

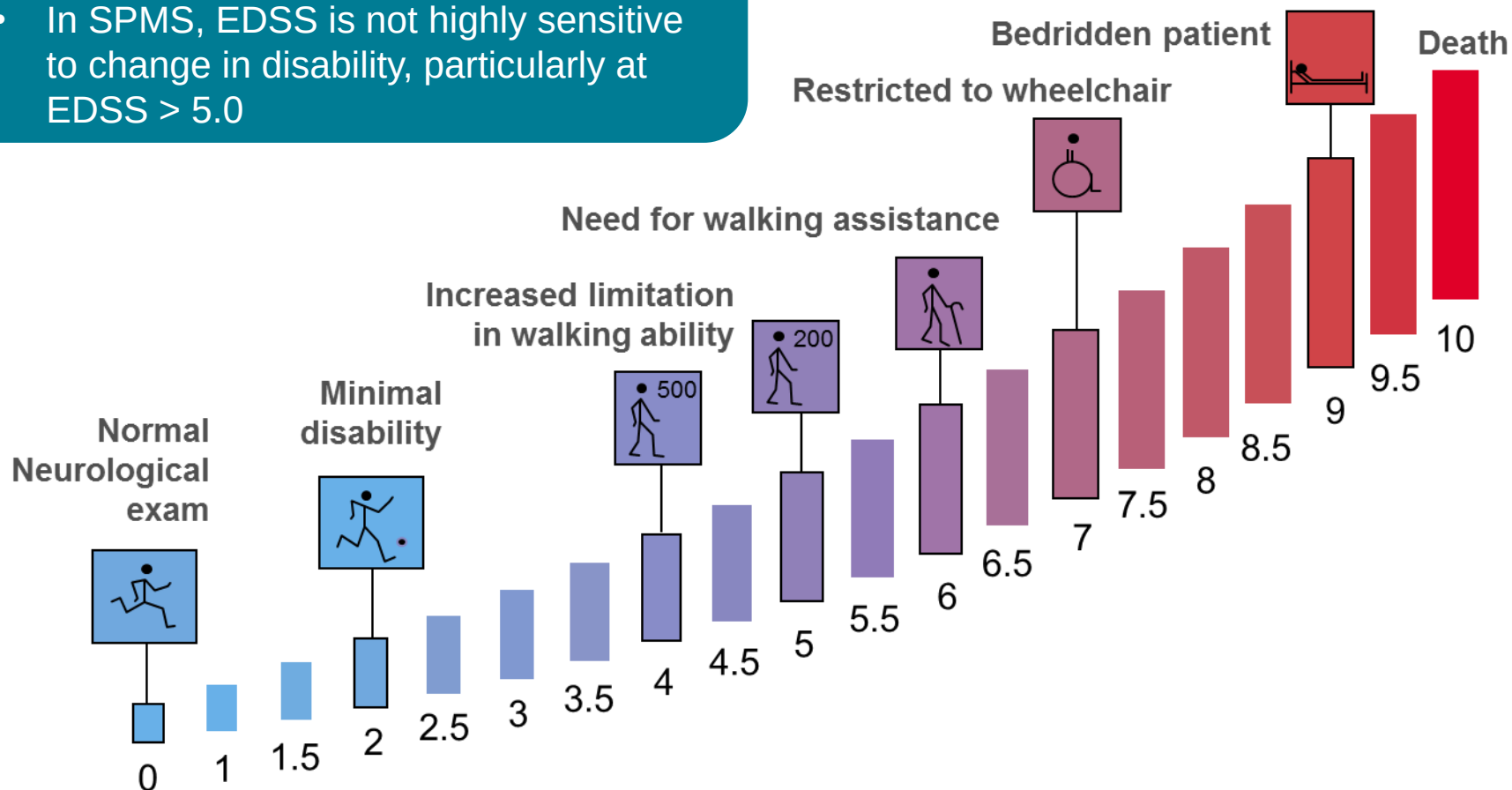
The new outcome measures in MS: possible better ways to assess disability that overcome the limitations of the EDSS

Gilmore O'Neill MB MRCPI MMSc
VP, Neurology Clinical Development
Biogen Idec Inc.

