Outcome Measures for Clinical Trials: Status of Task Force

ACTRIMS
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Multiple Sclerosis Outcome Assessments Consortium (MSOAC)

Timeline: New FDA-Approved MS Medications (Disease-Modifying)

Medication	Approved by FDA	
Interferon beta	1993 (Betaseron); 1996 (Avonex); 2002 (Rebif)	
Glatiramer acetate (Copaxone)	1996	
Natalizumab (Tysabri)	2004 (2006)	
Fingolimod (Gilenya)	2010	
Teriflunomide (Aubagio)	2012	
Dimethyl fumarate (Tecfidera)	2013	
Mitoxantrone (Novantrone)	2000	ONLY MEDICATION SPECIFICALLY APPROVED FOR SPMS

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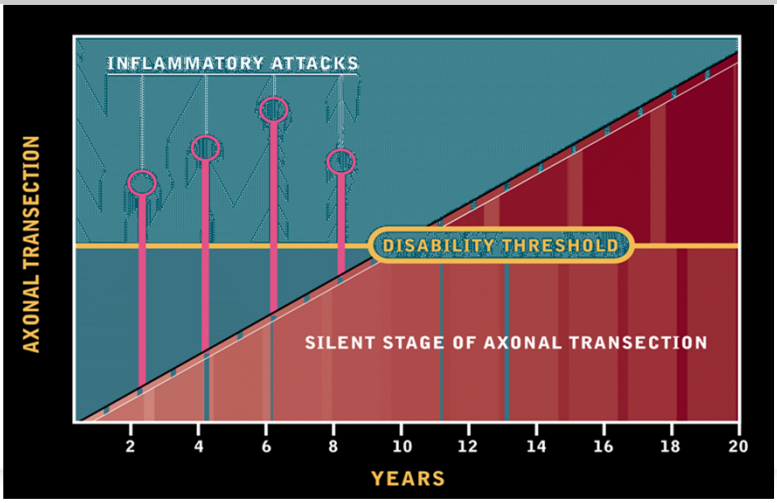
Etiopathogenesis May Differ in Relapsing vs. Progressive MS



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Current Clinical Outcome Assessments in MS Have Important Limitations

Mult Scler. 2013 May;19(6):775-81. doi: 10.1177/1352458512459685. Epub 2012 Oct 1.

View Full-Text Article at SAGE Publications

EDSS variability before randomization may limit treatment discovery in primary progressive MS.

Zhang J[1], Waubant E, Cutter G, Woli

Nat Rev Neurol. 2013 Sep;9(9):496-503. doi: 10.1038/nrneurol.2013.148. Epub 2013 Jul 30.

Treatment trials in progressive MS--current challenges and future directions.

Koch MW[1], Cutter G, Stys PK, Yong VW, Metz LM.

Author information

Abstract

The introduction of immunomodulatory treatments has transformed the management of patients with relapsing-remitting multiple sclerosis (MS), but has had no consistent benefit in progressive MS. Patients with primary or secondary progressive MS, therefore, are faced with relentless functional decline that remains without treatment. Clinical trials in progressive MS are clearly needed, but their design and conduct is challenging, and different from that of trials in relapsing remitting MS. Challenges to reliable measurement of clinical progression, uncertainties about the natural history of progressive MS, and the unclear role of imaging outcomes all impede optimal trial design. Clinical trials in progressive MS have used time to a predefined change on the Expanded Disability Status Scale as their main outcome measure, which has had important consequences for trial duration and has led to inclusion of only a highly selected minority of patients. Here, we review the current approach to clinical trial design in progressive MS, outline key ongoing challenges, and suggest strategies to overcome such hurdles.

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Anecdote: Progressive MS and EDSS

21-year-old patient with a 2-year history of progressive leg weakness and mild bladder dysfunction.

→Exam notable for left foot drop, spasticity, and bilateral lower extremity hyperreflexia; MRI, CSF consistent with MS

EDSS=2.0

Next visit…

Patient reported continued worsening

Examination revealed NO foot drop; otherwise unchanged

EDSS=1.0

- **Does this reflect a missed and then resolved relapse?**

The Reveal

The patient reported that at the previous visit, her car had broken down and she had walked 3 miles to the visit

→ Used valet parking this time

Mission of MSOAC

To develop and support adoption of a clinical outcome assessment (COA) tool for future MS clinical trials

→Designed to reflect disease progression

→ Will be adopted by the MS community (persons with MS, clinical investigators, pharmaceutical industry, regulatory agencies, and advocacy groups).

