July 15, 2016

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Via electronic mail: publiccomments@icer-review.org

Re: Draft Scoping Document for ICER Review of Drugs for Relapsing-Remitting Multiple Sclerosis

The National Multiple Sclerosis Society appreciates the opportunity to submit comments on ICER’s Draft Scoping Document for ICER Review of Drugs for Relapsing-Remitting Multiple Sclerosis (RRMS) released for public review on July 1, 2016. The Society works to provide solutions to the challenges of MS so that everyone affected by this disease can live their best lives. To fulfill this mission, we fund cutting-edge research, drive change through advocacy, facilitate professional education, collaborate with MS organizations around the world, and provide services designed to help people affected by MS move their lives forward.

MS is an unpredictable, often disabling disease of the central nervous system that disrupts the flow of information within the brain, and between the brain and body. A growing body of evidence indicates that early and ongoing treatment with an FDA approved disease modifying therapy (DMT) is the best way to modify the course of the disease, prevent the accumulation of disability, and protect the brain. MS presents and progresses differently in every individual, and there are multiple variables that go into decision making for the use of DMTs. As such, the goal of developing a reliable and accurate clinical guideline to aid decision-making about initial therapy and any medically necessary therapy change will be difficult, as there is an absence of head to head controlled randomized studies over a sufficient length of time to establish definitive effects on the MS disease course.

There are currently 14 DMTs available to people with RRMS and the Society strongly believes that ongoing access to these medications is essential for people with MS. Further, we believe that price of the MS DMTs, insurance formulary design, and utilization management practices pose significant challenges in people with MS getting the medication they and their healthcare provider have determined is the best course of treatment. Thus, the Society encourages ICER to carefully consider the real world implications (both positive and negative) of this review for people living with MS.

Background: We suggest that ICER review the source material of the draft background to ensure that the information is accurate and up to date. We have attached a list of references in an appendix to aid ICER in this review.

Scope: ICER states that it will explore the potential health systems budgetary impact of each treatment over a 5 year time; however, new data indicates that the beneficial effects of DMTs on disability progression may take 6 or more years to become statistically apparent. There is currently a paucity of data from the U.S. that is necessary to accurately examine the long-term benefit of DMTs throughout the lifetime of a person with MS. The draft scoping document does not address
how ICER will address these significant gaps in this data in its review.

The Society believes that only direct head to head trials are valid for comparisons between agents. ICER proposes to use data from randomized, controlled clinical trials (RCTs) of RRMS, designed to establish efficacy of an agent compared to placebo or active comparator. In most RRMS trials, annualized relapse rate was used as the primary outcome measure and short term (3-6 months) disability progression during the trial period was used as one of many secondary measures. Neither relapse rate nor short term disability change are likely to be useful measures of long-term effectiveness on MS disability in the real world. Additionally, RCTs are typically conducted over a short time interval and include participants that are often selected for their likelihood to respond to therapy based on a reduction in relapses and who have a reduced risk for side effects and adverse events. We trust that ICER understands that RCTs are not designed, controlled, conducted, or powered to establish the cost-effectiveness of a therapy or the impact of a therapy on the evolution of disability in the course of MS over a clinically-relevant time period (see Palace et al, Lancet Neurology 2015). Agents will have also been assessed in different clinical trials, conducted at different time periods, with different cohorts, variable entry criteria and selection, differences in outcome assessment criteria, and differing behavior of the comparator groups. Further, the definitions of MS subtypes have evolved during the development of MS DMTs; therefore, care should be taken that any comparisons are made between patient populations that are consistently defined (see Lublin-Reingold MS disease descriptors 1996).

