Multiple Sclerosis Outcome Assessments Consortium: Genesis and initial project plan

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Meeting Review

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Abstract

The need for improved clinical outcome measures in multiple sclerosis trials has been recognized for two decades, but only recently has the Food and Drug Administration (FDA) created a pathway for qualification of new clinician-reported outcome (ClinRO) assessments. Additionally, drug development in multiple sclerosis (MS) has been extraordinarily active, with numerous disease-modifying drugs now on the market. This shifting therapeutic landscape, along with the unmet need for drugs to treat the progressive forms of MS and the changing expectations of clinicians, patients, and payers, have led to the call for more sensitive and meaningful disability progression measures. In response to these drivers, the Multiple Sclerosis Outcome Assessments Consortium (MSOAC) was launched. A public-private partnership, MSOAC aims to accelerate the development of new therapies for MS by generating new tools for measuring outcomes in clinical trials. At the first annual MSOAC/FDA meeting, a regulatory path was outlined for qualifying a new tool for assessing efficacy in registration trials of MS. The European Medicines Agency (EMA) and FDA will provide parallel consultation and review. The consensus approach with engagement by all of the stakeholders, prominently including patients with MS, should also increase acceptance of the measure by clinicians and patients.

Keywords

Outcome assessments, progressive mutiple sclerosis, disability, regulatory science

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Introduction

The neurologic impairments and clinical manifestations of multiple sclerosis (MS) vary considerably across patients and over time, making assessment of disease status inherently difficult to quantify.[1] Limitations in some of the widely used disability measures, such as the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC), spurred interest in analyzing extant clinical trial data to identify improved measures of treatment effects.[2,3] Food and Drug Administration (FDA)'s Center for Drug Evaluation and Research (CDER) created a formal process through which analysis of such outcome data can produce a qualified drug development tool (DDT) to improve the efficiency and effectiveness of clinical trials.[4,5] Key to the successful development of DDTs is public-private collaboration. Critical Path Institute (C-Path) orchestrates seven consortia in which stakeholders share resources and expertise to research specific questions in drug development and arrive at a consensus.[6] The products of this collaborative research in the pre-competitive space include a number of tools, methods, databases, and data standards, all of which have the potential to accelerate drug development.

The Multiple Sclerosis Outcome Assessments Consortium (MSOAC), operating under the aegis of C-Path with support from the National Multiple Sclerosis Society (NMSS), is a coalition that includes representatives from industry, academia, regulatory agencies, advocacy groups, and persons with MS (Figure 1). MSOAC was established in 2012 to accelerate development of new therapies for MS through the development of new tools for measuring outcomes in clinical trials. The overarching goal of MSOAC is to develop a sensitive, clinically meaningful, and reliable

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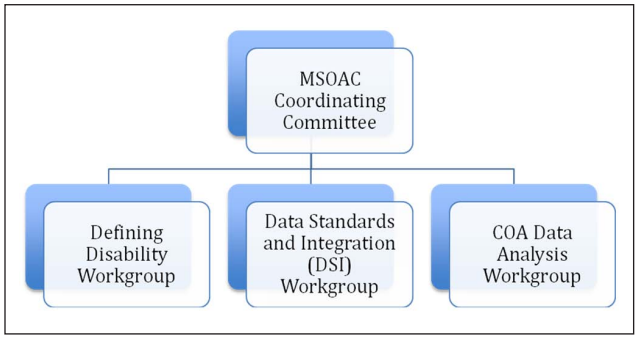

Figure 1. Multiple Sclerosis Outcome Assessments Consortium (MSOAC) governance and membership.
MSOAC operates through a governing body (the Coordinating Committee) and three workgroups. Member companies include: AbbVie, Acorda, Biogen Idec, Bristol-Myers Squibb, EMD Serono, Genzyme/Sanofi, GlaxoSmithKline, Novartis, Roche/Genentech, and Teva. Some academic members are engaged in other ongoing activities in the multiple sclerosis (MS) arena and serve as liaisons to these organizations: the International Progressive MS Collaborative (IPMSC), International Advisory Committee on MS Clinical Trials, European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS), and the Consortium of MS Centers (CMSC). Apart from the NMSS, other patient societies and foundations include Fast Forward, the Alberta MS Research Foundation, MS Society (UK), MS Society of Canada, and the AISM (Italian MS Society). People living with MS also have a voice on the Coordinating Committee. Finally, the Food and Drug Administration (FDA) and European Medicines Agency (EMA) advisors to MSOAC serve an integral role in the iterative exchange of scientific information and analysis between the regulators and the Consortium. For a complete list of MSOAC members, refer to http://www.c-path.org/MSOAC.cfm.

