PATIENTS RISING NOW

Guide for Commenting on ICER's Draft Evidence Report on Treatments for Relapsing Forms of Multiple Sclerosis

On October 17, 2022, ICER released its draft evidence report, "Oral and Monoclonal Antibody Treatments for Relapsing Forms of Multiple Sclerosis." This document provides a framework for considering what aspects of ICER's review are important to people with multiple sclerosis (MS), and how to consider presenting those perspectives. This guide specifically provides insights about how to read and respond to ICER's draft evidence report, as well as how to request a slot to make comments during ICER's public meeting.

Key Dates

October 17, 2022:	Draft Evidence Report released
Friday, November 11, 2022:	Written comments due by 5:00pm ET; deadline to submit request to speak at Public Meeting
December 21, 2022:	Updated Evidence Report released
January 20, 2023:	Public Meeting with ICER's New England Comparative Effectiveness Public Advisory Council (CEPAC)
February 17, 2023:	Final Evidence Report and Public Meeting Summary released

Background & How to Participate

The Institute for Clinical and Economic Review (ICER) is a private entity that uses its own analytical process and "value framework" to assess potential new treatments for a variety of diseases. Those assessments often occur before FDA approval, and may result in conclusions that could harm patients by limiting access to new and innovative treatments. You can learn more about ICER here.

There are two primary ways advocates and other stakeholders can give input:

1. **Submit written comments on the draft report, which are due to ICER on November 11th.**
2. **Request a slot to make oral comments during ICER's January 20th meeting.**

Submitting written comments on the draft report

Written comments must be submitted as a Word document via email to publiccomments@icer.org. Comments must be in 12-point Times New Roman font, and no more than 5 pages, not including references or appendices.

The deadline to submit written comments is 5:00pm ET on November 11, 2022.

Requesting a slot to make oral comments

ICER's public meeting on the revised report and discussion by one of its advisory committees will be held virtually on January 20, 2023. You can register for the meeting here. ICER's meetings devote only a short period to public comments by a small number of participants. Oral comments are limited to no more than five minutes per speaker.

To request a slot, send an email to publiccomments@icer.org and include the speaker's name, title, and organization.

The deadline speaking requests is 5:00pm ET on November 11, 2022.

NOTE: Not all requests to make public comments are granted. According to ICER: "We sort through all the requests to make an oral public comment at the meeting. Because we only have a limited time for oral comments at the public meeting, we can only allow a few stakeholders to share their perspective."

What Patients Need to Know about the Quality Adjusted Life Year (QALY)

What is a QALY?

- To understand how ICER's reports can impact patients, it is important to understand the Quality Adjusted Life Year (QALY) concept and how ICER uses it as the basis for much of its analysis and as a justification for its conclusions and recommendations.

- In simple terms, a QALY is a metric used by health economists to represent one year lived in "perfect health." A year for anyone living in a less than "perfect health" is automatically valued lower. Calculations to determine QALYs are based on numerical "utility" values assigned to health states associated with any illness or health event, such as an infection or relapse for MS. Thus, an illness can reduce a hypothetical patient's QALYs – by decreasing their lifespan and/or leaving them with

less than perfect health – while an effective treatment or prevention would increase them.

- Entities like ICER use the QALY to determine the "value" of the treatments they review. Insurance plans – including Medicare and Medicaid – may use those assessments of "value" to make decisions about which treatments are covered and which it will not pay for. This can severely limit patients' access to treatments.

- In November 2019, the National Council on Disability, which is an independent federal agency, issued a report "Quality-Adjusted Life Years and the Devaluation of Life with Disability," explaining why patients are not well served by use of the QALY:

  [S]takeholders fear that use of QALYs undervalues vital treatments that extend or improve the lives of people with disabilities. This is because the QALY calculation reduces the value of treatments that do not bring a person back to "perfect health," in the sense of not having a disability and meeting society's definitions of "healthy" and "functioning"; uses simplified assessments of value that do not account for the complexity of patient experience; and does not to take into account clinical expertise on rare disorders that may not have an extensive research literature available for use. Other stakeholders—often from the medical, health economics, and health insurance fields—argue that QALYs provide payers with valuable information on a treatment's potential benefits and costs and aid them in negotiating a reasonable price with the drug (or treatment)'s manufacturers.

