Clinical Outcome Assessments (COA) Qualification Program
DDT COA #000053: Symbol Digit Modalities Test
Qualification Plan

Section 1: Proposed COA Qualification

1.1 Introduction and Overview

Description of the Disease

Multiple Sclerosis (MS) is a chronic disorder characterized by central nervous system (CNS) inflammation with associated damage to neurons, axons, and myelin. According to an international consensus panel, the diagnosis of MS is based on typical clinical manifestations supplemented by magnetic resonance imaging (MRI) findings in an individual without an alternative diagnosis explaining the illness. Three common subtypes of MS, based on disease course, have been described by the MS Phenotype Group under the auspices of the International Advisory Committee on Clinical Trials in MS (supported by the European Committee for Treatment and Research in Multiple Sclerosis [ECTRIMS] and the National Multiple Sclerosis Society [NMSS] (Lublin et al., 2014), These subtypes are relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS). Most people begin with an RRMS course, which is characterized by new or worsening neurological symptoms, lasting days to weeks (relapse), followed by full or partial recovery (remission), followed by subsequent relapses occurring unpredictably over the ensuing years. Relapses are separated by periods of neurologic stability. Over time, people with RRMS may evolve to a SPMS course, characterized by continued, gradual worsening of disability with or without superimposed relapses. As noted by the MS Phenotype Group, "In most clinical contexts, SPMS is diagnosed retrospectively by a history of gradual worsening after an initial relapsing disease course, with or without acute exacerbations during the progressive course" (Lublin et al., 2014). SPMS can be classified as active (with or without progression) or not active (with or without progression), in which activity is determined by clinical relapses assessed at least annually and/or MRI activity (contrast-enhancing lesions; new and unequivocally enlarging T2 lesions) (Lublin et al., 2014). The distinction between RRMS and the active form of SPMS can be unclear, because of this continuum of early stage and later stage MS. There are many patients who could be categorized as having either form of the disease for long periods of time. In addition, irrespective of the patient's subtype classification, he/she may accumulate disabilities in the cognition domain that this COA instrument will measure throughout the disease continuum. The FDA has recently acknowledged this overlap of RRMS and SPMS in the product labeling of MS drugs used for the treatment of relapsing forms of MS. The "Indication and Usage" section of several drugs previously approved for treatment of RRMS now include "active SPMS". The new labeling reads "…*indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.*" Labels with this indication include both the recent initial approval for Mayzent® in March 2019, and revised product labeling in July and August 2019 for MS drugs previously approved for RRMS such as Avonex®, Tecfidera®, Plegridy®, Tysabri®, and Gilenya®. Ocrevus®, previously approved for both RRMS and PPMS, also had "active SPMS" added to the prescribing information in July 2019.

People with MS in whom disability progresses from the onset of disease are diagnosed with PPMS. The biological differences between SPMS and PPMS, if any, are a matter of debate in the scientific community. An additional subtype of MS was included in earlier clinical course definitions: progressive relapsing MS (PRMS) (Lublin et al., 1996). People with MS displaying gradual progression from onset

with subsequent superimposed relapses were considered to have PRMS. This subtype was eliminated by the MS Phenotype Group (Lublin et al., 2014), because subjects categorized in the past as PRMS would now be classified as PPMS with relapses as evidence for disease activity.

Limitations of Existing Assessments

This COA instrument that the Multiple Sclerosis Outcome Assessments Consortium (MSOAC) is proposing for qualification is intended to reflect the impact of an intervention on disease worsening as it relates to cognitive disability due to MS in both the RR and active SP stages of the disease. Inclusion of a cognitive COA instrument is considered critical for future MS clinical trials, because cognitive impairment is well established as an important contributor to overall impact of MS on the individual, and it has not been adequately assessed in most prior registration trials. Both drug developers and the FDA recognize this as a critical unmet need in disability assessment for MS clinical trials. Historically, the Kurtzke Expanded Disability Status Scale (EDSS) has been the most frequently used clinician-assessed measure of neurologic impairment/disability in MS clinical trials. The EDSS has a number of well recognized limitations (Cohen, et al., 2012; *in* Willoughby et al., 1988). It is based on the standard neurological examination, which is inherently subjective and imprecise. It is inadequate to capture specific MS-related visual dysfunction and cognitive impairment. In addition, cognitive decline occurs in some individuals in the absence of worsening physical or visual disability.

