December 21, 2016

Steven D. Pearson, MD, MSc
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Two Liberty Square, 9th Floor
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Submitted via email: publiccomments@icer-review.org

RE: Public Comment on Draft Evidence Report Disease-Modifying Therapies for Relapsing-Remitting and Primary Progressive Multiple Sclerosis: Effectiveness and Value and Draft Voting Questions

Dear Dr. Pearson,

The National Multiple Sclerosis Society (Society) appreciates the opportunity to submit comments on the Institute for Clinical and Economic Review’s (ICER) draft evidence report, Disease-Modifying Therapies for Relapsing-Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value. Multiple Sclerosis (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. The Society works to provide solutions to the challenges of MS so that everyone affected by this disease can live their best lives.

We commend ICER on their review of the MS medication class and for seeking to bring economic clarity to this expensive class of medications. High prices, along with increased out-of-pocket costs for people with MS, inconsistent formularies across different insurers, lack of price transparency and complex approval and appeals processes often create barriers to people with MS accessing the right treatment for them. The Society’s “Make Medications Accessible” Initiative seeks to find solutions to these challenges with all stakeholders involved in the healthcare system. We hope that ICER’s final evidence report can bring value to these important conversations.

We found the analysis of the clinical trial evidence to be a thorough summary of disease modifying therapies (DMTs) approved for use in the United States (U.S) market. We were also pleased to see some incorporation of the learnings ICER accumulated from outreach to people living with MS, patient advocacy groups, healthcare providers and other stakeholders. These included recognition of the economic burdens facing people with MS, a desire for patient-reported outcomes and the critical importance of shared decision making with their healthcare provider to ensure treatment choices that meet individual needs. However, not enough attention is paid to the heterogeneity of MS and the differences in the mechanisms of action associated with the DMTs, which are of high importance when choosing treatment. The type of analysis that ICER attempts is commendable; however, it is dependent on many variables that are further complicated by the heterogeneity of MS,
the variable individual response to medication, and a large number of quality of life factors. Studies show that early and ongoing treatment with a DMT effectively modifies the course of the disease, prevents the accumulation of disability and protects the brain from damage due to MS\(^1\). As such, we believe that a full range of treatment options should be available to every person living with MS, so that they - in collaboration with their health care providers - can make informed treatment decisions. Further, any person who is stable on a DMT should not be forced to switch to another agent because of changes in medication coverage or cost considerations. A delay in treatment can have a negative and permanent result.\(^2\) 

In our review of the draft evidence report, the Society has outlined some areas that need to be re-evaluated for accuracy and to improve the usefulness of the document. Some of the below inaccuracies are regarding alemtuzumab and glatiramer acetate, both of which figure prominently in the review and conclusions as a cost effective treatment and baseline treatment respectively.

- Within Table 1, ICER has listed alemtuzumab’s dosage as 12 mg per day for 3 days every year. The label for alemtuzumab, marketed as Lemtrada, states that the drug should be administered for 5 days at baseline, and then for 3 days a year later. Additional doses are only administered after that with new disease activity.\(^5\) 
- The American Academy of Neurology Draft Guidelines do not recommend testing for antibodies to John Cunningham virus (JCV) in patients taking fingolimod or dimethyl fumarate nor avoidance of these drugs in patients with JCV antibodies.\(^6\) 
- ICER reports the CONFIRM trial of glatiramer acetate and dimethyl fumarate versus placebo as a head to head trial: however, the CONFIRM trial was not powered as a head to head assessment.\(^7\) 
- The authors state that alemtuzumab was consistently better in preventing disability progression; however, in the Care-MS1 trial, there was no significant difference between the alemtuzumab and IFNB-1a in preventing disability progression.\(^8\) 
- Natalizumab, when compared to a generic glatiramer acetate, was given a B+ rating- however, the accompanying table (Table 13) had its designation listed as a C+. 
- In the U.S., alemtuzumab has a strong recommendation from the FDA to be used as a third-line therapy; however, within the review, the authors repeatedly refer to it as a second-line therapy.\(^9\) 

**Current Limitations of the Draft Evidence Report**

While the Society appreciates ICER’s thorough review, we are concerned by assumptions made within the document, the scientific validity of the comparisons used and the resulting value conclusions. Insufficient attention is paid to the heterogeneity of the MS population, quality of life factors and variable response to treatments. In the survey of people with MS, 90% rated continuing working/normal activities as important/very important- behind only delaying disability and preventing relapse (Table 3). The authors state this echoes what they heard from individual patients and patient advocacy groups, yet this doesn’t have a corresponding emphasis in the analysis. In our view, the report also draws incorrect conclusions from the widely differing opinions on treatment guidelines (American Academy of Neurology, Canadian Agency for Drugs and Technology in
Health, MS Coalition and National Institute for Health and Care Excellence) and the range of coverage policies by payers. The range of these guidelines and policies indicates the need for differing options due to the heterogeneity of MS. **Reviews like ICER’s that look at cost effectiveness may be used to limit access to DMTs for people living with MS. Therefore, we believe it is critical that ICER acknowledge the limitations of the review and clearly point out the many assumptions that were made that potentially undermine the validity of the cost conclusions.**

