Disease Modifying Therapies for Relapsing-Remitting Multiple Sclerosis: Effectiveness and Value

Background and Scope
July 22, 2016

Note:

This scoping document pertains only to the analysis of treatments for relapsing-remitting multiple sclerosis (RRMS). An addendum detailing considerations for the analysis of primary progressive multiple sclerosis (PPMS) treatments was released on June 18, 2016, and is open to public comment until August 12, 2016. Once the comment period for the addendum has closed, ICER will release a final scope that includes information about the PPMS analysis.

Stakeholder Input:

This scoping document was developed with extensive and critically important input from several multiple sclerosis patient advocacy organizations, which encouraged the inclusion of a broad range of disease-modifying therapies. ICER also engaged with and received detailed input from relevant specialty societies, practicing neurologists, pharmaceutical manufacturers, and payers to inform the research direction outlined in this scope. The updated scope additionally reflects input gathered from patients, advocacy organizations, clinicians, and manufacturers during a two-week public comment period. ICER looks forward to continued engagement with these stakeholders throughout its review of treatments for relapsing-remitting multiple sclerosis. We have summarized many of the key modifications to the scoping document in the following paragraph.

Patients and advocacy organizations suggested several clarifications and additions to the background section of the scope, including a greater emphasis on the importance of shared decision making. In addition, they recommended the inclusion of Multiple Sclerosis Functional Composite Measure (MSFC) outcomes, encouraged the reporting of absolute risk reductions, and the calculation of number needed to treat and harm when possible. The list of interventions is now grouped by route of administration, and we have clarified that it is our intent to compare all of the agents to one another regardless of grouping. These analyses will be supplemented by sensitivity analyses to assess the potential sources of heterogeneity due to the evolving definition of MS, differences in patient population, and differences in outcome definitions. While the primary economic analysis will take a health system perspective, focusing on direct medical costs, we will conduct a separate analysis that incorporates indirect costs based on feedback from patients, advocacy organizations, clinicians, and manufacturers on the broad impact that MS has on patients and their caregivers.

Background:

Multiple sclerosis (MS) is a chronic, immune-mediated inflammatory, neurodegenerative, and demyelinating disease of the central nervous system (CNS).[1] Approximately 400,000 Americans have MS, although this may be an underestimate, and the disease affects about three times as many women as men.[2] Some patient groups, such as African Americans, experience a more rapid and severe clinical course. The annual cost of MS in the United States is estimated to be $28 billion.[3] The most common presentation of the disease is RRMS, which affects 85% to 90% of patients with MS.[1] RRMS is characterized by periodic relapses characterized by neurologic symptoms that may diminish or resolve

with treatment. Over one to two decades, more than half of patients with RRMS transition to a disease course of slowly accumulating neurologic deficits known as secondary progressive MS.[4]

There are more than 10 disease-modifying therapies (DMTs) approved by the Food and Drug Administration (FDA) for the treatment of RRMS. The therapeutic goal of DMTs is to decrease the frequency of relapses and to prevent the disability that accumulates with disease progression over decades. Some neurologists believe that the goal of treatment should be to eradicate all evidence of disease activity including magnetic resonance imaging (MRI) findings. There is controversy about the relative efficacy of the drugs, and several of the newer drugs have been associated with life-threating adverse events (CNS infections, autoimmune diseases, liver toxicity, cancers). In addition, RRMS is a heterogeneous disease, which complicates comparisons across studies of DMTs.

There is no definitive clinical guideline to help clinicians and patients with decisions about both initial therapy and choices about subsequent therapies following treatment failure. Shared decision making plays an important role when choosing initial and subsequent therapy, as patients and providers must balance considerations around efficacy, potential harms, route and frequency of administration, cost, and personal experience. Advocacy organizations have noted that patient preference strongly influences treatment adherence and resultant clinical outcomes. Specifically, ICER received input from advocacy organizations that some patients have a strong preference for oral medications over injectable ones because of their dislike of needles, injection site reactions, and the difficulty of storing medications that require refrigeration. Other patients are equally comfortable with injectable medications.[5,6] In addition, the advocacy organizations that ICER has interacted with emphasized that some patients have a low tolerance for risk and are less likely to choose DMTs with known, potentially severe side effects. These combined factors demonstrate the considerable uncertainty about the interpretation and application of the current evidence base to guide clinical practice and insurance coverage policy.