Rationale for Choice of the Cognition Performance Measure Selected by MSOAC

While there are several domains of cognition (e.g. memory, executive function), information processing speed is the cognition subdomain that is the focus of this COA measure qualification. Processing speed is a basic, elemental cognitive function, and deficits in information processing speed result in limitation in activities, participation, or roles, which are understood to be important by persons with MS. Cognitive impairment, and specifically deficient information processing speed, is a common, often early manifestation of MS. Cognitive impairment has an established negative impact on how persons with MS feel, function, or participate in their societal and family roles.

Processing speed has been most commonly measured using the Symbol Digit Modalities Test (SDMT) or the Paced Auditory Serial Addition Test (PASAT), two well-established cognitive Performance Outcome (PerfO) measures used in the MS field. MSOAC seeks qualification of the SDMT, based upon advantages over the PASAT (Kalb et al., 2018 ; Sumowski et al., 2018. However, analyses of PASAT data will also be carried out with the MSOAC database, including trials in which the SDMT was not administered, to further support the importance of information processing speed in MS patients and to compare the performance of the two measures. The SDMT has been demonstrated to be a sensitive measure of cognition in all forms of MS, as the following evidence from the literature indicates:

1. Cognitive performance of patients with RRMS, SPMS, and PPMS compared to healthy controls was evaluated using a wide variety of tests (Huijbregts et al., 2004). Patients with all forms of MS performed significantly worse on the SDMT than controls. The mean scores for the SDMT were as follows: Healthy Controls = 60.2; RRMS = 54.3; SPMS = 45.1; PPMS = 47.8. A 4-point difference in the SDMT is generally considered to be clinically meaningful.

2. A meta-analysis of studies looking at cognitive performance in MS patients (N=1,845) compared to healthy controls (N=1,265) showed that the SDMT was the most sensitive measure discriminating healthy controls from patients with both RRMS and chronic progressive MS (CPMS) (Zakzanis, 2000). Out of several dozen test scores examined, the SDMT had the second largest effect size (-1.36) for both types of MS, second only to the Selective Reminding Test Delayed recall score.

3. A wide range of assessments were utilized to assess 1,040 patients including those with a diagnosis of clinically isolated syndrome (CIS), RRMS, PPMS, and SPMS (Ruano et al., 2017) Patients in all categories exhibited cognitive impairment ranging from 31.4% for CIS to 91.3% for PPMS. Information processing speed (incorporating the SDMT among other measures) was the most frequently affected cognitive domain with 47.9% affected.

4. Cognitive dysfunction as measured using the SDMT occurs in all types of MS, all durations, and all severities of physical disability. It has been utilized and studied in a wide variety of MS populations and cultures (Sumowski et al., 2018). Moreover, *it has been shown to be related to a variety of disease markers* including central atrophy (Benedict, et al., 2004b; Christodoulou et al., 2003; Cocozza et al., 2017) and gray matter volume (Sanfilipo et al., 2006) in progressive and relapsing remitting MS. Of all cognitive tests that have been studied in MS, the SDMT has been shown to have the most robust relationship to important life activities such as employment and daily activities (Benedict et al., 2017).

5. The degree to which Quality of Life (QoL) correlated with cognitive function as assessed using SDMT, PASAT, and the Trail Making Test-Part B in patients with PPMS and SPMS, revealed that SDMT had the highest correlation with the SF36 (Hojsgaard et al., 2018).