clinician-reported outcome (ClinRO) measure that can be qualified by the regulatory agencies for use as a primary endpoint in clinical trials aiming to reduce, stop, or reverse MS disability progression. In the process of generating this tool, several other resources will be created for the benefit of the MS research community. The first is a data standard for MS, which will be developed in collaboration with the standards setting organization Clinical Data Interchange Standards Consortium (CDISC). Second is a database of MS trials in which the legacy data is remapped to the CDISC standard so that studies can be pooled for analysis and submission to the FDA and European Medicines Agency (EMA) in partial support of new measure qualification. It is anticipated that a portion of this aggregated data, particularly the placebo arms of clinical trials, will be made available to qualified researchers.

MSOAC held its first annual workshop with the US FDA and the EMA on 1–2 April 2013, in Silver Spring, Maryland. The purpose of this report is to describe the highlights from the first meeting and summarize the MSOAC plan.

Qualifying a new ClinRO measure

Janet Woodcock (FDA) launched the meeting by reinforcing the value of an accepted composite measure to stimulate drug development in MS, eliminate second-guessing during the development and review process, and provide more information than single domain endpoints. The consortium process of creating consensus with a range of experts and patients increases the value and acceptance of a new outcome measure. Moreover, the FDA welcomes community input in developing the evidentiary standards for new endpoints as well as contributing to drafting guidance on the conduct of trials.

Qualification of a ClinRO measure requires evidence supporting the use of the measure to assess a specific concept of interest for a specific context of use (COU). An example of a concept of interest is performance of vision-dependent activities during a normal day; the meaningful functions of interest that would map to that concept include reading a magazine or computer screen, driving a car, or using a smartphone. Marc Walton, the FDA liaison to MSOAC, emphasized that an outcome measure used as an endpoint in a clinical trial must enable the assessment of treatment benefits; in other words, how does the treatment impact the way a patient feels, functions or survives? He noted that the COU must include the full set of parameters that describe: (a) the disease definition and patient population; (b) how to measure the concept(s) of interest; (c) when to measure; (d) how to analyze measurements; (e) how to interpret measurements. He also pointed out that multicomponent measures may help to ensure that in a complex disease, the desired clinical impact is measured, because such measures are sensitive to several facets of patient function and may be additive within a single patient and/or applicable to patients with different symptom patterns.

Establishing what is meant by "clinically meaningful" and how to assess treatment benefit are key requirements for a ClinRO measure. An outcome that is statistically significant may not be clinically meaningful, namely the outcome may not affect the way a patient feels or functions. This is of particular concern with neuropsychological tests, which may have psychometric validity but no associated patient-perceived benefit, or for composite (multivariate) measures.[7] Nonetheless, some measures that have been widely used in clinical trials, such as the Timed 25-Foot Walk (T25FW), have been shown to be clinically meaningful.[8]

Operating under a memorandum of understanding, the FDA and EMA are working to harmonize their ClinRO qualification programs so that only one set of documents need be created. The EMA advisor for MSOAC, Maria Isaac, and the head of FDA's Study Endpoints and Labeling Development (SEALD) team, Laurie Burke, will provide parallel advice and consultation to MSOAC. Using clinical trial data, the measure will be evaluated in terms of content validity, construct validity, reliability (particularly test-retest reliability), and sensitivity to change.

Defining disability and identifying measures

In keeping with the guidelines described by speakers from the FDA, MSOAC will begin by developing the COU for the new disability measure. When selecting or constructing a disability measure, a clear definition of disability is

needed so that scores on the instrument can be mapped back to this definition. This definition should encompass the different components of disability intended for inclusion (e.g. ambulation, upper extremity function, cognition, visual function), and these components will inform the selection of the measurement methods, which may include multiple measures to assess different aspects of a single component. For example, there are many aspects of ambulation that can be assessed through different measures, although not all of these aspects and measures may be important to the particular COU. MSOAC's Defining Disability Workgroup will define the construct of MS disability and identify hypothesized important components of that construct. As discussed at the 1–2 April meeting, it is not necessary to include measures for each and every component of disability in MS, and there may be aspects of MS that contribute to disability (e.g. fatigue), which are inherently subjective and not subject to clinical quantification.

