MS CDE Outcomes and Neurological and Physical Exam Subgroup Summary Statement

Determining the correct outcomes assessment tool for clinical studies in MS is complex, largely because there are dozens of possible tools spanning a range of neurological and non-neurological clinical domains that affect individuals with MS and that could be affected by therapeutic intervention. The task of the "Outcomes and Neurological/Physical Exam" Subgroup was to assess available outcomes domains and assessment tools and to provide guidance, where possible, about their administration, scoring, psychometric properties and other aspects of their utility in an MS setting.

The Subgroup began its task by reviewing available scales and scoring systems developed for use in MS, as well as those used more widely in neurology or medicine but also potentially informative for tracking clinical symptoms and/or signs in this disease. Many of relevant metrics that the Subgroup has chosen to emphasize are listed and described on a website maintained by the US National Multiple Sclerosis Society (http://www.nationalmssociety.org). This source was used to develop an initial list of possible scoring systems, to which Subgroup members then added additional metrics not included on the NMSS website and expanded upon information available on that website. The Subgroup met on several occasions by phone, and had one in-person meeting, in an iterative process that over time allowed the group to review the scoring systems and to remove those that had a limited evidence base, uncertain clinical impact for MS, or were largely duplicative without a better-validated metric.

The Subgroup also considered categorizing scoring systems by whether they were deemed as absolutely essential (Tier 1 or "Core Common Data Elements" - CDEs) or useful in some situations only (Tier 2), with the expectation that Tier 1 metrics would be considered "mandatory" in all MS clinical studies, whereas Tier 2 metrics would be used depending on the specific design and goals of a study. Given that use of the Tier 1/Core CDEs will be mandated in every NINDS-funded study, the Subgroup has recommended a minimal number of Core CDEs. In multi-center trials it is impossible to control each study site or sponsor's facility's policies and some elements used internationally may vary from what is used in the U.S.

The Expanded Disability Status Scale (EDSS) is the only Core CDE recommended for MS studies by the Subgroup. The Subgroup recognizes that, depending on the design of the clinical study, not all patients will be physically examined, but the EDSS can be estimated e.g. by chart review, phone interview, or patient self-report. In addition, in some studies, it may be appropriate to measure EDSS only at enrollment to define the study population but not during on-study follow-up. Other CDEs listed by the Subgroup do not have the same historical and/or clinically relevant value in describing patients across the spectrum of MS clinical studies as does the EDSS.

The Subgroup also recommends that other listed CDEs be considered for inclusion in an MS clinical study depending on the type of study (i.e., clinical, therapeutic, natural history, etc.), and the specific goals of the study. The Subgroup does not think it wise to mandate particular

instrument versions but it recommends instead that researchers document the version of the instrument used and state the basis for this decision.

It needs to be emphasized that this listing of possible CDEs is not exhaustive: other outcomes, such as relapse parameters, imaging outcomes and biomarker assays, were dealt with by other Subgroups and need to be considered along with the use of appropriate clinical endpoints in the design and assessment of any MS clinical study. In addition the art and science of outcomes assessment is not static and new or revised metrics are under development.

Finally, while this effort at describing CDEs for MS clinical studies represents the consensus view of the Subgroup members, we emphasize that some needs of clinical MS research and researchers will not fit neatly into the proposed categories or tiers. For instance in a clinical study of an agent intended to treat a symptom of MS, the role of the EDSS (the only “Core” CDE we recommend) may be less relevant than a metric targeted to the specific symptom. The inclusion of EDSS as a primary outcome – or as a measured metric at all – in such a study should be dictated by the needs of the study. In sum, the specific clinical study design will and should dictate the outcome metrics to be used and it is therefore not possible to propose detailed standardized outcomes that should be used in all studies. The purpose of this effort is to ensure the outcome that is measured is approached in a standardized way and reported in a common format that will facilitate meta-analysis across studies.