SDMT reflects the similarities and commonalities of all MS types, in keeping with the recommendations of two international expert groups) (Kalb et al., 2018 ; Sumowski et al., 2018,). This type of evidence is reinforced and continues to emerge in other recent clinical trials in which SDMT was found to be sensitive to treatment effects in both RRMS and in secondary progressive MS. Kappos and colleagues recently published results from a trial of siponimod in SPMS. In a double-blind, placebo-controlled RCT study siponimod reduced EDSS disability progression in SPMS by 21% (Kappos et al., 2018). Using data from the same EXPAND study in a post-hoc analysis, Benedict reported a 21% reduction in the probability of > 4 point worsening on SDMT ($p = 0.015$)) (Benedict et al., 2018). This suggests that the treatment effect of siponimod for cognitive worsening is of similar magnitude to EDSS worsening in progressive MS, and supports use of SDMT in progressive forms of MS. Finally, 4-point change in SDMT following treatment with ocrelizumab was documented in RRMS patients (Cohan, 2003).

A plan for a literature review was developed to assess published evidence on the significance of the cognition domain, particularly processing speed, for people living with MS, the ways in which the cognition domain can be measured, the psychometric properties of extant measures of cognition, particularly the SDMT, how changes on the SDMT measure are related to daily activities, and the suitability of such a measure as a clinical trial outcome measure.

Data from 14 MS clinical trials conducted from 1996 to 2014, which include approximately 12,766 individual patient records, have been obtained by MSOAC for analysis of performance measures that correspond to the major aspects of function affected by MS, and which are thought to relate closely to the underlying pathological process of MS. MSOAC used the recently created Clinical Data Interchange Standards Consortium (CDISC) therapeutic area data standard for MS (*http://www.cdisc.org/therapeutic#MS*) to remap data from these MS clinical trials. The standardized data were pooled for statistical analysis. Both the selection of MS dimensions and measures, and the design of statistical models have been guided by expert opinion. The statistical analysis plan includes approaches to analyzing patient-reported data from both these pooled trials and other clinical studies to define the extent of change on any derived performance measure that is meaningful to people with MS. The design of the entire process is data driven and leverages the wealth of the 12,766 individual patient records from clinical trials as well as a thorough review and synthesis of the published literature.

In summary, the goal of this qualification plan is to provide details on the approach to acquire evidence to support the SDMT PerfO measure as a qualified COA instrument to the MS field that measures an aspect of cognition, i.e. information processing speed, which is associated with limitations that are caused by MS in activities, participation, or roles and considered important by persons with MS.

Rationale for Use in Drug Development:
MSOAC considers that the qualification of the SDMT as the most informative COA instrument for cognition will enable sponsors to test potential disease-modifying interventions and accelerate the pace of clinical research for MS, particularly for persons with MS who have a progressive disease course. As a qualified COA instrument for cognition, the SDMT could be used as a primary outcome measure in clinical trials, potentially in conjunction with a range of other performance measures as well as other secondary outcome measures, such as relapse assessment, PRO measures including measures of QoL, or imaging measures. Its use will inform stakeholders, for the first time, about the impact of symptomatic or disease-modifying intervention on cognition. This will address a major unmet need for drug development through the work of MSOAC, representing the multi-stakeholder MS community. An improved outcome measure for worsening disability that includes cognition would have great value, as it has been repeatedly demonstrated that cognitive impairment is associated with substantial economic and socioeconomic burden and compromised quality of life for persons with MS. Additionally, cognitive decline can occur in some MS patients independently from sensory or motor decline. Ongoing trials are assessing the impact of MS interventions on cognitive function. Qualification of the SDMT as a COA for information processing speed will help address this measurement gap.

1.2 Concept of Interest (COI) for Meaningful Treatment Benefit

The COI is “cognitive disability in MS”, characterized as deficits in information processing speed that result in limitation in activities, participation, or roles, which are understood to be important by the person with MS.

