The Multiple Sclerosis Outcome Assessments Consortium

National Multiple Sclerosis Society
Critical Path Institute
And Many Others . . .

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National MS Society@mssociety
The Problem

“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 difficulty to quantify”

(Rudick, R et al, 1997)
A New Scale for Evaluating Disability in Multiple Sclerosis

John F. Kurtzke, 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 measurement 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 from the hospital in order to establish a baseline with which to compare the in-hospital course of groups of patients.

STATUS IN MULTIPLE SCLEROSIS

0.—Normal neurologic examination.
1.—Nu dysfunction, minimal rigor (Babinski, minimal sensory loss, diminished vibration sense).
2.—Minimal dysfunction (slight weakness or stiffness, mild disturbance of gait, awkwardness, mild visual or motor 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 inability to work or carry on normal activities of living, excluding sexual function. This includes the ability to lie up and about 12 hours a day.
5.—Dysfunction severe enough to preclude working, with maximal motor function and walking limited up to several blocks.
6.—Assistance required for walking (cables, crutches, braces).
7.—Restricted to wheelchair (able to wheel self and use toilet and leave chair alone).
8.—Restricted to bed but with effective use of arm.
9.—Totally helpless bed patient.
10.—Death due to multiple sclerosis.
The Expanded Disability Status Scale

10.0 = Death due to MS
9.0–9.5 = Completely dependent
8.0–8.5 = Confined to bed/chair; self-care with help
7.0–7.5 = Confined to wheelchair
6.0–6.5 = Walking assistance is needed
5.0–5.5 = Increasing limitation in ability to walk
4.0–4.5 = Disability is moderate
3.0–3.5 = Disability is mild to moderate
2.0–2.5 = Disability is minimal
1.0–1.5 = No disability
0 = Normal neurologic exam
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
- Reproducibility questionable
A Consensus Emerges

Need for a new measure

- Multidimensional
- Quantitative
- Automated scoring (objective)
- Adequate evaluation of cognition and vision
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
MS 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
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
The Genesis of the 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 and use of performance rather than rating for better psychometric qualities (Ontaneda et al., Multiple Sclerosis Journal 18(8):1074-1080, 2012).
MSOAC Engages Many Stakeholders

- 43 member international organization
  - 10 pharmaceutical companies
  - 27 academic medical centers
  - 6 MS patient advocacy organizations
- Created and managed by C-Path with funding and input from the National MS Society (NMSS).
- FDA Liaison, Dr. Sarrit Kovacs
- EMA Advisor, Dr. Maria Isaac
- NINDS Liaison, Dr. Ursula Utz
- MSOAC Co-Directors:
  - Richard Rudick, M.D., Biogen Idec
  - Nicholas G. LaRocca, Ph.D., NMSS
  - Lynn Hudson, Ph.D., C-Path
National Multiple Sclerosis Society

• Founded in 1946 by Sylvia Lawry in response to her brother’s MS
• Research budget in FY2014 $50+ Million
• Broad range of programs and services to help people with MS live their best lives
• A history of innovation:
  • Clinical trial design
  • Pediatric MS Research Network
  • Collaborative research centers
  • Progressive MS Alliance
Critical Path Institute

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.
Mission of the MSOAC

MSOAC will develop and support adoption throughout the MS community (patients, clinical investigators, pharmaceutical industry, regulatory agencies, and advocacy groups) of a clinical outcome assessment tool for future MS clinical trials.
Purpose of the New Clinical Outcomes Assessment

The purpose of this COA will be to reflect the impact of an intervention on the disability due to MS. MSOAC will obtain regulatory qualification of the COA for registration trials. Therefore, the COA must be useful for demonstrating clinical change due to MS.
Features of the New Measure

The COA will be multidimensional to reflect the principal ways MS affects an individual, use performance rather than ratings, have high reliability and validity (including importance to the patient), be sensitive to change over time to permit demonstration of a therapeutic effect, be acceptable to the patient, practical, and cost-effective.
MSOAC Project Components