Health Care Utilization Outcomes: Examining appropriate health outcomes will improve the ICER review. We recommend examining health care utilization outcomes for MS by gauging direct and indirect costs of the disease, including long-term care (LTC). Lost wages, cost of drugs, cost of outpatient care, cost of rehabilitation, and cost of assistive technology including wheeled mobility are all important and should be taken into account. These outcomes incorporate aspects of disability progression and the broader costs of living with MS that are not captured by only examining emergency room visits and inpatient stays. Further, MRI findings are not currently accepted by the Food and Drug Administration as indicators of clinical meaningfulness. Given this, it is unclear how ICER would extrapolate a value framework using MRI findings. We encourage ICER to review the literature and reconsider whether this is the best approach.

Clinical and Patient-Centered Outcomes: The Society believes that people with MS should be at the center of their healthcare decision-making. In order to gain valuable insight into how patient preference impacts the selection and utilization of DMTs and influence clinical and patient-centered outcomes, we strongly urge ICER to engage directly with people with MS and renew our offer to assist in this engagement. Comorbidities of MS that impact the quality of life are also important to consider as they often factor into the benefit/risk assessment and patient preferences when selecting a DMT. The impact of some outcomes on DMT utilization may be difficult to ascertain, as very few head to head studies have been done to examine these additional outcomes. For example, cognitive function is an important outcome for people with MS but there is inadequate data to assess its impact on DMT utilization.

ICER states that the Expanded Disability Status Scale (EDSS) will be used to assess the impact of the DMTs on either the annual relapse rate or progression of disability. As noted above, current RCTs in RRMS were not conducted over sufficient time periods to assess impact on MS disability over a clinically-meaningful time period. A more relevant comparator would be benefits compare to the natural history data of the evolution of the disease over a sufficient time period. Additionally, EDSS is a non-linear scale that places a large amount of emphasis on lower extremity function. We
recommend the inclusion of cognitive and fatigue data as well as multiple sclerosis functional composite (MSFC) to appropriately emphasize important clinical dimensions that are not included within EDSS (Cutter et al, 1999).

**Interventions:** The Society encourages ICER to include recently-approved medications and medications pending approval, including daclizumab and ocrelizumab. ICER should clarify this section, as it currently states that ICER is excluding rituximab and mitoxantrone but lists rituximab as one of the "other infused products." Given low utilization in practice, we believe it is appropriate to exclude Mitoxantrone.

**Comparators:** Healthcare providers and people living with MS do not see the value in ICERs focus on comparing two competing formulations of interferon beta-1a. We feel this limits the value of the review, as the use of interferons is evolving due to the availability of other treatments. There are numerous comparison trials, which will be more relevant to the review and prescribing practices. Additionally, the term “platform agents” implies consensus that these agents are starter medications for all people with MS. **Such consensus does not exist in the healthcare provider community.**

**Simulation Models Focusing on Comparative Value:** More detail is needed in the simulation model. We encourage ICER to review Noyes et al. (Neurology, 2011), which evaluated the cost-effectiveness of DMTs in the U.S. compared to basic supportive therapy without DMT for patients with RRMS. EDSS is a problematic gauge for people with MS and we encourage ICER to utilize the MSFC in order to gauge cognitive impairment. Clarification is also needed on how ICER plans to calibrate the quality adjusted life year (QALY) and if the disease costs that are to be assessed are direct payments for medical care or will include other costs, such as activities of daily living. Further, ICER should consider evaluating data for each of the available DMTs to assess the cost-effectiveness price range at which the drug would be effective, using an appropriately defined QALY metric and incorporating both relapse reduction and reduction of disability progression as compared to the MS natural history data over an appropriate level of time.

As detailed above, **we believe there is currently insufficient data available for ICER to conduct the evaluation that it has outlined within the scoping document. As its review will have real world implications for people with MS, we urge ICER to instead offer recommendations on the data necessary to appropriately determine the cost-effectiveness on DMTs over the course of MS.**

Thank you for the opportunity to comment. If you have any questions, please contact Leslie Ritter, Senior Director, Federal Government Relations at leslie.ritter@nmss.org or 202-408-1500.

Thank you,

Bari Talente, Esq.
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APPENDIX