MSOAC Engages Many Stakeholders

- 43 member international organization
  - 9 pharmaceutical companies
  - 27 academic medical centers
  - 6 MS advocacy organizations
- Created and managed by C-Path with funding and input from the National MS Society (NMSS).

- FDA Liaison, Dr. Marc Walton
- EMA Advisor, Dr. Maria Isaac
- MSOAC Co-Directors:
  - Richard Rudick, M.D., Biogen Idec
  - Nicholas G. LaRocca, Ph.D., NMSS
  - Lynn Hudson, Ph.D., C-Path

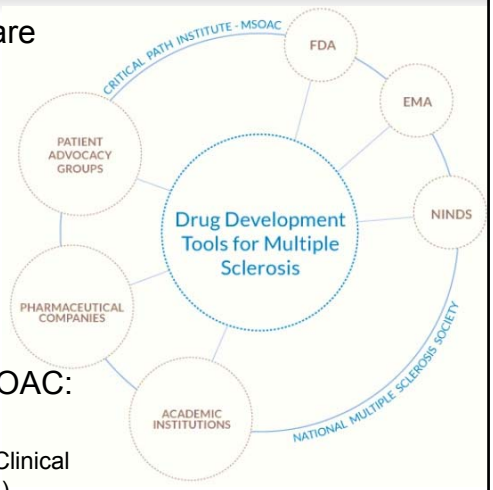
MSOAC Collaborates

6 MS advocacy organizations are MSOAC members:

- National MS Society
- AISM (Italian MS Society)
- MS Society of UK
- MS Society of Canada
- Alberta MS Research Foundation
- CMSC

Initiatives coordinated with MSOAC:

- Progressive MS Alliance
- International Advisory Committee on Clinical Trials of New Drugs in MS (IACCTMS)



Purpose of the Clinical Outcomes Assessment Tool (COA)

To reflect the impact of an intervention on disease progression as it relates to disability due to MS.

MSOAC will obtain regulatory qualification of the COA for registration trials.

→Must be useful/show clinical change caused by MS.

Criteria For Desirable COA Components

1. Multidimensional to reflect key aspects of MS
2. Measurable by clinicians
3. Be highly reliable
4. Have high validity, including importance to the patient
5. Change with time (show therapeutic effect)
6. Be acceptable to persons with MS, practical, and cost-effective

MSOAC Project Focus

- Primary outcome measure for interventions targeting the disease process (not symptom Rx)
- Selected quantitative neuroperformance measures related to functions directly affected by MS and important to persons with MS
- Measures of pain, fatigue, sexual dysfunction, depression, bowel and bladder dysfunction should be included in comprehensive outcomes assessment but are not measurable by clinicians
  -thus not intrinsic to the planned COA

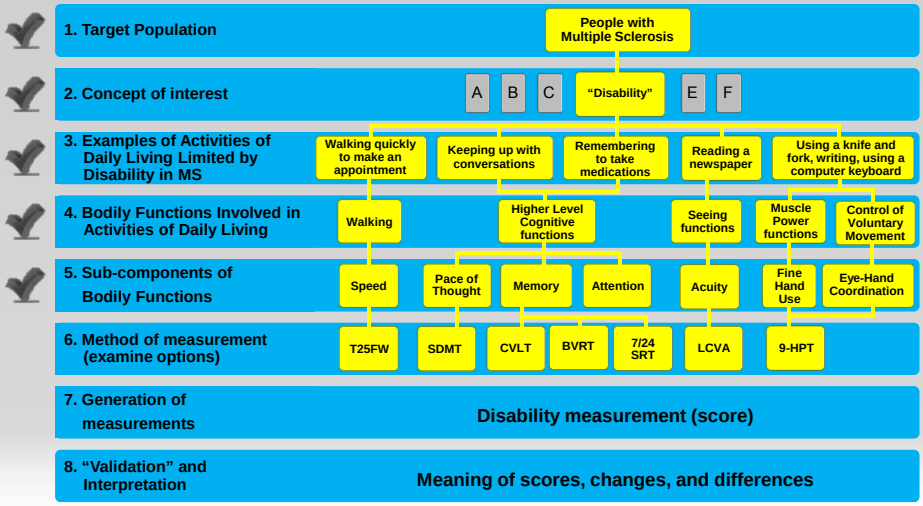
Why Do We Need This?