- What is the EDSS?
- EDSS limitations
- “Gaps in EDSS to be addressd”
- There have been and are multiple ongoing efforts to address the gaps in EDSS:
 - MSFC
 - EDSS-plus
 - Freedom from disease acitivity
 - MSOAC
- Conclusion & Recommendations

EDSS

- EDSS is a widely accepted measure of Physical Disability in MS
- In SPMS, EDSS is not highly sensitive to change in disability, particularly at EDSS > 5.0



- “The disadvantages and advantages of the EDSS in assessing disability in MS are well known.”
 - It is based on the standard neurological examination, which is inherently subjective
 - As a result, the scale has poor reliability within and between raters
- Scores of 4.0–7.5 are based primarily on the distance the patient can walk and the need for an assistive device
- EDSS captures MS related cognitive impairment poorly
- EDSS is a non-linear ordinal scale:
 - populations show a bimodal distribution of EDSS categories, and the rate of progression through the scale by individual patients over time varies as a function of baseline score
- **CONCLUSION:** Modification of the EDSS would be desirable to improve linearity of measurement, which would facilitate statistical analysis and clinical interpretation.

“Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis” (Doc. Ref. CPMP/EWP/561/98 Rev. 1

Jeffrey A Cohen, Stephen C Reingold, Chris H Polman, Jerry S Wolinsky, for the International Advisory Committee on Clinical Trials in Multiple Sclerosis
Disability measures in MS clinical Trials. Lancet Neurology 2012; 11: 467

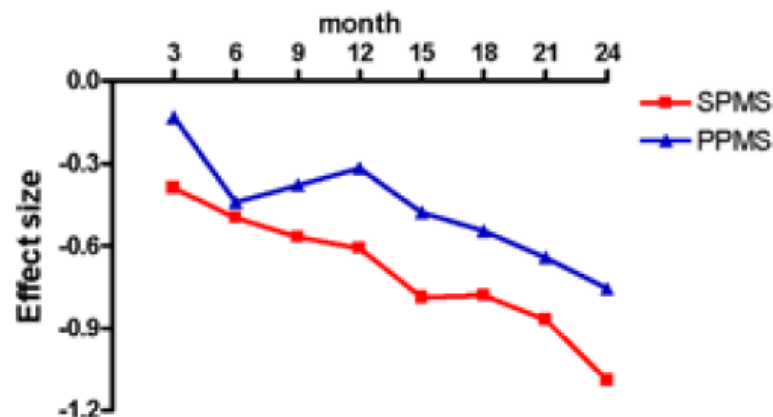
EDSS GAPS TO ADDRESS

Gaps in endpoints to address unmet need

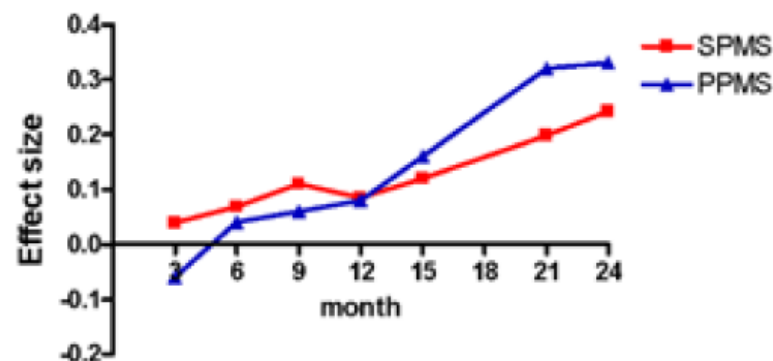
- SPMS/ PPMS:
 - Effect size
 - Variability in sensitivity
- RRMS objectives:
 - Control of disease activity