- Patients may find these reports from the Patient Access and Affordability Project (PAAP) and the Pioneer Institute helpful in understanding how the use of the QALY impacts patients:
  - "ICER uses QALYs to evaluate healthcare," PAAP
  - "Study Urges Caution Before Adopting ICER Reviews to Determine Cost Effectiveness of Treatments," Pioneer Institute
  - "Bad Science: How the use of QALYs creates biased and unreliable outcomes for patients," PAAP
  - "A Better Way: Replacing the QALY with a true, patient-centered quality-of-life measure," PAAP

Key Points to Consider for Stakeholder's Written or Oral Comments

Clinical Effectiveness

- Multiple sclerosis (MS) is an autoimmune inflammatory condition that affects the central nervous system. Most prominently, it results in a cascading loss of the myelin covering nerve cells, which leads to the decreased function and eventual death of those nerve cells. Multiple sclerosis symptoms include weakness, fatigue, vision changes, pain, and balance problems. Symptoms and loss of function typically accumulate and get worse over many years as the patient undergoes new episodes of inflammation, which is described as relapsing-remitting MS (RRMS). Roughly 85% of MS patients suffer from this form of the disease.

- MS affects almost one million people in the United States and is roughly three times more common in women than in men. Symptoms usually appear when patients are in their 20s to 40s. Without treatment, patients will typically need a walking aid after about 20 years and their life expectancy is reduced by an average of about seven years. Notably, patients with RRMS live longer than those with other types of MS. Black people with MS are more likely to have more severe disease progression and different symptoms, though it is unclear if the differences result from physiological factors or disparities and inequities in quality and access to care.

- When providing their perspectives, patients and caregiver focus on preventing disease progression to maintain independence, mobility, and avoid new or worsening symptoms – like pain, fatigue, and cognitive difficulties – that can dramatically impact daily life and productivity.

- Early diagnosis and comprehensive treatment are critical to achieving those goals. Advances in clinical diagnostics and monitoring are enabling people more MS patients and their clinicians to better monitor the state of their condition. Because MS causes progressive disability, caregivers' burdens increase over time, which can affect their quality of life.

- Much of the primary data from research trials focus on annual relapse rates (ARR), as well as confirmed disability progression (CDP) at 3 and 6 months after start of treatment. The Expanded Disability Status Scale (EDSS), a commonly used measure for quantifying and monitoring changes in disability, presents additional challenges for patients and their care teams evaluating and comparing treatment options. By focusing primarily on a patient's ability to walk without adequately considering

smaller changes in disease progression, many argue the EDSS may not be optimal for assessing the condition of MS patients.

- ICER's draft report provides class review on MS medications designated as disease modifying therapies (DMTs), which means they are intended slow the course of the disease rather than just treating symptoms or complications. The assessed treatments include both injected monoclonal antibodies and oral medicines that work through different physiological pathways, or "mechanisms of action" (See chart below).

Table 1.1. Interventions of Interest

Intervention Brand Name (Generic Name)	Mechanism of Action	Delivery Route	Prescribing Information (Maintenance Dose*)
Monoclonal Antibodies			
Tysabri® (Natalizumab)	$\alpha_4\beta_1$-integrin antagonist	IV	300 mg every 4 or 6 weeks
Kesimpta® (Ofatumumab)	Anti-CD20	Subcutaneous	20 mg once monthly
Ocrevus® (Ocrelizumab)	Anti-CD20	IV	600 mg every 6 months
Rituxan® (Rituximab)	Anti-CD20	IV	500 mg every 6 months
Ublituximab	Anti-CD20	IV	450 mg every 6 months
Oral Therapies			
Tecfidera® (Dimethyl Fumarate)	Anti-oxidative	Oral	240 mg twice daily
Vumerity® (Diroximel Fumarate)	Anti-oxidative	Oral	462 mg twice daily
Bafiertam® (Monomethyl Fumarate)	Anti-oxidative	Oral	190 mg twice daily
Gilenya® (Fingolimod)	S1P receptor modulator	Oral	0.5 mg once daily
Zeposia® (Ozanimod)	S1P receptor modulator	Oral	0.92 mg once daily
Ponvory® (Ponesimod)	S1P receptor modulator	Oral	20 mg once daily
Mayzent® (Siponimod)	S1P receptor modulator	Oral	2 mg once daily
Aubagio® (Teriflunomide)	Dihydro-orotate dehydrogenase inhibitor	Oral	7 mg or 14 mg daily

