A New MS Consortium for
A New MS Clinical Outcome Measure

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Multiple Sclerosis Outcome Assessments Consortium (MSOAC)
“Precise measure of the clinical manifestations of MS is difficult because neurological impairment and disability vary in different patients and over time, and neurological function is inherently difficult to quantify.”

(Rudick, R et al, 1997)

Multiple Sclerosis Outcome Assessments Consortium (MSOAC)
A New Scale for Evaluating Disability in Multiple Sclerosis

John F. Kurtske, M.D.

It has long been apparent that an objective and reproducible method of evaluating patients with multiple sclerosis was necessary. Next to the unpredictable course for the individual with this disease, the absence of such a means of measuring disability has been a prime factor in the known difficulty of evaluating proposed therapies in multiple sclerosis. Prior attempts at mensuration range from the all-or-none categorization of MacLean and Berkson1 (incapacitated or not incapacitated) to the complex schema of Alexander,2 but there is no generally accepted scale in present use.

The goal of a rating-scale is threefold: 1) that the sum-total of any patient's disabilities should fit him into a suitable category; 2) that any change in disability should be reflected in a corresponding change of status; and 3) that the scale be simple enough to be manageable.

The scale to be presented was devised to evaluate a possible therapeutic agent for multiple sclerosis.3 In the course of

1955

STATUS IN MULTIPLE SCLEROSIS

0—Normal neurologic examination.
1—No dysfunction, minimal signs (Babinski, minimal finger to nose ataxia, diminished vibration sense).
2—Minimal dysfunction (slight weakness or stiffness, mild disturbance of gait, awkwardness, mild visuomotor disturbance).
3—Moderate dysfunction (monoparesis, mild hemiparesis, moderate ataxia, disturbing sensory loss, prominent urinary or eye symptoms, or combinations of lesser dysfunctions).
4—Relatively severe dysfunction not preventing ability to work or carry on normal activities of living, excluding sexual function. This includes the ability to be up and about 12 hours a day.
5—Dysfunction severe enough to preclude working, with maximal motor function walking unaided up to several blocks.
6—Assistance required for walking (canes, crutches, braces).
7—Restricted to wheelchair (able to wheel self and eat or leave chair alone).
8—Restricted to bed but with effective use of arms.
9—Totally helpless bed patient.
10—Death due to multiple sclerosis.
The Expanded Disability Status Scale

(adapted from Kurtzke, J. 1983)
1983

**M.R.D.**

Minimal Record of Disability for Multiple Sclerosis

DEVELOPED BY
INTERNATIONAL FEDERATION OF MULTIPLE SCLEROSIS SOCIETIES

PUBLISHED BY
NATIONAL MULTIPLE SCLEROSIS SOCIETY

(MINIMAL RECORD OF DISABILITY IN MULTIPLE SCLEROSIS)

M S 障害度評価

(INTERNATIONAL FEDERATION OF MULTIPLE SCLEROSIS SOCIETIES)

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Limitations of the EDSS

- A rating scale rather than a performance measure
- Not an equal interval scale
- Relatively insensitive to change
- Has a bimodal distribution
- Underlying meaning of scores vary along its scale
- Too dependent on ambulation
A consensus emerges

Need for a new measure
- Multidimensional
- Quantitative
- Automated scoring (objective)
- Adequate evaluation of cognition

(NMSS Advisory Committee on Clinical Trials of New Agents in MS, 1994)
The proposed solution

- Form Clinical Outcomes Assessment Task Force
- Develop recommendations for optimal clinical outcome measures (existing or new) for MS CT’s
Task Force recommendations

- Measure should reflect the extent of the MS disease process
- Multidimensional
- Practical, acceptable to patients, cost-effective
- Sensitive to change over time
- Sensitive to treatment effects
- Predictive of **clinically meaningful change**
Multiple Sclerosis Functional Composite

- Final Task Force recommendation was a 3-part “functional composite”
  - Ambulation and leg function: *Timed 25-Foot Walk*
  - Arm Function: *9-Hole Peg Test*
  - Neuropsychological function: *Paced Auditory Serial Addition Test*
- Individual tests scores converted to z-scores and combined into a composite z-score
The limitations of the MSFC