EDSS “gaps to fill”: Effect size of T25FW > EDSS

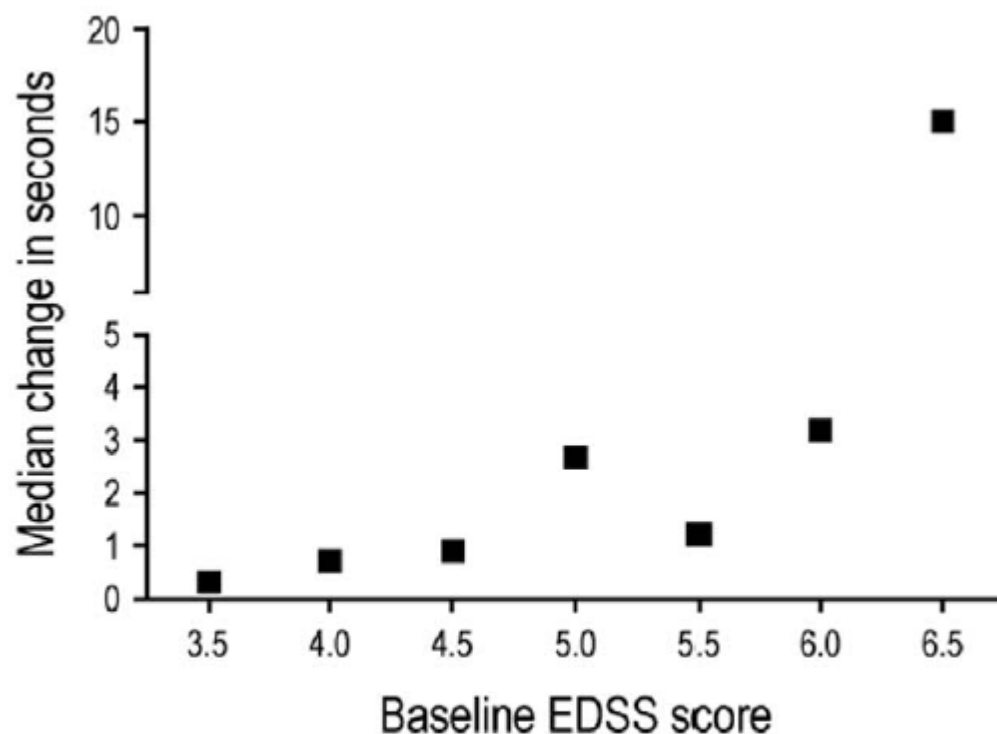
Timed 25 foot walk



EDSS



Cadavid D, Tang Y, O'Neill G.
Responsiveness of the Expanded
Disability Status Scale (EDSS)
to disease progression and
therapeutic intervention in
progressive forms of multiple
sclerosis. Rev Neurol 2010;
51: 321-9.

EDSS “gaps to fill”: T25FW more sensitive to
change in patient-subjects more disabled at
baseline

Diego Cadavid, Stephanie
Jurgensen, Sophia Lee
Effect of Natalizumab on
ambulatory improvement in
SP and Disabled RRMS
PLoS ONE 8(1): e53297

Figure 1. Median change in T25FW over 2 years by baseline EDSS score in patients with SPMS. Patients randomized to the placebo arm of the IMPACT study. T25FW, timed 25-foot walk; EDSS, Expanded Disability Status Scale; SPMS, secondary progressive multiple sclerosis.

EVOLVING EFFORTS TO ADDRESS GAPS IN DISABILITY ENDPOINTS

	Test	Unit of measurement
Ambulation	Timed walk over a distance of 25 ft	Time to completion (seconds)
Upper-extremity function	Nine-hole peg test	Time to completion (seconds)
Cognition	Paced auditory serial addition test	Number of correct responses (of a total of 60)

Table: The multiple sclerosis functional composite^{3,4}

Rudick R, Antel J, Confavreux C, et al. Recommendations from the National Multiple Sclerosis Society Clinical Outcomes Assessment Task Force. *Ann Neurol* 1997; 42: 379–82.

