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

Draft Background and Scope
July 1, 2016

Stakeholder Input:

This draft 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 draft scope. ICER looks forward to continued engagement with these stakeholders throughout its review of treatments for relapsing-remitting multiple sclerosis.

Background:

Multiple sclerosis (MS) is a chronic, immune-mediated inflammatory 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 twice as many women as men. Some patient groups, such as African Americans, experience a more rapid and severe clinical course. MS is the most common non-traumatic cause of permanent disability among young adults.[2] The annual cost of MS in the United States is estimated to be $28 billion.[2] The most common form of the disease is relapsing-remitting MS (RRMS), which affects 85% to 90% of patients with MS.[1] RRMS is characterized by periodic relapses characterized by neurologic symptoms that diminish or resolve with treatment.

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 can cause life-threating adverse events (CNS infections, autoimmune diseases, cardiac toxicity, 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 with decisions about both initial therapy and choices about subsequent therapies following treatment failures. Patient preference plays a role in the selection of therapy, and the advocacy organizations that ICER received input from indicated that 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. In addition, the advocacy organizations 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.

Scope of the Assessment:

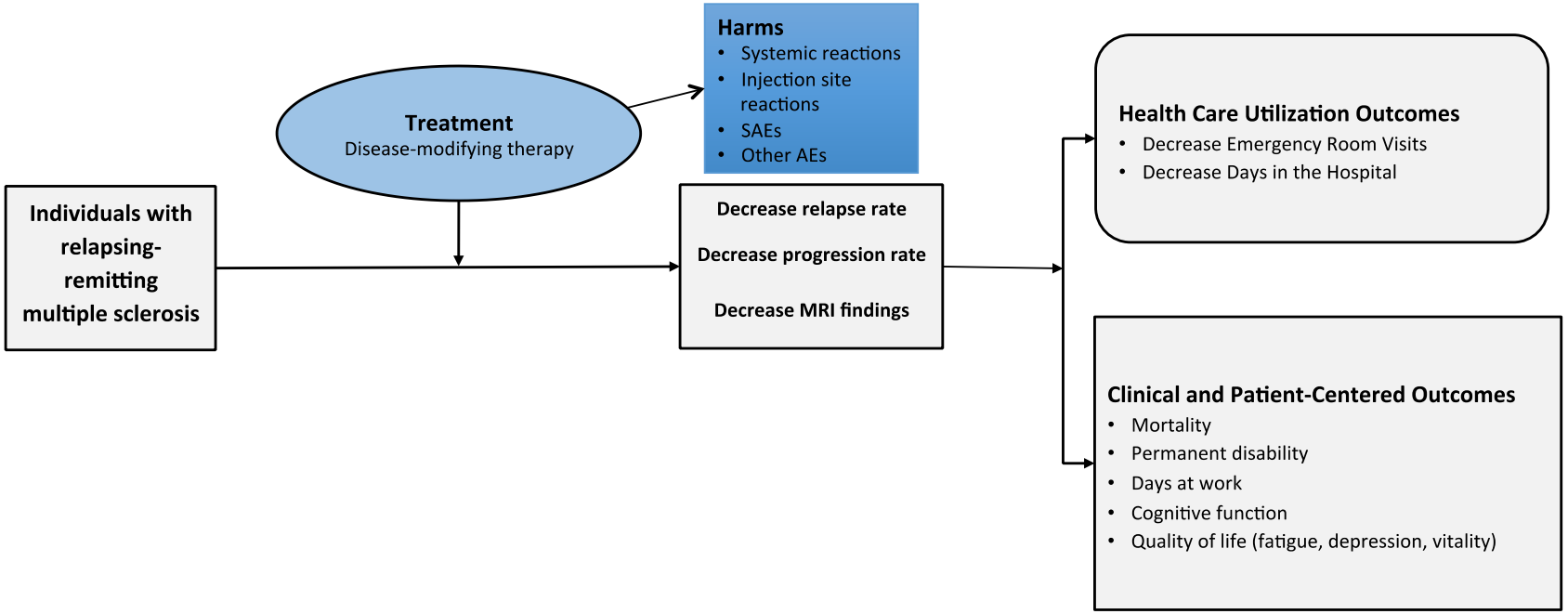
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be culled from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative 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 http://www.icer-review.org/policy-on-inclusion-of-grey-literature-in-evidence-reviews/).

Wherever possible, we will seek out head-to-head studies of these interventions, both within and across the three groupings of interest (see page 3). 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



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 in our analysis of the comparative efficacy of DMTs.

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 additionally 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:

- Platform agents (interferon beta-1a, peginterferon beta-1a, interferon beta-1b, glatiramer acetate)
- Oral agents (fingolimod, teriflunomide, dimethyl fumarate)
- Other injectable or infused MS agents (natalizumab, alemtuzumab, rituximab, daclizumab, ocrelizumab)

Comparators

Data permitting, we intend to compare the agents both within and across groups. For the platform agents, the primary comparison will be between Avonex® (Biogen, Inc.) and Rebif® (EMD Serono, Inc.), two competing formulations of interferon beta-1a.[*]

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 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. 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
- 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)

[*]Feedback from stakeholders demonstrated greatest interest in the comparison between Avonex and Rebif. That comparison will be evaluated in detail, with evidence on other agents summarized from the literature.

- Adherence
- Treatment-related adverse events
- Time to secondary progressive MS
- Time to death
- Costs and cost-effectiveness of DMTs

Timing

Evidence on intervention effectiveness and harms will be derived from studies of at least one year'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).[3-10] 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 1-year cycle over a lifetime time horizon, modeling patients from treatment initiation until death; a patient can progress to death or have a relapse from any state.

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 intervention-specific costs. The health outcome of each intervention will be evaluated in quality-adjusted life years (QALYs). Quality of life weights will be applied to each health state, defined by EDSS level. Additionally, quality of life decrements will be applied for each relapse event. The model will include costs related to drugs, drug administration, supportive care, and adverse events. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained.

In an additional analysis, we will also explore the potential health system budgetary impact of each treatment over a 5-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 5-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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