- Traditional measures – relapse and EDSS – are imprecise and have uncertain relationships to the underlying concept of interest
- Quantitative performance testing offers an alternative to clinician rating scales
- Quantitative neuroperformance measures have favorable psychometric properties

Concept of Interest for the COA

- MS Disability: Limitation in activities, participation, or roles, caused by MS, and considered important by the person with MS
- May include measures of walking, dexterity, vision, and cognition
- Other important problems that contribute to disability (e.g. pain, fatigue) = patient-reported outcomes (out of scope for this project)

Framework For Performance Measure for MS Clinical Trials



Multiple Sclerosis Functional Composite

Rudick, Antel, Confavreux, et al. *Annals of Neurology,* 1997

- An International NMSS Task Force recommended the quantitative neuroperformance assessment as an alternative to clinician rated outcomes
- Recommended a 3-part "Multiple Sclerosis Functional Composite"
  - Walking: *Timed 25-Foot Walk (T25FW)*
  - Manual Dexterity: *9-Hole Peg Test (9HPT)*
  - Cognitive Function: *Paced Auditory Serial Addition Test (PASAT)*
- Individual tests scores combined into a composite 'z-score'

Response to this Recommendation

> 30 clinical trials and countless clinical studies incorporated the MSFC or its components; >15 years worth of prospectively collected MSFC data

A large collection of datasets containing MSFC, and other outcomes (EDSS, QoL, MRI, relapses, etc.).
These data have not been fully analyzed

MSOAC Project

1. Create Clinical Data Interchange Standards Consortium (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 neuroperformance-based composite outcome measure and recommended approach to using it.
4. Seek regulatory approval of a new MS outcome measure.

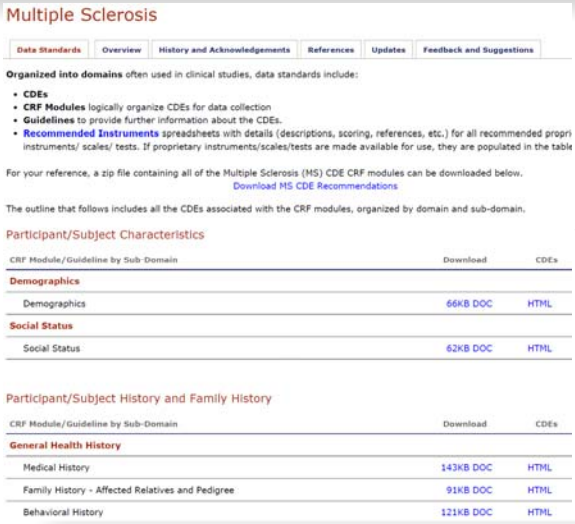
Spotlight On: Data Standards and Integration Activities

Evaluate the NINDS Common Data Elements to select those that will be informative for this project

Determine if other CROs or PROs should (and can) be added (DSI and CDA workgroups)

The elements chosen will form the “MS CDISC Standard”

NINDS Common Data Elements


Multiple Sclerosis

Data Standards | Overview | History and Acknowledgements | References | Updates | Feedback and Suggestions

Organized into domains often used in clinical studies, data standards include:

- **CDEs**
- **CRF Modules** logically organize CDEs for data collection
- **Guidelines** to provide further information about the CDEs.
- **Recommended Instruments** spreadsheets with details (descriptions, scoring, references, etc.) for all recommended proprietary instruments/ scales/ tests. If proprietary instruments/scales/tests are made available for use, they are populated in the table

For your reference, a zip file containing all of the Multiple Sclerosis (MS) CDE CRF modules can be downloaded below.
Download MS CDE Recommendations

The outline that follows includes all the CDEs associated with the CRF modules, organized by domain and sub-domain.