We remain concerned that the comparisons that ICER used to evaluate the different treatment trials are based on data that are more than two decades old. These data and the study populations for older therapies do not represent modern populations or current practice. People entering trials for relapsing remitting (RRMS) MS for the older therapies were generally in a later state of disease than those currently entering RRMS trials due to improved diagnostic tools. Further, the randomized controlled trials (RCT) only show data over a relatively short time frame (usually a maximum of 2 years). Beyond that time period, there is very limited data available to validate the assumptions that ICER makes in the document. **Given these significant study population differences, the RCTs are not directly comparable, thus making the resulting comparative efficacy conclusions in the analysis unreliable.** ICER acknowledges the challenges of trying to compare therapies based on registration trials, but does not adequately account for this challenge in the result and cost-analysis. The lack of reliable estimates of MS progression in newly diagnosed patients is another major limitation for estimating cost effectiveness of MS treatment modalities; its implications on the results of any predictive modeling need more attention in the review.

Additionally, the review makes the assumption that a person with MS goes off treatment after failure with second-line therapies. This assumption is not consistent with current medical practice or payer policies. There are many reasons why someone may need to switch to another DMT after the second therapy: allergy, adverse side effect (e.g. laboratory abnormalities), new contraindication, etc. While many people with MS will take more than one DMT throughout the course of the disease, it is also common for people to take more than one medication that ICER refers to as first-line before moving to a medication that ICER refers to as second-line. Often, this is due to payer policies. People with MS may also take more than one of the “second-line” therapies. These assumptions should be changed in the final review to reflect current practices.

The draft evidence report also lacks reliable data on patient reported outcomes, which as the authors state (Table 3) are the most important outcomes for patients. Furthermore, the utility data that the authors used in their modeling came primarily from non-U.S. studies. Utility data are known to be reflective of cultural and societal preferences, therefore it is likely that these data do not represent the true preferences of a person in the U.S. who lives with MS. Changes in relapse management, as well as other healthcare delivery changes are also likely to affect costs.  

In our review, it appears that indirect and direct health costs are missing health expenditures that are common for people with MS. For example, when a person with MS switches or begins a new DMT,
this often requires additional physician visits for medication adjustments and side effect management. Regular MRIs may also be used to monitor or assess DMT effectiveness.

**Possible Areas of Improvement for Final Evidence Report and Final Voting Questions**

The Society has outlined several areas that the authors should reevaluate in the final evidence report. We believe that these revised components will improve the review for providers and people living with MS.

- The authors should reconsider the exclusion of clinically isolated syndrome studies as the implications of treatment decision on people with this early form of MS are particularly important.\(^{11, 12, 13}\)
- ICER should reconsider their projected number of relapses on page 69 to better align with modern treatment guidelines.
- Ocrelizumab, to date, has not received approval from the Food and Drug Administration (FDA), and is unlikely to be approved prior to the review of this report; therefore much information concerning benefit/risk and price is speculative. The authors should reevaluate the information contained in the review on ocrelizumab once FDA’s approval decision is made and more precise data and pricing information on the drug is known.
- It is currently unclear how the model used calculates and allocates indirect costs. More details on components used to calculate indirect costs and how they are valued is needed to truly identify and present cost. In addition, it would enhance confidence in the model if ICER were to publish the details of the model in a peer-reviewed publication.
- The economic evaluation that the authors utilize (Table 20) is based on a single NARCOMS survey from 2004. The prices of all MS therapies and reimbursement amounts for services and delivery have changed dramatically since that time. The authors should note in the final evidence review how their economic evaluation accounts for price differences since 2004 and how associated healthcare costs were estimated for other DMTs which were not available in 2004.
- Real world practice and treatment should be factored in with the cost analysis. For example, alemtuzumab is FDA approved as a third-line therapy. FDA makes a strong recommendation in the labeling that this treatment is to be used only after inadequate response to two or more DMTs. Thus, even though the review rates it as cost effective, this treatment is likely not an available option for many people with MS due to the labeling information and medical practice.
- ICER should add an answer choice of “insufficient data” to their draft voting questions. The limitations of the review impact the efficiency and cost conclusions drawn and currently there is a lack of scientifically validated data to answer the questions posed.

As ICER moves to finalize its review and voting questions, the Society believes it is important to acknowledge the benefit of this type of analysis to inform providers and people affected by MS about the full spectrum of approved treatment options. The heterogeneity of the MS population and the clinical variability of MS between individuals make access to the full range of therapies critically important. Treatment that may be effective and well tolerated in one may fail in another person, and people with MS may utilize several treatments in their lifetime. We believe
that individualized treatment plans, created by shared decision making between people with MS and their physicians will produce the best result and cost effectiveness by maximizing efficacy and adherence, while balancing risk tolerance.

On behalf of the National MS Society, thank you for your consideration of our comments, which we hope will improve the final evidence review. If you have any questions, please contact Leslie Ritter, Senior Director, Federal Government Relations at leslie.ritter@nmss.org or 202-408-1500.

Sincerely,

Bari Talenti, Esq.
Executive Vice President, Advocacy
National Multiple Sclerosis Society


Kappos L, Polman CH, Freedman MS, et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology. 2006;67(7):1242-1249