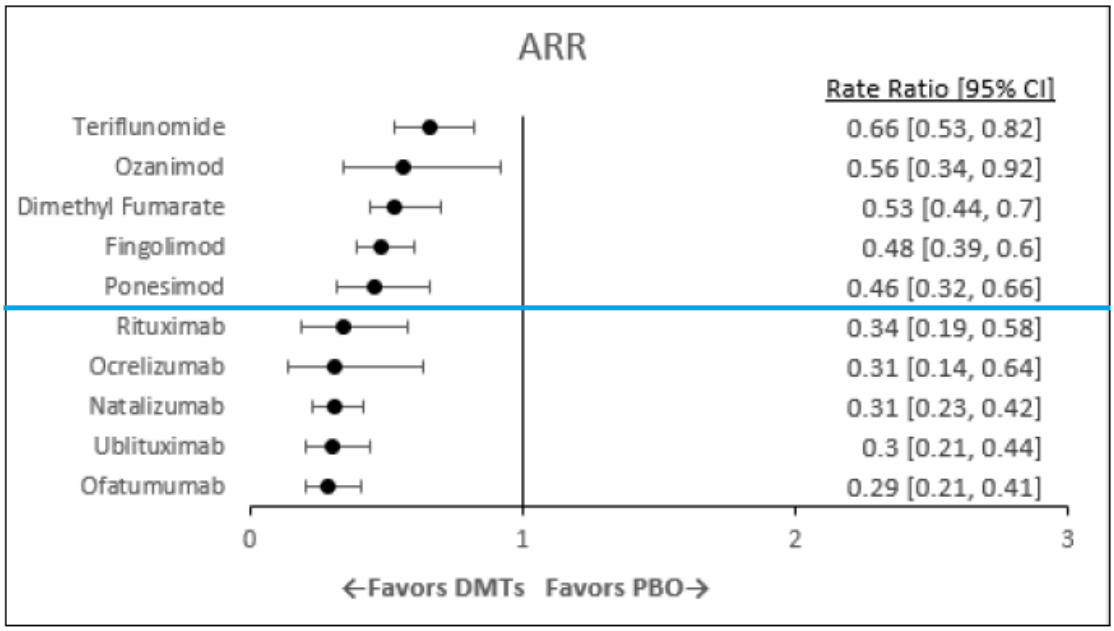
IV: intravenous, mg: milligram, S1P: sphingosine-1-phosphate

*Dose listed is the maintenance dose. Some treatments require induction doses.

- ICER specifically focuses on ublituximab, which is an injectable compound currently under FDA review, with a decision expected by the end of the year. The review found that ublituximab was effective for treating MS, and that data from two phase three trials showed people receiving ublituximab had much less disease activity from 24 to 96 weeks after starting treatment compared to oral teriflunomide.

- ICERs review also found that all the monoclonal antibodies were effective to roughly the same degree and were categorically more effective than the oral medicines. However, both types of treatment are better than not using any DMTs. Specifically, the report found that all five of the monoclonal antibodies had an estimated reduction in ARR of 70%, while the oral agents reduced ARR by around 50% (See chart below for data comparing the effectiveness of various medicines in preventing relapses compared to placebo. The blue line separates monoclonal antibodies from oral DMTs).

Figure 3.1. Base-Case Forest Plot for DMTs versus Placebo for ARR



(ARR = Annual Relapse Rate)

- According to the report, "all DMTs decreased the annualized relapse rate (ARR) compared with placebo. Ublituximab showed comparable reduction in ARR versus other monoclonal antibodies and a relatively greater reduction compared with oral DMTs." The report also concluded that "the monoclonal antibody class had a greater magnitude of benefit versus placebo than oral DMTs versus placebo on the risk of time to disability progression measured at 3 and 6 months."

