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Patient-reported outcomes, biomarkers and novel methodologies, and their role in the development of new multiple sclerosis medicines

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Patient Reported Outcomes (PROs) in MS

"Any outcome evaluated directly by the patient himself and based on patient's perception of a disease and its treatment(s) is called patient-reported outcome (PRO).

The term PRO is proposed as an umbrella term to cover both single dimension and multi-dimension measures of symptoms, health-related quality of life (HRQL), health status, adherence to treatment, satisfaction with treatment, etc."

EMEA/CHMP/EWP/139391/2004, London, 27 July, 2005

PROs in MS (examples)	
HRQOL	MSQL* MSQLI*; MusiQol*, MSQol-54*, MSIS-29
Health status	SF-36*, /SF-12* EQ-5D*
Fatigue	FAMS; FSMC*; MFIS* (uFIS*); FSS*
Walking	MSWS-12*
Disability	PDDS, GNDS
Bowel Function	BWCS
Bladder function	BLCS
Spasticity	MSSS-88
Pain	BPI*; MOS-PES;
Visual Function	VFQ-25**
Treatment Satisfaction	TSQM**
Cognitive Impairment	EMQ*
Activity limitation	PRIMUS*
Depression	HDRS BDI-II

*Reliability and validity assessed in MS patients and published

**Reliability and validity assessed in general population

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Patient Reported Outcomes (PROs)

- PROs are important tools to capture patient's perspective and complement and support the meaningfulness of other outcomes.
- Draft Guideline[1]
  - Limited to Quality of Life (QoL)
  - Only non-specific guidance is given regarding the quality of scales to be used ('reliable and validated') in order to support label claims.
- Several PROs have undergone psychometric testing and have demonstrated validity, reliability and responsiveness in the MS population.
  - MS Walking Scale -12 (MSWS-12), reflecting perception of ambulatory ability and considered validated in EPAR of recently approved drug, thus supporting clinical meaningfulness of improved walking speed.[2]

1. Draft Guideline 6.4., 365-367 (QoL) and 5.2.2. , 296-298 Secondary efficacy variables) 2. Assessment Report Fampyra EMA/55661/2011

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Recommendations

- Consider coverage of PROs beyond QoL in the guidance and their potential role in clinical investigations
  - Valid, reliable PRO instruments beyond QoL, addressing symptoms and functions in MS and supporting clinical meaningfulness are available
  - MSWS-12 could be specifically mentioned as an example
- Collaboratively (academia, industry, EMA) developed criteria for appropriate PROs would encourage rigor in the further development, validation, and selection of PRO instruments for investigation in MS

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Molecular/cellular Biomarkers (BMs) (cells, proteins, DNA, RNA, miRNA)

- Draft Guideline[3]
  - Encourages use of BM to identify patient subgroups (e.g. risk for progression or treatment responders)
  - Acknowledges the importance of a search for valid BMs (e.g. disease activity, prognosis) to improve trial efficiency in exploratory trials
  - Encourages BM to be an integrated part of drug development program
- Molecular BMs: Currently very few sufficiently validated; none established to predict therapeutic response
- Discovery and validation often require larger sample sizes and/or longer-term data,
  - Difficult to accomplish in academic settings or by small exploratory trials

3. Draft Guideline 7.2. (393-395) and 8.4. (442-446)

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Recommendations

- In general in agreement with draft guideline
- Consider mentioning that “phase 2 and/or 3 studies could be potentially used for BM validation”

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Imaging Biomarkers
(MRI based)

- Draft Guideline[4]
  - Acknowledges role of established MRI measures (e.g. Gd-enhancing lesions, new/enlarging T2 lesions) to screen for anti-inflammatory effects in exploratory trials and to monitor CNS lesions in MS.
  - Considers established imaging measurements less useful to study effects on tissue loss or potential drug effects beyond inflammation.
  - Suggests that in non-relapsing SPMS and PPMS, measures of CNS atrophy including grey and white matter volumes, and new MRI techniques may be particularly useful