Participant/Subject Characteristics

CRF Module/Guideline by Sub-Domain	Download	CDEs
Demographics		
Demographics	66KB DOC	HTML
Social Status		
Social Status	62KB DOC	HTML

Participant/Subject History and Family History

CRF Module/Guideline by Sub-Domain	Download	CDEs
General Health History		
Medical History	143KB DOC	HTML
Family History - Affected Relatives and Pedigree	91KB DOC	HTML
Behavioral History	121KB DOC	HTML

Main Headings

Demographics
Social Status
General Health History
Relapse History
MS Type
Neurologic Exam Findings
Vital Signs
Lab Test Results
Genetics
MRI
OCT
Neurophysiology (e.g. EPs)
Activities of Daily Living scales
Neuropsychology
Performance Measures
Quality of Life scales

National Multiple Sclerosis Society

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Which Elements Needed…

→To ensure success of MSOAC project (CDISC 1.0)

→To ensure any future prospective studies will contain assessment tools of interest (CDISC 2.0)

Caveats (for MSOAC COA Development):

→Most datasets contain some of the measures

→Must be mindful of burden each additional data element request puts on data owners

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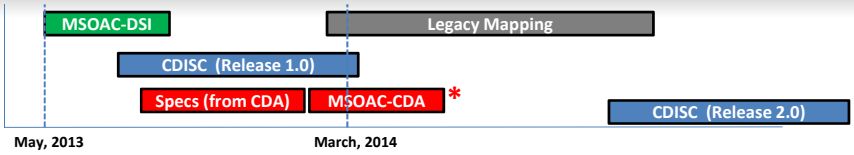
Development of CDISC Standard for MS

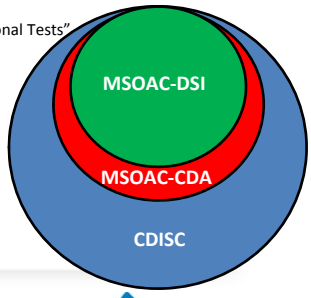


* Delivery date for MSOAC-CDA is contingent on specifications from CDA Workgroup

"MSOAC-DSI" = standard to map MS legacy data (e.g. EDSS, 25FW, 9HPT, PASAT, and DSI additions from 102 NINDS Common Data Elements)

"MSOAC-CDA" = standard to map MS legacy data (includes all "Other Functional Tests" potentially identified by CDA WG)

"CDISC" = the CDISC standard for future clinical trials (may include selected imaging standards)



DSI Deliverables:

1a – MSOAC-DSI & MSOAC-CDA

1b – CDISC

2 – Mapping of all selected legacy datasets / CDEs

CDISC SDTM MS Therapeutic Area User Guide v 1.0

Content Covered by the New Standard

- 23 performance outcome (PerfO) measures, patient-reported outcome (PRO) measures, and clinician-reported outcome (ClinRO) measures
- Medical history and MS disease course
  - Diagnostic criteria
  - Relapse criteria
  - Symptoms
  - Localization of onset
- Visual acuity/contrast sensitivity
- Optical coherence tomography
- Visual evoked potential