- ICER's findings on potential serious adverse effects off all the assessed treatments are summarized in the chart on the following page:

Table 3.2. Harms of DMTs

Intervention	Black Box Warning	Serious Adverse Events	Serious AEs at Two Years	Discontinuation due to AEs at Two Years
Monoclonal Antibodies				
Ublituximab	N/A (FDA approval pending)	Neoplasm, infection	**ULTIMATE I & II** Ublituximab: 10.8% Teriflunomide: 7.3%	**ULTIMATE I & II** Ublituximab: 4.2% Teriflunomide: 0.7%
Natalizumab	PML	Cholelithiasis, hypersensitivity, infections (urinary tract), need for rehabilitation	**AFFIRM** Natalizumab: 19% Placebo: 24%	**AFFIRM** Natalizumab: 6% Placebo: 4%
Ocrelizumab	N/A	Neoplasm, infection, or infestation	**OPERA I** Ocrelizumab : 6.9% Interferon β-1a 44: 8.7%	**OPERA I & II** Ocrelizumab: 3.5% Interferon β-1a 44: 6.2%
Ofatumumab	N/A	Infection, injection-related reaction, neoplasm	**ASCELPIOS I & II** Ofatumumab: 9.1% Teriflunomide: 7.9%	**ASCELPIOS I & II** Ofatumumab: 5.7% Teriflunomide: 5.24%
Rituximab	Fatal infusion-related reactions, severe mucocutaneous reactions, hepatitis B virus reactivation, and PML*	Bleeding ulcer, bronchiectasis, infection, neutropenia, sinus tachycardia	**RIFUND-MS** Rituximab: 8.2% DMF: 5.2%	**RIFUND-MS** Rituximab: 3.1% DMF: 0%
Oral Therapies				
Dimethyl Fumarate	N/A	Abdominal pain, back pain, gastroenteritis, infection, pneumonia	**CONFIRM & DEFINE** DMF: 17.6% Placebo: 21.4%	**CONFIRM & DEFINE** DMF: 14.2% Placebo: 12.1%
Fingolimod	N/A	Atrioventricular block, bradycardia, chest pain, back pain, macular edema, neoplasm, urinary tract infection, herpetic infection‡	**FREEDOMS I & II** Fingolimod: 12.3% Placebo: 13.1%	**FREEDOMS I & II** Fingolimod: 12.5% Placebo: 8.9%
Ozanimod	N/A	Influenza, neoplasms, insomnia	**RADIANCE** Ozanimod 1 mg: 6.5% Interferon β-1a 30: 6.4%	**RADIANCE** Ozanimod 1 mg: 3% Interferon β-1a 30: 4.1%
Ponesimod	N/A	Hepatobiliary disorder or liver enzyme abnormality, Infections and infestations, nervous system, and gastrointestinal disorders	**OPTIMUM** Ponesimod: 8.7% TER: 8.1%	**OPTIMUM** Ponesimod: 8.7% TER: 6.0%
Siponimod	N/A	Alanine aminotransferase and aspartate aminotransferase increase, basal cell carcinoma, urinary tract infection	**EXPAND** Siponimod: 18% Placebo: 15%	**EXPAND** Siponimod: 4% Placebo: 3%
Teriflunomide	Hepatotoxicity and embryofetal toxicity†	Infection	**TEMSO** TER 14 mg: 15.9% Placebo: 12.8%	**TEMSO** TER 14 mg: 10.9% Placebo: 8.1%

AE: adverse event, DMF: dimethyl fumarate, mg: milligram, N/A: not applicable, PML: progressive multifocal leukoencephalopathy, TER: teriflunomide

*Black box warnings derived from FDA label. Rituximab is not currently approved for MS. †Black box warnings based on indirect evidence of animal data and leflunomide. ‡Two fatal cases of infection in the one-year TRANSFORMS trial.