1. Create CDISC Standard for MS, based initially on elements from the NINDS MS CDE project
2. Create a pooled data set from completed clinical trials containing traditional clinical outcomes (relapses and EDSS), neurological performance measures (e.g. MSFC), and patient reported outcomes
3. Analyze pooled data set to determine components of a neuro performance based composite outcome measure, and recommended approach to using the composite outcome
4. Conduct a literature review and modified Delphi process
5. Seek regulatory approval of a new MS outcome measure
Framework for Developing a COA Performance Measure for MS Clinical Trials

1. Target Population
   - People with Multiple Sclerosis

2. Concept of Interest
   - “Disability”
   - A, B, C

3. Examples of Activities of Daily Living Limited by Disability in MS
   - Walking quickly to make an appointment
   - Keeping up with conversations
   - Remembering to take medications
   - Reading a newspaper or screen
   - Using a knife and fork, writing, using a computer keyboard

4. Bodily Functions Involved in Activities of Daily Living
   - Walking
   - Higher Level Cognitive functions
   - Vision functions
   - Muscle Power functions
   - Control of Voluntary Movement

5. Sub-components of Bodily Functions
   - Speed
   - Information Processing Speed
   - Memory
   - Acuity
   - Fine Hand Use
   - Eye-Hand Coordination

6. Methods of Measurement (examine options and data)
   - T25FW
   - PASAT
   - SDMT
   - CVLT2
   - BVMTR
   - 7/24 SRT
   - LCV
   - 9-HPT

7. Generation of Overall Measurement
   - Disability measurement (score)

8. “Validation” and Interpretation
   - Meaning of scores, changes, and differences
Status of the Project

1. MS CDISC standard V1.0 completed and published
2. Completing data sharing agreements with pharma and academic investigators
3. Mapping data sets to the CDISC standard to create a pooled data set for analysis
4. Preparing a comprehensive literature review
5. Planning a modified Delphi process for input from people living with MS
6. Formulating statistical analysis plan for test and validation of datasets derived from the pooled data
CDISC User Guide for MS

Therapeutic Area Data Standards
User Guide for Multiple Sclerosis
Version 1.0

Prepared by the
Multiple Sclerosis Outcome Assessments Consortium and
the CFAST Multiple Sclerosis Development Team

#P4C2014
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PRO Instruments: MSIS-29-PHYS: MS Impact Scale - 29 items, FAMS, SF-36A, MSQLI: MS Quality of Life Inventory- 10 individual scales
MFIS - Modified Fatigue Impact Scale, EQ5D - Euro-QOL, PRIMUS - Patient Reported Indices in MS

1CT.gov refers to the ClinicalTrials.gov website, where clinical trials are registered.
What’s Innovative?

- A consortium approach
- A diverse community of stakeholders
- The development of tools for the entire community
- The development of data standards
- Utilization of shared data
- A global focus
Publications and Press

- **Multiple Sclerosis Outcome Assessments Consortium: Genesis and initial project plan**
  - Richard A. Rudick, Nicholas LaRocca, Lynn D. Hudson and MSOAC
  - *Mult Scler Journal*, published online 20 September 2013

- **The Multiple Sclerosis Outcome Assessments Consortium: Bringing the Community Together to Shape the Future of Multiple Sclerosis Drug Development**
  - Janet Woodcock and Anne M. Rowzee
  - *Therapeutic Innovation & Regulatory Science*, published online
  - 12 September 2013

- **An Expanded Role for Patients in Clinical Trial Design**
  - Anne M. Rowzee and Stephen Spielberg
  - [http://dij.sagepub.com/site/misc/index/podcasts.xhtml](http://dij.sagepub.com/site/misc/index/podcasts.xhtml)
MSOAC Collaborators

Industry Members

[Logos of various pharmaceutical companies]

Partners

[Logos of organizations like MS Society, CDISC, FDA, etc.]