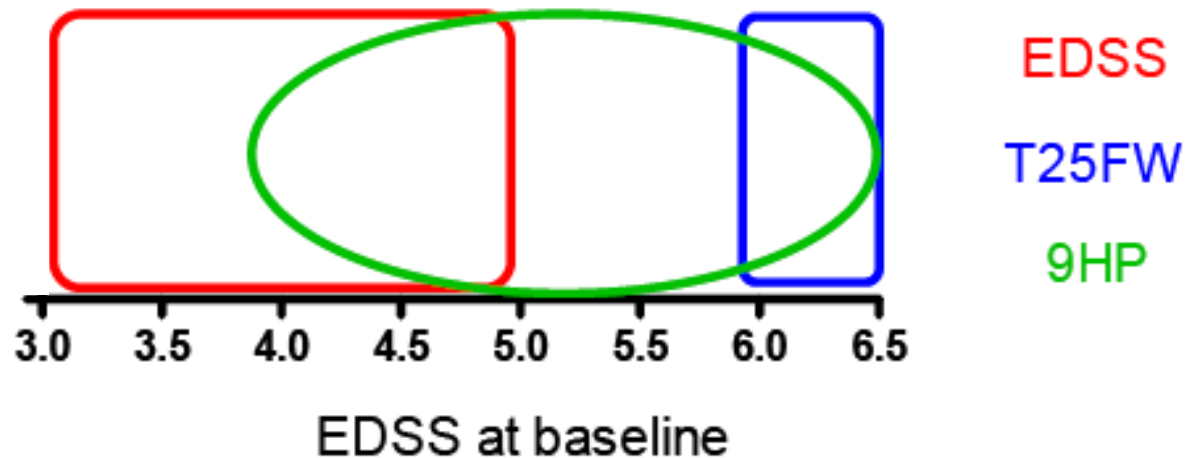
Cutter GR, Baier ML, Rudick RA, et al. Development of a multiple sclerosis functional composite as a clinical trial outcome measure. *Brain* 1999; 122: 871–82.

Jeffrey A Cohen, Stephen C Reingold, Chris H Polman, Jerry S Wolinsky, for the International Advisory Committee on Clinical Trials in Multiple Sclerosis
Disability measures in MS clinical Trials. *Lancet Neurology* 2012; 11: 467

- Abstract and dimensionless nature of the summary score.
 - Many clinicians are unfamiliar with Z scores
 - the reference population affects the absolute values for the components and their weighting
- As a result, MSFC scores cannot be easily interpreted clinically or compared across studies
- **CONCLUSION:** An alternative analytical approach is to define worsening as a decrease in score by a prespecified amount in any of the component tests, which can be determined reliably and has clinical relevance (eg, 20%), and to show worsening in the same component at two sequential time points.

Jeffrey A Cohen, Stephen C Reingold, Chris H Polman, Jerry S Wolinsky, for the International Advisory Committee on Clinical Trials in Multiple Sclerosis
Disability measures in MS clinical Trials. Lancet Neurology 2012; 11: 467

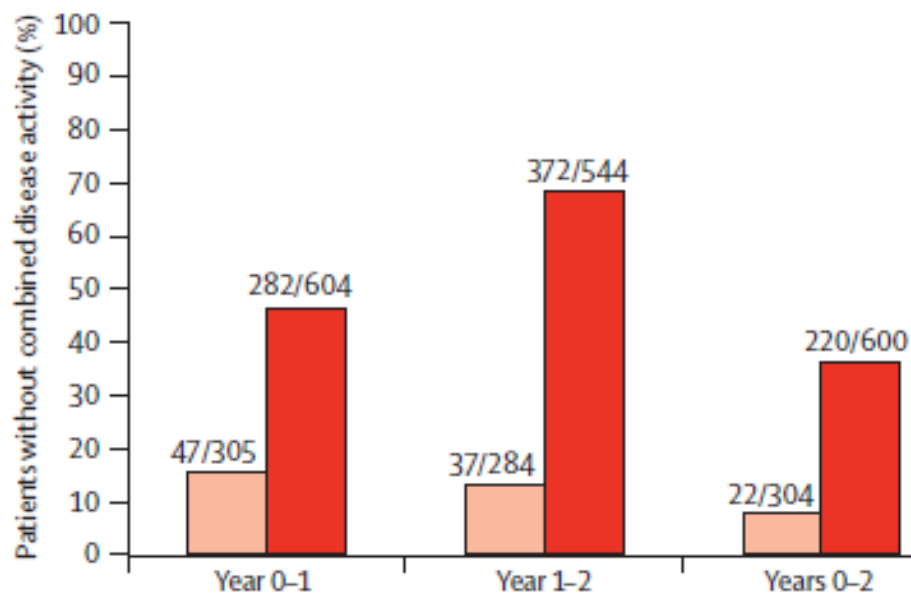
Composite endpoint “EDSS plus”