- Interestingly, the chart above shows that discontinuation rates at two years were variable across the different compounds and trials, but direct comparisons are difficult because of the differences in the comparator arms. Significant variability was also seen in the rate of discontinuation from placebos – 3.0-12.1%. However, for its cost-effectiveness modeling, ICER used a discontinuation rate after 2 years of 3.9% for ublituximab, 4.7% for the monoclonal antibody comparator ocrelizumab, and 8.8% for the oral treatment of dimethyl fumarate.

- Because the report looks at groups of medicines (i.e., monoclonal antibodies and oral therapies), and each of the different treatments has various pros and cons – including risks of infections due to the immune suppression or lowered effectiveness of vaccines – it is important that individuals engage in shared decision making with their clinical team. As the report summarizes, "Due to significant disease heterogeneity, current clinical practice guidelines recommend considering the risks and benefits of each treatment strategy on a patient-by-patient basis…..with some clinicians and people with MS opting to begin treatment with a lower efficacy DMT and escalating as needed; other clinicians and people with MS opt to begin treatment with more aggressive therapy such as monoclonal antibodies."

- Concerning the importance of shared decision making, the report also cites expert consensus guidance from the American Academy of Neurology published in 2018 that "The choice of therapy should consider patient preferences in terms of safety, route of administration, lifestyle, cost, efficacy, and tolerability. Comorbidities such as depression, anxiety, vascular risk factors, and adverse behaviors should be assessed and treated before starting DMT therapy, as those may be associated with worse outcomes." Similarly, according to ICER's report, in 2022 the Consortium of MS Centers stated that "In terms of therapeutic selection for MS, the best practices include offering a shared decision-making process that considers evidence-based information about the available options, the provider's knowledge and experience, and the patient's values and preferences." Interestingly, none of the clinical guidelines summarized in the report mention rituximab, which ICER prominently includes in its report even though it is not approved by the FDA for treating MS.

Recommendation: Advocates for better treatments for multiple sclerosis should consider making the following points in their written or oral comments:

- Multiple sclerosis is a serious, life-altering condition that results in progressive disabilities over many years. Disease modifying treatments – particularly monoclonal antibodies – can slow disease progression and help people with MS maintain their independence.

- Advocates should provide their personal perspectives and insights about the effects of MS and the importance of having more and better treatment options.

- Discuss how the pain, inability to walk, vision problems, cognitive changes, and declined work productivity resulting from MS affects the daily lives of MS patients as well as their families and caregivers.

- Because of the complexity of treating MS and the need for ongoing monitoring and treatment of symptoms, people with MS should engage in shared decision making with their clinicians to collaboratively develop individualized treatment plans. Shared decision making is particularly important at the early stages of the illness when maintenance of function and independence may be most critical – as well as for symptom control and management.

Cost Effectiveness

- As noted above, ICER's economic modeling and analysis uses the concept of Quality Adjusted Life Years (QALYs) and "utilities" as fundamental components of its economic modeling and analysis. Using QALYs for decisions about payment, coverage, and rationing of care has been widely criticized because QALY calculations assume that people with less than perfect health have diminished quality of life. Therefore, QALYs inherently discriminate against people with chronic conditions and disabilities. People with MS likely begin experiencing symptoms when they are reaching their prime working years, therefore, QALY based analyses may under-estimate the impact of MS on people's work productivity and earnings.

- In its cost effectiveness analysis, ICER found that ublituximab increased QALYs more than the oral medicine ICER used as a comparator, but not as much as ocrelizumab. The chart below shows some of the other quality of life and longevity aspects of ICER's cost-effectiveness analysis, including the ability to walk without restrictions.

Table 4.3. Base-Case Model Outcomes Over a Lifetime Time Horizon

Treatment	Treatment Cost	Total Cost	Years Without Ambulatory Restrictions*	Years Without a Wheelchair†	QALYs	Life Years	evLYs
Ublituximab‡	$1,193,000	$1,914,000	14.58	18.02	13.40	21.36	13.56
Natalizumab	$1,982,000	$2,755,000	15.69	18.91	14.09	21.62	14.30
Ofatumumab	$1,466,000	$2,131,000	14.47	17.93	13.33	21.33	13.48
Ocrelizumab	$1,220,000	$1,912,000	16.55	19.56	14.62	21.82	14.86
Dimethyl Fumarate	$421,000	$1,112,000	12.58	16.22	12.08	20.86	12.08

EDSS: Expanded Disability Status Scale, evLY: equal-value life year, QALY: quality-adjusted life year

*As measured by time in EDSS health states less than 5.