The MSOAC database and published literature provide important insights concerning information processing speed in both relapsing and progressive MS populations, based upon assessment by the SDMT and PASAT. Data from relapsing MS populations on a range of PerfO measures demonstrate the importance of information processing speed in cognitive function in persons with MS. Three points are important to emphasize to understand the rationale for this focus on cognition. First, cognitive impairment and specifically, deficient information processing speed, is a common, often early manifestation of MS. Cognitive impairment has an established negative impact on how persons with MS feel, function, or participate in their societal and family roles. Second, the current standard clinical trial outcome measures – EDSS and relapse rate – do not address cognitive impairment. Consequently, the impact of treatment on cognitive impairment is not known, despite the approval in the U.S. of approximately fifteen disease-modifying drugs for MS. Third, cognitive impairment is not strongly linked to physical disability. Some patients suffer cognitive impairment with minimal physical disability, and vice versa. Consequently, exclusive use of EDSS fails to assess treatment impact on a major aspect of MS disability.

1.3 Context of Use

Targeted Study Population:
The target population is adults with a diagnosis of MS and a relapsing clinical course, to include relapsing remitting MS (RRMS) and active secondary progressive MS (active SPMS).

Targeted Study Design:
The intent is for the SDMT to serve as a primary, co-primary or key secondary endpoint to assess efficacy in clinical trials at various stages, including proof of concept, dose-ranging, confirmatory and registration trials. A qualified SDMT could be used in clinical trials of RRMS or active SPMS as a primary outcome measure if the target is worsening in cognitive function, or as a co-primary or secondary measure, with other outcome measures – e.g. EDSS, relapse rate, walking speed, manual dexterity, or vision. RRMS trials are increasingly designed as active comparator trials where poor sensitivity and reliability of EDSSbased endpoints become major obstacles to feasible trial design with respect to disability comparisons. Qualification of the SDMT would provide an outcome instrument to address this unmet need in MS by enabling a more accurate assessment of treatment benefit on cognition in people with RRMS or active SPMS.

Applicable Study Settings for Future Clinical Trials:
SDMT is accepted internationally and has been converted by several groups into computerized formats with multi-language support and validation that will further enhance reliability and ease of administration. Cultural or language differences have negligible impact on SDMT but cause significant complexities for memory tests that involve word recall.

Other Study Setting Specifics
The oral form of the SDMT is used in outpatient settings and is administered by trained healthcare professionals. The examiner uses a scorer form on which he/she records the subject's voiced responses.

1.4 Critical Details of the Measure to the Degree Known
Reporter, if applicable: The administrator/reporter of the measure manually records the examinee's verbal response on a separate scoring sheet throughout the administration of the test.

Item Content or Description of Measure: The SDMT is a measure of information processing speed. Participants are provided an 8 ½ x 11-inch sheet of paper consisting of nine unique symbols, each paired with a number (single digits 1-9) on top of the page (testing key). The remainder of the page presents a pseudo-randomized sequence of 120 of these symbols with empty boxes underneath. The first 10 symbols are used for the learning phase. Patients are asked to respond orally with the number that corresponds with each symbol as rapidly as possible, without skipping any. The dependent variable is the total number correct in 90 seconds. The standard form provided by Western Psychological Services was the only form used for the data analyzed in the MSOAC submission. Alternative forms, which employ the same symbols but different symbol-digit pairings, yield data nearly identical with the standard form (LaRocca et al., 2017).

Mode of Administration: The SDMT is owned by Western Psychological Services and is administered according to the company instructions. The two versions of the test entail oral or written responses; the data analyzed in the MSOAC package were from the oral version. Training staff in the administration of the SDMT for the data presented in this package (ADVANCE and STRATA) was provided by Dr. Ralph Benedict, according to Western Psychological Services' administration manual. The instructions to the participant include directions to "tell me the number" rather than "fill in the number" as for the written version of the SDMT. The subject is timed to determine how many responses can be made in a 90 second period.

Data collection method: Examinees' responses are recorded during the task. The number of total correct responses is calculated and serves as the primary data point. Scores range from 0 – 110.