Gathering the data necessary to support a qualification submission

Once the individual components of a disability measure have been identified, the next step will be to leverage existing datasets to see how well a composite performs as a disability measure in longitudinal studies. A wealth of legacy data from MS clinical trials exists and these studies include a wide range of functional measures (Table 1). In aggregate, over 20,000 patients have participated in these trials, which provide longitudinal data on a range of measures: the MSFC, EDSS, Low-Contrast Letter Acuity (LCLA) tests that capture visual impairments[9,10], the Rao adaptation[11] of the Symbol Digit Modalities Test (SDMT)[3] that assesses cognitive dysfunction, and other measures. Importantly, many studies have a patient-reported outcome component that will enable MSOAC to potentially determine clinical meaningfulness of the measures. MSOAC's clinical outcomes assessment (COA) Data Analysis Workgroup will develop criteria for selecting data sets and specific functional measures appropriate for the COU. These individual functional measures could be combined into a composite score, or subjected to statistical analysis based on direct use of multiple outcome measures.

Each of the studies in Table 1 included the EDSS and the Fatigue Severity Scale (FSS). While the EDSS is the most widely used clinical disability measure of MS clinical trials, a number of other tools have been used as outcome measures in various trials, including the MS Severity Score (NMSS),[12] which is the EDSS plus disease duration to establish a percentile for disease severity using a reference population; the MSFC, the FSS;[13] the SDMT;[6] and the Scripps Neurological Rating Scale (SNRS).[14] Patient-reported outcome (PRO) measures have also been used, including the Medical Outcome Study Short Form-36 (SF-36)[15] and Functional Independence Measure (FIM),[16] and the Guy's Neurological Disability Scale (GNDS),[17] which is a mixture of PRO and ClinRO measures. None of these outcome measures cover all domains nor fully capture the experience of living with MS, which includes the burden imposed by fatigue and impairments in vision, gait and balance, cognition, and mood.

The COA Data Analysis workgroup will design and execute the statistical analysis, with a full understanding of the meaning of scores, score changes, and differences, to ensure the end result of a meaningful measure that has content validity and represents a definable concept. The behavior of this new measure will need to be related not only to patient self-reports, but to other more traditional outcome measures such as relapse rate and the EDSS.

Recognizing the complexities

While the qualification process for ClinRO assessments has been outlined, evidentiary standards for adoption of a ClinRO assessment are not well defined. An absolute requirement for a new ClinRO assessment is that the outcome be clinically meaningful. Certain aspects of MS are known to be important to patients, but are more effectively assessed via direct patient self-report than with a ClinRO measure. Examples include pain, fatigue, bladder, bowel, or sexual dysfunction. Of note is the willingness of the FDA to consider "mixed" composite measures in which both patient–reported and clinician-reported measures are combined; while not presently within the scope of MSOAC, such mixed PRO/ClinRO measures may be developed in the future. At the workshop, Consortium members grappled with how one could determine that a change in a ClinRO is clinically meaningful, how one would determine the level of evidence needed to achieve qualification by regulatory agencies, and where that evidence will come from. An important example of this concern relates to neuropsychological testing. Demonstrating that cognitive test results are meaningful is challenging, because by nature of the deficits, patients may be unaware of or misinterpret the deficits.

It was pointed out by numerous meeting participants that no single outcome measure would suffice to serve all purposes and all populations. For example, while children with MS represent a small fraction of the MS population, they manifest somewhat different clinical and imaging characteristics.[11] Because the highest unmet need in drug development is for progressive forms of MS, the MSOAC members rallied behind developing a ClinRO measure applicable to progressive MS. Some meeting participants noted that disability progression occurs during the relapsing stage of MS, but manifestations may be much more subtle than in later stages of the disease. Thus, the precise application of a new ClinRO may differ in early versus late stages of MS.

Another complexity is the ever-changing measurement sciences field. Data to be evaluated through the MSOAC is by definition "old data" collected in the past. This initial approach is necessary, because qualification of an outcome

Table 1. Data sets from randomized controlled trials in relapsing–remitting multiple sclerosis (RRMS) and primary progressive MS (PPMS) and secondary progressive MS (SPMS).

