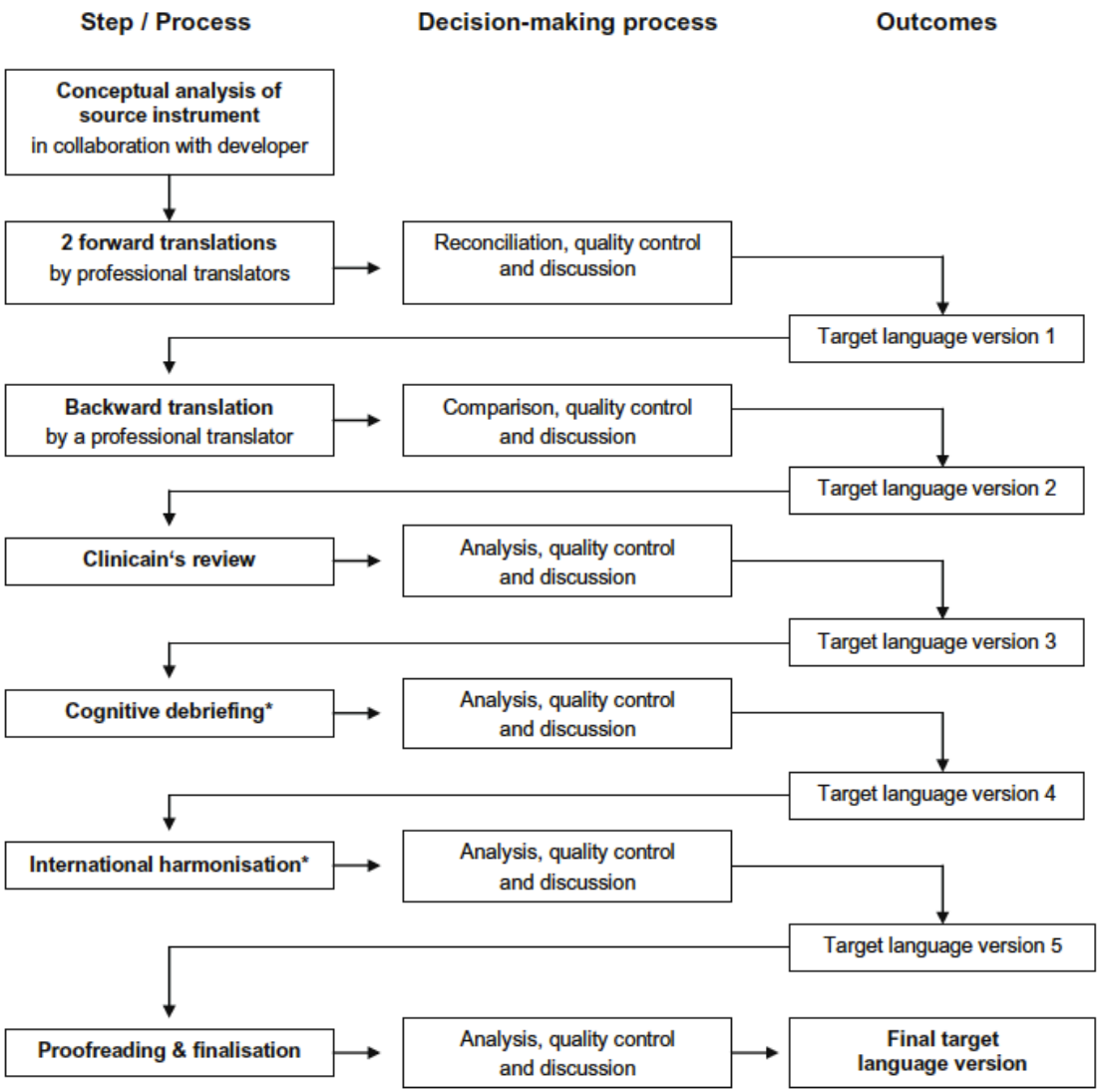
ZMNH Center for Molecular Neurobiology Hamburg