1.5 Description of the Consortium

The MSOAC project launched on April 1, 2013 with the consortium's first annual workshop at the FDA. Over the past 6 years, the consortium has brought together 23 academic investigators, 12 companies, and 4 advocacy organizations to collectively work on different aspects of the research plan. Several colleagues from FDA and EMA served as regulatory liaisons to MSOAC. A list of the members is published (LaRocca et al., 2017) and included in this QP. Thus, this qualification plan represents a substantial effort by a large number of MSOAC members that included prospectively defined objectives, systematic review of both literature and expert opinion, data acquisition and analysis, and an iterative process of multiple stakeholder engagement.

Section 2: Executive Summary

The Multiple Sclerosis Outcome Assessments Consortium (MSOAC) seeks qualification of the Symbol Digit Modalities Test (SDMT) as a Performance Outcome (PerfO) measure to assess treatment benefit in clinical trials of therapies for MS. The Concept of Interest (COI) for meaningful treatment benefit is "cognitive ability in multiple sclerosis", characterized as deficits in information processing speed that result in limitations in activities, participation, or roles that are understood to be important by persons with MS. The Context of Use (COU) focuses on the target population of adults with a diagnosis of MS and a relapsing clinical course, to include relapsing remitting MS (RRMS) and active secondary progressive MS (active SPMS). An improved outcome measure would enable a more accurate assessment of the therapeutic benefits in people with MS.

The intent is for this Clinical Outcome Assessment (COA) instrument to serve as a primary endpoint to assess efficacy in clinical trials at various stages, including proof of concept, dose-ranging, confirmatory and registration trials. Its use could be in conjunction with a range of other performance measures as well as other secondary outcome measures, such as imaging, relapse assessment, and Patient-Reported Outcome (PRO) measures.

MSOAC includes representatives from advocacy organizations, National Institute of Neurological Disorders and Stroke (NINDS), academic institutions, and industry partners along with persons living with MS, all collaborating to develop improved measures of multiple sclerosis (MS) – related disability (LaRocca et al., 2017). Several staff members of the Food and Drug Administration (FDA) and European Medicines Agency (EMA) served as agency liaisons to MSOAC. Among the MSOAC goals is qualification of a cognition performance outcome assessment that is clinically valid, highly reliable, practical, costeffective, and meaningful to persons with MS. Processing speed is a basic, elemental cognitive function. One cognitive measure, the SDMT, has been documented as being particularly sensitive to the slowed processing of information that is commonly seen in MS (Benedict et al., 2017; Kalb et al., 2018; Sumowski et al., 2018). Published evidence supports the reliability and validity of this test and its relevance to daily activities, and indicates that a clinically meaningful change in the SDMT score is approximately 4 points or 10% (Kappos et al., 2018; Benedict et al., 2018; Cohan, 2003).

The SDMT form shows a key, consisting of nine abstract symbols. Each symbol is paired with a number ranging from 1 to 9. The test consists of 120 abstract symbols presented in random order. Patients are asked to associate the symbols with the correct corresponding number, as shown in the key. Two versions of the SDMT are available: an oral version and a written version. The oral version was administered for data acquired by MSOAC. Patients respond orally as quickly as possible. The number of correct responses is recorded and represents the test result.

The Paced Auditory Serial Addition Test (PASAT) is another measure of cognitive processing speed that has been widely used in MS trials. The PASAT specifically assesses auditory information processing

speed and flexibility, as well as calculation ability. The PASAT is presented on audiocassette tape or compact disc (CD) to control the rate of stimulus presentation. Single digits are presented 3 seconds and the patient must add each new digit to the one immediately prior to it. The test score is the number of correct sums given (out of 60 possible) in each trial. To determine which measure of information processing speed has superior measurement properties, MSOAC will carry out detailed analyses of both the SDMT and the PASAT.