4. Draft Guideline 6.3. (344-367)

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Consider strengthening role of brain volume loss

- Guideline coverage of whole brain volume loss may not adequately reflect potential usefulness
  - Academic support as most advanced imaging BM of brain tissue preservation[5-6]
  - Well developed methods to quantify brain volume change and successfully used in multicentre trials, although methodological differences exist between software and centre experience with testing/analysis is required
  - Sensitivity to pharmacological interventions in the 1-2 year timeframe in RRMS pivotal studies and in exploratory trials in SPMS [7-10]
  - Correlation of brain atrophy with neurological disability[11-13]
  - Correlation of treatment effects on disability progression with treatment effects on brain atrophy[14]
- Confounders, such as pseudo-atrophy or pathologically non-specific volume changes, can potentially be addressed by study design (e.g. deferred baseline)[15]

5. Barkhof et al Nat Rev Neurol. 2009; 6. Rudick & Fischer 2013; 7. Cohen JA et al 2012; 8. Kappos L et al 2010; 9. Cohen JA et al 2010; 10. Chataway et al Neurology [abstract] 2013; 11. Fisher et al, Neurology (2002) ; 12. Rudick R et al, J Neurol Sci (2009); 13. Horakova D et al J Neurol Sci (2009); 14. Sormani MP et al Ann. Neurol. 2013 [accepted]; 15. Miller DH et al Clin Pharmacol & Therapeut 2012

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Recommendations, 1

- In general, in agreement with draft guideline
- Recommend to mention whole brain atrophy as an endpoint in exploratory trials where objective may be to halt/delay disability progression and MoA is not primarily anti-inflammatory
- Recommend to mention whole brain atrophy as a secondary endpoint in pivotal trials where primary goal is to halt/delay disease progression

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Recommendations, 2

- MRI lesion activity measures (Gd-enhancing lesions) could also “facilitate dose-finding in exploratory trials”
- MRI to provide “independent and fully-blinded evaluation and confirmation of drug anti-inflammatory effects as secondary or tertiary endpoint(s) in pivotal trials”
- The goal to establish surrogacy for MRI outcomes, as proposed in 2006 Guideline (4.3.), should be maintained

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Novel Methodologies: OCT (Optical coherence tomography)

- Objective, non-invasive, painless, patient-friendly technology to study the retinal nerve fibre layer (RNFL) and neurons (retinal ganglion cells) in vivo at high resolution[16]
- High reproducibility (spectral-domain OCT) and independent, fully-blinded, central evaluation[17]
  - Thinning of RNFL indicates axonal loss of the anterior visual pathway
  - Thinning of ganglion cell layer (GCL) indicates neuronal loss
  - Low-contrast letter acuity and contrast sensitivity correlate with RNFL thickness, and provide link between changes of anatomical structures as measured by OCT and visual function[16]

16. Galetta K et al, Neurotherapeutics 2013;; 17. Saidha S et al JAMA Neurol 2013.

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OCT in acute Optic Neuritis

- Degree of RNFL thinning in general MS population likely too small for exploratory trials
  - Annual RNFL decrease in MS patients with no ON history: ~ 0.5-2 µm compared with 0.1 µm in healthy controls [18-19]
- Exploratory trials in acute optic neuritis (AON) as MS proxy
  - Suitable dynamics can capture extent of axonal loss in 3 - 6 months
  - Several AON trials, a condition with suitably dynamic RNFL thinning, supports its use as an outcome measure for treatment response[20-21]
  - May be hard to recruit (short recruitment time window, no pre-planning due to emergent nature of AON)

18. Petzold A et al Lancet Neurol 2010; 19. Talman LS et al Ann Neurol 2010; 20. Sühs KW et al. Ann Neurol 2012; 21. Esfahani MR et al Graefes Arch Clin Exp Ophthalmol. 2012:

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Recommendation

- Guideline should acknowledge that “the improved visualisation by, and performance of OCT technology suggests an increasingly important role to measure axonal and neuronal degeneration”