Combined endpoint (“EDSS Plus”) enables more sensitive detection of change in disability across EDSS range

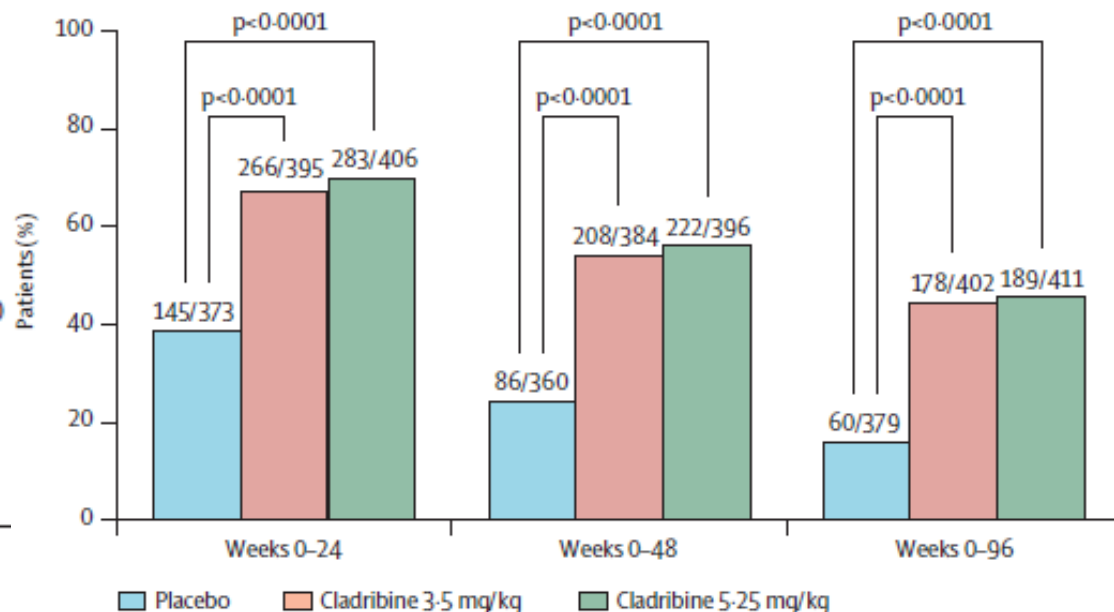
“Freedom from Disease Activity”: Remission Endpoint

Clinical and Radiological Composite: (no relapses, no progression of disability [sustained for 12 weeks], no gadolinium-enhanced lesions, and no new or enlarging T2-hyperintense lesions)



Eva Havrdova, Steven Galetta, Michael Hutchinson, Dusan Stefoski, David Bates, Chris H Polman, Paul W O'Connor, Gavin Giovannoni, J Theodore Phillips, Fred D Lublin, Amy Pace, Richard Kim, Robert Hyde

Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) study
Lancet Neurol 2009; 8: 254-60