- No visual measure
- PASAT has imperfections
- z-scores “float” depending on reference population
- Modern scaling models (IRT, Rasch) not used in original construction
- FDA consigns it to secondary outcome status
- **Clinically meaningful change** of z-score changes/differences are elusive

(Adapted from Rudick, R. 2011)
The Genesis of MSOAC

- May 2011 - NMSS-ECTRIMS Workshop on Disability Outcome Measures in MS

- December 2011 – MSFC Task Force Meeting
  - General agreement on the value of analyzing existing clinical trial data to optimize a clinical outcome measure (Ontaneda et al., Multiple Sclerosis Journal 18(8):1074-1080, 2012).
The Multiple Sclerosis Outcome Assessments Consortium (MSOAC), funded by the NMSS, aims to:

Evaluate existing clinical trial data to qualify a new primary clinical outcome measure for disability in MS clinical trials.
MSOAC Members

- **MSOAC Leadership**
  Lynn Hudson, PhD; Nick LaRocca, PhD; Richard Rudick, MD
- **Industry**
- **Patient Advocacy**
  NMSS, AISM, MS Society of UK, MS Society of Canada, Alberta MS Research Foundation, CMSC
- **Regulators and Government Funding Agencies**
  FDA, EMA, NINDS
- **Academic Investigators**
WHO WE ARE: a nonprofit, public-private partnership with the Food and Drug Administration (FDA), created in 2005 under the auspices of FDA's Critical Path Initiative.

C-Path's MISSION: accelerate the pace and reduce the costs of medical product development through the creation of new data standards, measurement standards, and methods standards that aid in the scientific evaluation of the efficacy and safety of new therapies.
Compressing the Drug Development Timeline for MS Therapeutics

MSOAC will generate:

- A new Clinician-reported Outcome (Clin-RO) assessment qualified by the FDA and EMA for use as a primary endpoint in MS clinical trials
- A Study Data Tabulation Model (SDTM) data standard for MS
- A database of pooled, de-identified clinical trial data
Guiding Principles

• To the extent possible, analyze data that’s already been collected during the course of the past 15-20 years

• Engage the major sectors in the MS clinical trial enterprise in the discussion – Academics, Government, Industry, and Patient Representatives

• To the maximum extent possible, share information and engage the broader community
Specific Aims

- Create MS therapeutic area data standards, leveraging efforts already underway
- Remap legacy MS clinical trial data into common MS therapeutic area data standards
- Create an online MS database of aggregated, standardized clinical data, and make this resource publicly available to qualified researchers
- Create scientific consensus on the optimal components of a new clinician-reported outcome measure
- Advance a new clinical outcome assessment drug development to the FDA and EMA for regulatory qualification.
Current Activities

- Securing clinical trial data
  - Finalizing agreements to secure 7 phase III trial data sets (6 industry-sponsored and 1 government-sponsored)
  - Engaging other industry leaders to secure additional data sets

- Regulatory Engagement
  - Submitted comments on EMA MS guidelines
  - April 1 – Meeting with FDA leadership
### Creating Consensus

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<tr>
<th>Consortia</th>
<th>Description</th>
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<tr>
<td>CAMD <strong>CRITICAL PATH INSTITUTE</strong></td>
<td>Coalition Against Major Diseases UnderDISEASES OF THE BRAIN</td>
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<tr>
<td>CPTR <strong>CRITICAL PATH INSTITUTE</strong></td>
<td>Critical Path to TB Drug Regimens Testing Drug Combinations</td>
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<td>Multiple Sclerosis Outcome Assessments Consortium Drug Effectiveness in MS</td>
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<td>PKD Consortium <strong>CRITICAL PATH INSTITUTE</strong></td>
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<td>Electronic Patient-Reported Outcome Consortium Drug Effectiveness</td>
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<td>PSTC <strong>CRITICAL PATH INSTITUTE</strong></td>
<td>Predictive Safety Testing Consortium Drug Safety</td>
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**FDA**
- Biomarkers
- Clinical Outcome Assessment Instruments
- Drug Disease Trial Models
- Data Standards

**CDISC**