Report Aim:

This project will evaluate the health and economic outcomes of multiple treatment regimens for relapsing-remitting multiple sclerosis. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms - including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs - are considered in the judgments about the clinical and economic value of the interventions.
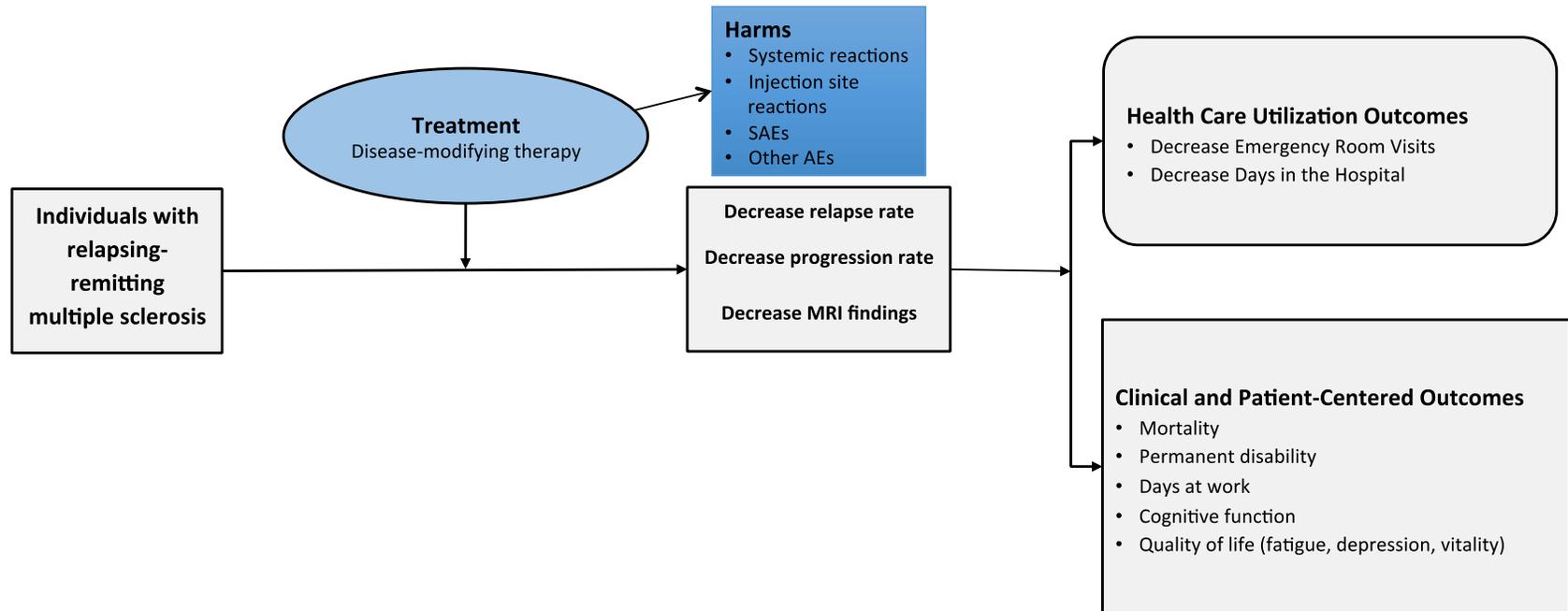
Scope of the Assessment:

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be culled from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Wherever possible, we will seek out head-to-head studies of these interventions, both within and across the three general groupings of interest (see page 4). In the absence of head-to-head studies, we will use placebo-controlled studies and derive indirect comparisons from a network meta-analysis.

Analytic Framework:

The general analytic framework for assessment of DMTs for RRMS is depicted in Figure 1 on the following page.

Figure 1. Analytic Framework: Disease Modifying Therapies for Relapsing-Remitting Multiple Sclerosis

Harms
- Systemic reactions
- Injection site reactions
- SAEs
- Other AEs

Treatment
Disease-modifying therapy

Individuals with relapsing-remitting multiple sclerosis

Decrease relapse rate

Decrease progression rate

Decrease MRI findings

Health Care Utilization Outcomes
- Decrease Emergency Room Visits
- Decrease Days in the Hospital

Clinical and Patient-Centered Outcomes
- Mortality
- Permanent disability
- Days at work
- Cognitive function
- Quality of life (fatigue, depression, vitality)

Populations

The population of focus for the review is adults ages 18 and older with relapsing-remitting multiple sclerosis. We are cognizant that the diagnostic criteria for MS have changed over time, beginning with the Poser Criteria and continuing through the evolution of the McDonald Criteria. We will evaluate the impact of these changes and other sources of heterogeneity in our analysis of the comparative efficacy of DMTs. We will not include studies focused solely on clinically isolated syndrome (CIS), but will include trials that study mixed populations with RRMS and CIS if data on key outcomes are stratified by form of MS.