†As measured by time in EDSS health states less than 7.

‡Assuming a placeholder price for ublituximab equivalent to the net price of ocrelizumab.

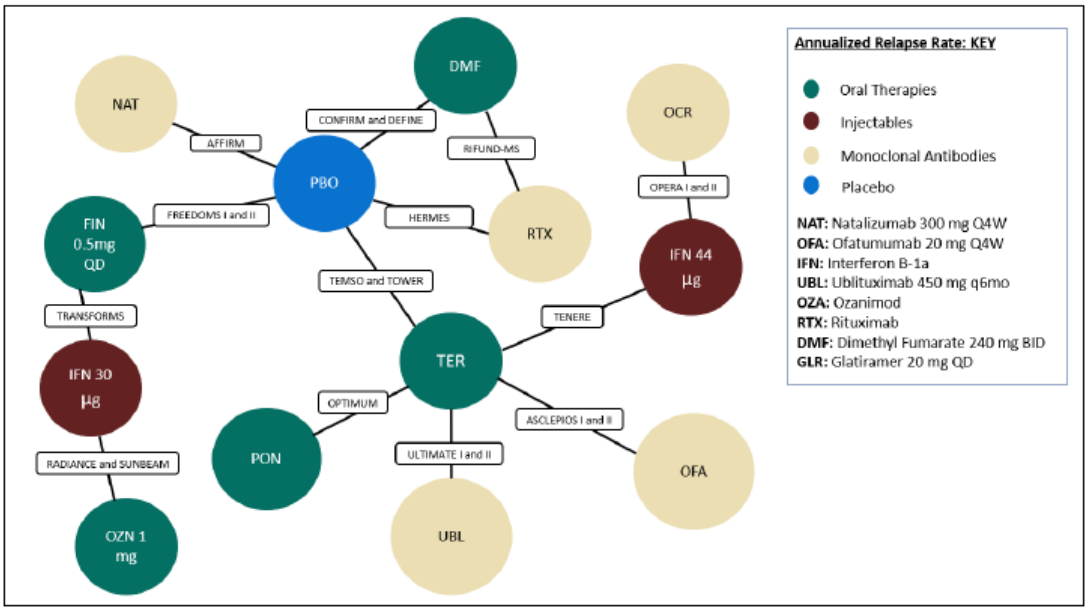
- In the report's supplemental materials, ICER reported the range of QALY estimates for ublituximab as being much wider than for the other medicines – presumably because there is less data available for ublituximab. However, this data also shows considerable overlap with the range of QALYs for ocrelizumab:

Compound	Range of Estimates for QALYs	Mean Estimate of QALYs
Ublituximab	8.46 – 16.70	13.15
Ocrelizumab	10.73 – 16.70	14.39
Dimethyl Fumarate	11.76 – 12.43	12.10

Data from ICER Draft Report Table E25 "Results of Probabilistic Sensitivity Analysis"

- A majority of ICER's analysis of ublituximab's cost effectiveness is based upon a networked meta-analysis, which essentially combines data from many different trials into one model. However, because of the number of different monoclonal antibody and oral treatments for MS that ICER included in its analysis – and the lack of data comparing each medicine to the others – ICER's "network" involved connecting data using the transitive concept of A is to B is to C is to D, resulting in some association of A is to D. The draft report depicts this "network meta-analysis" relationship in the chart below:

Figure D2. ARR Network Diagram



- This graphic shows the disconnected data relationships that ICER built into its cost-effectiveness model, and represents some of the many assumptions and uncertainties contained in that modeling. As the report itself notes, "Because there were very few head-to-head trials between our treatments of interest, we conducted indirect comparisons via a network meta-analysis (NMA)."