Data Acquisition Status

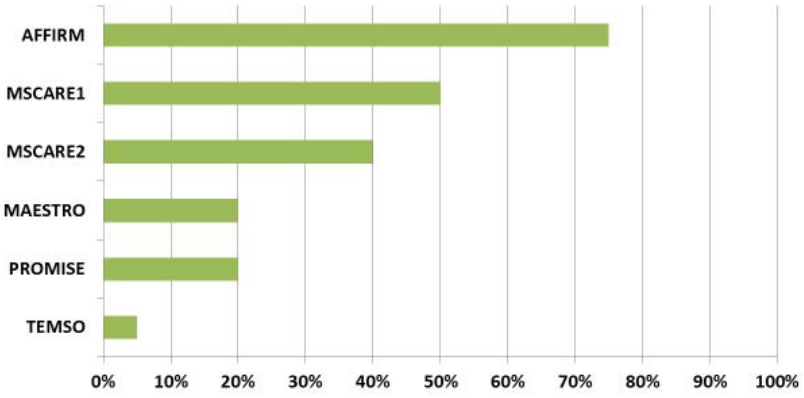
April 30, 2014

Study	Year	n	Type	CT.gov #	EDSS	FSS	25FW	9HPT	PASAT	LCVA	SDMT	Image	PROs
Dose Comparison		802	RRMS	N/A	√	√	?	√	√	?	No	?	?
ACT		313	RRMS	NCT00112034	√	√	√	√	√	?	No	?	?
DEFINE		1237	RRMS	NCT00420212	√	√	√	√	√	√	No	?	√
CONFIRM		1232	RRMS	NCT00451451	√	√	√	√	√	√	No	?	√
MSCRG		301	RRMS	N/A	√	√	√	√	√	?	No	?	√
AFFIRM		942	RRMS	NCT00027300	√	√	√	√	√	√	No	√	√
SENTINEL		1171	RRMS	NCT00030966	√	√	√	√	√	√	No	?	√
CHOICE		230	RRMS	NCT00109161	√	√	√	√	√	?	?	?	?
CombiRx		1008	RRMS	NCT00211887	√	√	√	√	√	√	No	√	√
FREEDOMS		1272	RRMS	NCT00289978	√	√	√	√	√	No	No	?	EQ5D,MFIS,Primus
FREEDOMS 2		1083	RRMS	NCT00355134	√	√	√	√	√	√	No	?	EQ5D,MFIS,Primus
TRANSFORMS		1153	RRMS	NCT00340834	√	√	√	√	√	No	No	?	EQ5D,MFIS,Primus
CARE-MS 1		581	RRMS	NCT00530348	√	√	√	√	√	√	No	No	FAMS, SF-36
CARE-MS 2		840	RRMS	NCT00548405	√	√	√	√	√	√	No	No	FAMS, SF-36
TEMSO		1088	RRMS	NCT00134563	√	√	√	√	√	No	No	No	SF-36
IMPACT		436	SPMS	N/A	√	√	√	√	√	√	No	?	√
MAESTRO		596	SPMS	NCT00869726	√	√	√	√	√	No	No	√	√
Olympus		439	PPMS	NCT00087529	√	√	√	√	√	?	?	?	?
PROMISE		943	PPMS	N/A	√	√	√	√	√	No	No	√	MSQLI
Azathioprine		98	PP/SP	N/A	√	√	No	No	No	No	√	No	No
MS Study Group		547	PP/SP	N/A	√	No	No	No	No	No	QENF	MRD, AI	No
Total = 21		**16312**						= In Process				= Received	

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

Data Mapping Progress*

(as of April, 2014)



*Percent complete based on progress on demographics, relapse, EDSS/FSS, LCVA, 9HPT, 25FW, and PASAT. Does not include imaging nor medications data

Current Status

1. MS CDISC data standard V1.0 completed.
2. Data sharing agreements have yielded over 5,000 individual patient records at C-Path to date, with another 11,000 in process.
3. Mapping data sets to the CDISC standard to create a pooled data set for analysis.
4. Preparing a comprehensive literature review to incorporate the voice of persons with MS.
5. Formulating a statistical analysis plan to reliably and sensitively capture composite measures.

MSOAC "Deliverables" and Implications

1. CDISC data standard for MS: Will improve ability to compare data across studies, to interpret findings, and to analyze pooled datasets.
2. A database of pooled, de-identified clinical trial data mapped to the CDISC standard: Will allow studies of clinical outcomes assessment tools, disease modeling, and potentially imaging or biomarker studies.
3. A new methodology to measure performance: Could provide approved disability endpoint in future MS clinical trials.
4. Use of the EMA and FDA outcome measure qualification pathways: Will provide an example for other groups interested in pursuing better outcome measures through regulatory sciences

MSOAC 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

- **CDISC Therapeutic Area Data Standards User Guide for Multiple Sclerosis Version 1.0**, in press 2014.

MSOAC Collaborators

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Industry Members

abbvie · EMD Serono · gsk GlaxoSmithKline · ACORDA THERAPEUTICS · Genentech A Member of the Roche Group · NOVARTIS · biogen idec · genzyme · TEVA

Partners

National Multiple Sclerosis Society · CDISC · European Medicines Agency Science Medicines Health · FDA · NIH National Institute of Neurological Disorders and Stroke

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Thank You