MS study	Number of Subjects	Drug	Sponsors	MS type	NCT Number	Reference
Dose comparison	802	IFNß-1a	Biogen Idec	RRMS	N/A	18
ACT	313	IFNß-1a+MP+MTX	Biogen Idec	RRMS	NCT00112034	19
DEFINE	1237	BG-12	Biogen Idec	RRMS	NCT00420212	20
CONFIRM	1232	BG-12	Biogen Idec	RRMS	NCT00451451	21
MSCRG	301	IFNß-1a	Biogen Idec	RRMS	N/A	22
AFFIRM	942	Natalizumab	Biogen Idec / Elan	RRMS	NCT00027300	23
SENTINEL	1171	Natalizumab	Biogen Idec / Elan	RRMS	NCT00030966	24
CombiRx	1008	IFN+GA	NIH / Lublin	RRMS	NCT00211887	25
FREEDOMS	1272	Fingolimod	Novartis	RRMS	NCT00289978	26
FREEDOMS 2	1083	Fingolimod	Novartis	RRMS	NCT00355134	NYP
TRANSFORMS	1153	Fingolimod	Novartis	RRMS	NCT00340834	27
CHOICE	230	Daclizumab+IFNb-1a	PDL Biopharma	RRMS	NCT00109161	28
CARE-MS 1	581	Alemtuzumab	Sanofi Genzyme	RRMS	NCT00530348	29
CARE-MS 2	840	Alemtuzumab	Sanofi Genzyme	RRMS	NCT00548405	30
TEMSO	1088	Teriflunomide	Sanofi Genzyme	RRMS	NCT00134563	31
BRAVO	1331	Laquinimod	Teva	RRMS	NCT00605215	NYP
ALLEGRO	1106	Laquinimod	Teva	RRMS	NCT00509145	32
IMPACT	436	IFNß-1a	Biogen Idec	SPMS	N/A	33
MAESTRO	596	Dirucotide (MBP8298)	Eli Lilly	SPMS	NCT00869726	34
Betaseron PPMS	63	IFNß-1b Open Label	Investigator	PPMS	N/A	35
Olympus	439	Rituximab	Roche/Genentech	PPMS	NCT00087529	36
PROMISE	943	GA	Teva	PPMS	N/A	37
CUPID	493	Dronabinol	MRC, MS Society of Great Britain, MS Trust	PPMS, SPMS	N/A[a]	38
Fampridine-SR	240	Fampridine-SR	Acorda	All	NCT00483652	39

[a]ISRCTN62942668. EudraCT 2005-002728-33. GA: glatiramer acetate; IFN: interferon; NYP: not yet published MP = methylprednisolone; MTX = methotrexate.

measure requires evidence provided by data analysis. As newer measures are developed, prospective testing will require time and resources. In the meantime, there may be sufficient data in aggregate to support a much improved disability measure that could be used in the near-term. One suggestion was to take a two-staged approach. The first stage would be to analyze available clinical trial data to develop and qualify an improved ClinRO measure. The second stage would focus on longer-term opportunities, which would include prospective studies on neuropsychological measures or other clinically meaningful measures that are not adequately represented in existing data sets. There may also be an opportunity to incorporate ongoing studies into the project, adding data to the pooled database as it becomes available, to partially address the need for more contemporaneous data.

Crystallizing the regulatory path forward

Although there are currently 10 disease-modifying drugs (DMDs) for MS on the market, significant unmet needs remain. In particular, none of the DMDs have been observed to entirely stop disease progression, and there are no drugs approved specifically for MS disability progression not mediated by brain inflammation and relapses. This first annual meeting of MSOAC initiated the consultation process that will enable development of a qualified tool for assessing progression of disability in registration trials.

The benefits of MSOAC's collaborative approach are multifaceted:

- Establishing a mechanism for the various participants in the MS drug development enterprise (i.e. industry, academia, and government) to engage with patients and patient advocates to work collaboratively toward better tools to accelerate drug development in MS. The mechanism established in this initial project could be used for future collaborative projects with a slightly different focus – development of MS PRO measures, biomarkers, or imaging studies, or generating a MS disease progression model.
- Generating a data standard for MS, starting with the National Institute of Neurological Disorders and

Stroke (NINDS) Common Data Elements that have already been developed for MS. Such a standard would improve definitions, facilitate communication across studies, allow pooling of data, and contribute to the need for standardization in clinical practice.

- Developing a mechanism for data sharing, and analysis of data already collected but largely unanalyzed. This approach is viewed as highly cost-efficient, since data already collected for a primary use (drug registration) could be used for secondary purposes (developing an improved ClinRO measure).
- Establishing a pathway for qualifying better outcome measures for use in future MS clinical trials.
- Contributing to international harmonization of methods and standards, which could improve the efficiencies of world-wide drug development for MS.
- Ensuring that those aspects of disability that are of most importance to patients and families are taken into consideration.

Achieving consensus and qualification of a new ClinRO measure should stimulate development of new therapies for MS. Clinicians and researchers may also apply the improved ClinRO measure for a wide variety of purposes, ranging from clinical monitoring to pathogenesis research.

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Conflicts of interest

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