In order to analyze available data on cognition measures in trials of MS therapies, MSOAC member organizations contributed patient-level treatment and control arm clinical data from approximately 12,766 participants from 14 trials. A CDISC data standard for MS was developed, published, and applied, in order to integrate the data from different sources. The MSOAC database is a rich source of data on functional assessments, including PerfO measures such as the Timed 25 Foot Walk (T25FW), 9 Hole Peg Test (9HPT), and PASAT. Also, a well-validated, standardized patient reported outcome measure of health-related quality of life, the 36-Item Short Form Survey (SF-36), was used in many trials, allowing for the calculation of correlations with the PerfO measures. The following attributes of the SDMT are addressed in the Statistical Analysis Plan: floor and ceiling effects, test-retest reliability, change over time, construct validity, convergent validity, extent of practice effects, known group validity, sensitivity to change, treatment effects, and the minimum clinically important change scores.

Presently no measure to assess cognitive function has been qualified for use in trials of MS therapies; consequently, the qualification of SDMT would fill an unmet need. Importantly, worsening cognitive function, as measured by SDMT, occurs largely independently from worsening physical function, as captured by the EDSS or motor PerfO measures. Therefore, measuring cognition with SDMT, in combination with physical measures, provides a much more complete assessment of MS-related disability by including a critical functional dimension of MS - cognition - that accounts for much of the socioeconomic impact of MS, and is thus extremely important to patients.

This Qualification Plan (QP) is designed to provide compelling data and a very strong rationale for the use of a test of processing speed as the single best dimension of cognitive function to assess in clinical trials. Processing speed is a foundational cognitive function, and deficits in processing speed correlate with (and probably underlie) deficits in higher cognitive functioning such as episodic memory or executive function. Cognitive change frequently occurs independently from physical change. It seems highly likely that some relapses are entirely cognitive in nature, and unaccompanied by motor or sensory deficits. These “cognitive relapses” have not generally been captured in clinical trials or clinical practice. Based on published evidence, SDMT is the best measure of information processing speed for MS. Positive features of the SDMT include the following:

- SDMT change is associated with higher likelihood of disease activity measured by MRI.
- The SDMT is widely accepted by experts in the cognitive aspects of MS. It is included in all short batteries developed for patients in all stages of MS disease over the past 10 years.
- The SDMT is easy to administer, brief, requires no expensive equipment, and, because the test uses symbols and numbers, it is not significantly affected by language or cultural factors, unlike semantic memory tests. The SDMT has proven applicability and adaptability in many languages.
- The SDMT is available in multiple alternate forms, mitigating practice effects.
- Patient experience with the SDMT is extremely positive. Patients enjoy taking the test, in marked contrast to PASAT, which is often considered undesirable, or even punitive by patients.
- The literature documents that the SDMT has strong ecological validity, because it has significant correlations with employment and real-life functions such as managing finances and household chores. Compared with motor tasks or the EDSS, the SDMT has stronger correlation with multiple imaging parameters in all disease stages of MS patients, notably whole brain atrophy.

- Computer-based adaptations of the SDMT are available on tablet devices, which could facilitate use of the SDMT in practice settings as well as clinical trials. This could serve to standardize measurement of an important dimension of MS across healthcare settings.
- Decline in the SDMT is significantly related to patient self-reports of decline in quality of life as measured by the Physical Component Summary (PCS) of the SF-36.

MSOAC's approach (literature review and analyses of the large MSOAC clinical trial database), as presented in this QP is anticipated to support the qualification of the SDMT as a clinically meaningful clinical outcome measure to detect and quantify clinically meaningful change in a major aspect of cognitive function in patients with MS. MSOAC members view this aspect of MS as one that has been disregarded far too long in the testing of new therapies for MS, since cognitive impairment is well recognized as an independent dimension of MS, and is known to contribute at least as much as physical or visual impairment to the impact of the disease on employment and real world daily activity. The members of MSOAC unanimously support the plan to qualify SDMT as a COA measure for cognitive disability in MS.

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