COSMIN taxonomy

Mokkink et al., Qual Life Res 2010

ZMNH Center for Molecular Neurobiology Hamburg

MAPI institute translation process



ZMNH Center for Molecular Neurobiology Hamburg

HAQUAMS international study

- Large international study conducted by Adelphi Real World

Table 1. Characteristics of the sample												
	Total sample		French (=243)		German (n=758)		Italian (n=623)		Spanish (n=381)		English (n=1040)	
	N	%	N	%	N	%	N	%	N	%	N	%
Age Mean/SD	40.8	11.62	40.4	12.52	40.4	12.52	40.4	12.52	40.4	12.52	40.4	12.52
Gender												
Male	1039	34.12	81	33.33	269	35.49	261	41.89	156	40.94	272	26.15
Female	2003	65.78	162	66.67	488	64.38	362	58.11	225	59.06	766	73.65
Missing	3	0.1	-	-	1	0.13	-	-	-	-	2	0.19
Ethnicity												
White/Caucasian	2729	89.62	202	83.13	724	95.51	613	98.39	358	93.96	832	80
Asian - Indian	23	0.76	-	-	5	0.66	-	-	2	0.52	16	1.54
Afro-Caribbean	122	4.01	2	0.82	3	0.4	2	0.32	1	0.26	114	10.96
Spanish/Hispanic	108	3.55	38	15.64	13	1.72	1	0.16	9	2.36	47	4.52
Asian - other	14	0.46	1	0.41	2	0.26	-	-	-	-	11	1.06
Other	8	0.26	-	-	2	0.26	-	-	-	-	6	0.58
Missing	41	1.35	-	-	9	1.19	7	1.12	11	2.89	14	1.35
EDSS_gr												
<3.9	1490	63.57	139	61.5	398	63.88	321	60.57	205	56.47	427	70.93
4-6.9	724	30.89	68	30.09	186	29.86	186	35.09	146	40.22	138	22.92
7+	130	5.55	19	8.41	39	6.26	23	4.34	12	3.31	37	6.15

Anatchkova et al., in preparation

ZMNH Center for Molecular Neurobiology Hamburg

HAQUAMS international study

Table 1: HAQUAMS mean subscale scores, internal consistency coefficients and estimates of floor/ceiling effects for the entire sample (n=3012).

Subscale	*Number of items*	*Mean (s.d.)*	*Coefficient alpha*	*% scoring 1 or 5*
Fatigue/thinking	4	2.24 (1.01)	0.90	17.2 / 1.6
Mobility (lower limb)	5	2.39 (1.21)	0.93	17.8 / 3.5
Mobility (upper limb)	5	1.82 (1.00)	0.94	37.7 / 0.8
Social function	6	2.18 (0.76)	0.71	10.6 / 0.2
Mood	8	2.71 (0.88)	0.90	3.0 / 1.0
HAQUAMS total	28	2.32 (0.78)	0.95	1.4 / 0
Short form total score	5	2.34 (0.93)	0.82	5.5 / 0.5

Anatchkova et al., in preparation

ZMNH Center for Molecular Neurobiology Hamburg

HAQUAMS international study

Table 2:Internal consistency of HAQUAMS subscales by country. Almost all coefficients exceed the value of 0.75 indicating good reliability. Notable exceptions are the social function scale coefficients for Italy and Spain.

	Coefficient alpha					
	Germany n=756	*Italy* n=616	*Spain* n=379	*UK* n=131	*USA* n=890	*France* n=240
Fatigue/thinking	0.90	0.88	0.94	0.84	0.93	0.83
Mobility (lower limb)	0.95	0.93	0.89	0.94	0.94	0.91
Mobility (upper limb)	0.95	0.93	0.95	0.90	0.94	0.89
Social function	0.75	*0.65*	*0.59*	0.81	0.75	0.76
Mood	0.95	0.85	0.84	0.83	0.91	0.86
HAQUAMS total	0.96	0.95	0.93	0.94	0.97	0.93
Short form total	0.83	0.83	0.78	0.79	0.85	0.74

Anatchkova et al., in preparation

Conclusions: Implications for clinical trials

- Selection of instrument should be based on measurement properties
- Instrument should be sensitive and provide data for interpretation of changes
  - On a group level (MID)
  - On an individual level (responder definition)
- Instrument must be appropriate for study population
  - Duration of study
  - Clinical characteristics of population (current and future)
  - Cross-cultural validity

ZMNH Center for Molecular Neurobiology Hamburg

Acknowledgements

University Hospital Hamburg
Dept Neurology
C. Heesen, A. Mönch, K. Solf, M. De Groote,

Institute for Medical Psychology
K.H. Schulz, H. Schulz

Dept Psychosomatic Medicine
M. Rose

University of Massachusetts
Quantitative Health Sciences
M. Anatchkova

Adelphi Real World

MAPI Institute

Funding

Gemeinnützige Hertie-Stiftung

Forschungs- & Wissenschaftsstiftung Hamburg

Deutsche Forschungsgemeinschaft

European Union

MARIE CURIE ACTIONS
RG268381