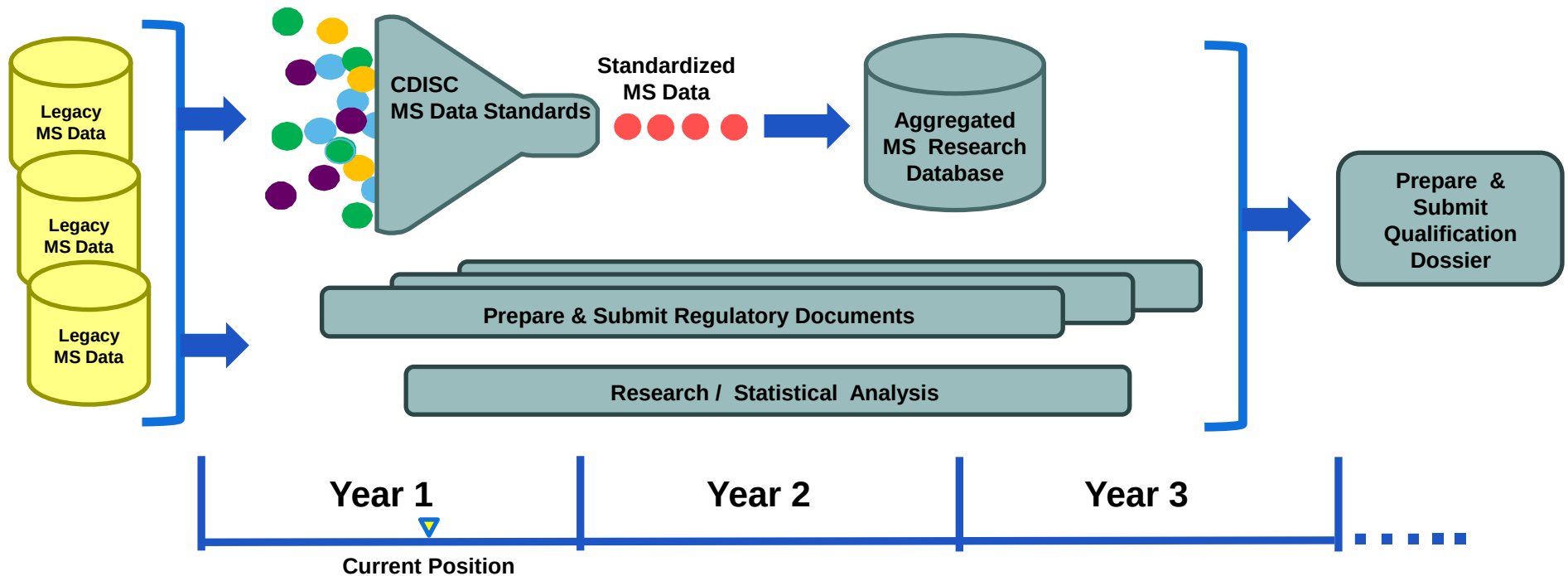


Gavin Giovannoni, Stuart Cook, Kottil Rammohan, Peter Rieckmann, Per Soelberg Sørensen, Patrick Vermersch, Anthony Hamlett, Vissia Viglietta, Steven Greenberg

Sustained disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets in the CLARITY study: a post-hoc and subgroup analysis
Lancet Neurol 2009; 8: 254-60

MSOAC Project Mission

- Develop and support adoption of a multi-dimensional clinical outcome assessment tool, and obtain regulatory qualification for use as a primary or secondary endpoint in MS clinical trials.
- The qualified methodology will measure neuroperformance and will be sensitive to limitations in daily living activities of patients affected by MS.



- EDSS has been successfully used in the development and approval of a number of DMTs for RMS.
 - Nevertheless: EDSS has limitations
- Actively evolving landscape is developing alternative/ novel outcome measures that might address identified gaps in disability endpoints:
 - in use in clinical trials
 - e.g. “EDSS plus” in SPMS Tysabri
 - under development
 - e.g. MSOAC collaboration

- Agree that the guidance continuing to acknowledge the limitations of EDSS
- Guidance should be open to novel endpoints of disability as primary efficacy outcomes
- Guidance should ensure that novel outcome measures that fill existing recognized gaps in disability endpoints will not be rejected (over the lifetime of this document)