Interventions

The list of interventions was developed with extensive input from patient organizations, which counseled ICER to include nearly all DMTs with current or projected FDA-labeled indications for RRMS. Practicing clinicians, specialty societies, manufacturers, and payers also provided essential input. Mitoxantrone will be excluded from the review and rituximab will be included based on feedback from the previously mentioned groups. The full list of interventions is as follows, grouped by route of administration:

- Injectable agents (daclizumab, glatiramer acetate, interferon beta-1a, peginterferon beta-1a, interferon beta-1b)
- Oral agents (dimethyl fumarate, fingolimod, teriflunomide)
- Infused agents (alemtuzumab, natalizumab, ocrelizumab, rituximab)

Comparators

Data permitting, we intend to compare all of the agents both within and across the routes of administration as described above. With two exceptions, we do not anticipate including a detailed description of the comparisons among the injectable agents unless the results of ICER's analysis differ substantially from the existing literature. The first exception is daclizumab, which was recently approved by the FDA and thus has not yet been extensively compared to other agents in the literature. The second exception is the comparison between Avonex® (Biogen, Inc.) and Rebif® (EMD Serono, Inc.), two distinct formulations of interferon beta-1a, as multiple stakeholders indicated an interest in a detailed comparative analysis of these agents.

Outcomes

In conversations held to develop the draft scoping document, patient organizations advised us that their primary goal for therapy is to remain independent. They also recommended the inclusion of fatigue, depression, and cognitive function among other symptoms, as these are common issues that affect their quality of life, but have not been widely reported in the seminal clinical trials. This review will also examine clinical and health care utilization outcomes of DMTs. To be included, studies must report the impact of the intervention on either annual relapse rate or progression of disability assessed by the Expanded Disability Status Scale (EDSS). Throughout the review, we will continue to engage with patient groups and clinical experts to identify and include patient-reported outcomes or other evidence sources can be found to enrich the available data. Many of these outcomes will be evaluated descriptively because they have not been consistently evaluated in the randomized trials demonstrating efficacy, and thus cannot be included in a network meta-analysis. For example, data on harms have not been consistently reported, while annualized relapse rates and confirmed disability progression have been reported in a standardized manner across trials and would therefore lend themselves to quantitative analysis. Additional outcomes of interest include:

- Disability
- Skilled nursing facility placement
- Need for caretaker/health aide
- Cognitive function

- Fatigue
- Depression
- Timed 25-foot walk
- Manual dexterity
- Visual acuity
- Multiple Sclerosis Functional Composite Measure (MSFC)
- Acceptability of route of administration
- Other measures of functional status, and/or health-related quality of life
- Magnetic resonance imaging (MRI) outcomes (T2, T1, brain volume changes)
- No evidence of disease activity (NEDA 3 and/or 4)
- Adherence
- Treatment-related adverse events including:
  - Serious adverse events
  - Adverse events leading to discontinuation of therapy
  - Adverse events unique to specific drugs
- Time to secondary progressive MS
- Time to death
- Costs and cost-effectiveness of DMTs

Where possible we will report the absolute risk reduction and number needed to treat in addition to the relative risk reduction for the treatment comparisons.

Timing

Evidence on intervention effectiveness will be derived from studies of at least one year's duration and evidence on harms from studies of at least three month's duration.

Settings

All relevant settings will be considered, with a focus on outpatient settings in the United States given the prolonged natural history of RRMS.

Simulation Models Focusing on Comparative Value:

Discussions with patient organizations indicated that MS treatment is considered to be expensive, and that some patients report coverage-related barriers to access. As a complement to the evidence review, we will develop a simulation model to assess the lifetime cost-effectiveness of the treatments of interest relative to relevant comparator treatments. Model structure will be based in part on a previous lifetime model of MS from a health-system perspective (i.e., focus on direct medical care costs only).[7-14] The target population consists of patients with RRMS, however the model will include the potential to progress to secondary progressive MS (SPMS). The model consists of health states based on EDSS levels and death. A cohort of patients will transition between states during each one-year cycle over a lifetime time horizon, modeling patients from treatment initiation until death.

Key model inputs will include probabilities of progression between EDSS levels, relapse rates, quality of life values, and health care costs. Probabilities and relapse rates will differ to reflect differences in effectiveness between interventions. Treatment effectiveness will be estimated using network meta-analyses of relapse-free and disability progression-free time.

Health outcomes and costs will be dependent on time spent in each health state, relapse events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of relapses avoided, life-years, and quality-adjusted life years (QALYs). Quality of life weights will be applied to each EDSS health state. Additionally, quality of life decrements will be applied for each

relapse event and for adverse events. The model will include costs related to drug administration, drug monitoring, supportive care, and adverse events and other MS-related costs. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained, cost per life-year gained, and cost per relapse avoided. We will also conduct a separate analysis evaluating indirect costs to account for productivity losses, caregiver burden, and other important concerns for an MS population.

In an additional analysis, we will explore the potential health system budgetary impact of each treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the simulation model for treatment costs and cost offsets. These budgetary impact analyses will assume specific "uptake" rates over a five-year period for specific populations of interest, given the availability of relevant data. This analysis will indicate the potential budgetary impact of widespread implementation of each treatment, and allow assessment of any need for managing the cost of such interventions.

More information on ICER's methods for estimating product uptake and calculating potential budget impacts can be found at: http://www.icer-review.org/wp-content/uploads/2014/01/Slides-on-value-framework-for-national-webinar1.pdf.

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