- The report also describes how its analyses required a range of assumptions that resulted in various uncertainties because of improving methods for diagnosing and monitoring people with MS. For example, more powerful MRI machines and "changing imaging protocols have improved the utility of MRI in the diagnosis and monitoring of patients with MS." Those uncertainties – and many others underlying ICER's modeling – raise questions about the validity and reliability of ICER's analyses. As ICER notes, its conclusions are limited by the "changing diagnostic

criteria for MS over time such that trial populations may not be entirely comparable and uncertainty in the data for CDP outcome that limits how informative this outcome is in distinguishing between DMTs, despite its importance to patients."

- In its discussions, ICER evaluates the cost-effectiveness of ublituximab against both the oral treatment dimethyl fumarate and ocrelizumab, which ICER assumes is a comparable monoclonal antibody treatment. However, ICER also compares ublituximab to rituximab, which is available as a much lower cost biosimilar. In doing that additional analysis in its cost-effectiveness modeling (and its "budget impact analysis" – see below), ICER is sending a clear signal to insurance companies and other payers that (even though rituximab is not approved by the FDA for treating MS), the lowest cost treatment option should be given priority in any benefit structure through cost-sharing and prior authorization barriers. Unlike many other of its reports, ICER makes its perspective very clear in this statement: "When it comes to determining a fair price for new monoclonal antibody treatments, one may ask what evidence supports a comparative clinical advantage for the new monoclonal antibody treatment over the existing options and similarly at what cost tradeoff? If no known clinical advantages are demonstrated, one may also consider what price premium if any, is reasonable for labeled monoclonal antibody treatments over that of agents such as biosimilar rituximab. The present price premium between rituximab and the net price of ocrelizumab is between 600% and 1300%."

- An additional concern about ICER's economic cost effectiveness modeling is that it does not consider how treatments will improve over time with newer medicines or treatment combinations. The draft report does not discuss that despite the report noting that there are other treatment options in development, including Bruton's tyrosine kinase inhibitors (at least two of which are in phase 3 clinical trials), and that "hematopoietic stem cell transplantation has shown promise as a treatment for MS." Such a consideration would seem important for a condition that progresses over many decades.

- The "budget impact" analysis is another controversial aspect of ICER's report. In that analysis ICER assumes that the U.S. healthcare system is a monolithic single payer entity, and that in any year, all new medicines should not receive more than a certain amount of money in total – regardless of how much they benefit patients. That dollar amount is based upon the average total spending on medicines in prior years divided by the average number of new treatments the FDA had approved in recent

years – which is then increased by U.S. GDP +1.0% per year.

- ICER's "budget impact analysis" for MS treatments found that compared to a market basket of monoclonal antibody treatments approved to treat MS, the number of people that could be treated with ublituximab did not breach ICER's fictional spending ceiling. However, when ICER including the biosimilar form of rituximab as part of its budget impact analysis – because rituximab biosimilars are much less expensive – then the percentage of people with MS who could be treated before hitting ICER's budget limit, is only 17% per year.

Recommendation: Advocates for better treatments for multiple sclerosis should consider making the following points in their written or oral comments:

- Question ICER's use of QALYs as a fundamental basis for its cost effectiveness evaluation, particularly because of how it discriminates against people with chronic and progressive diseases such as MS that affects people during their prime working years. Similarly, strongly question ICER's modeling methodology that has an extreme number of assumptions and uncertainties that make the report's conclusions questionably useful for real-life situations faced by patients and clinicians.

- Insurance companies and other payers should not establish very high co-payments, or erect cost-based barriers – such as prior authorization or similar policies. Such access restrictions for MS treatments significantly undermines shared decision making. That is, a patient's clinical team should not be second-guessed and blocked by insurance company rules or barriers. Advocates should raise those concerns and include their own experiences with not being able to get – or having to overcome significant hurdles to access – medicines recommended by their clinicians because of insurance company rules or processes, such as high-co-payments or prior approval paperwork and reviews.

Conclusions

- Highlight the importance of new treatment options for people with MS – particularly for those newly diagnosed who may benefit greatly from delaying progression of their symptoms when they are in their 20s, 30s and 40s, when they may be working and raising families.

- Recognize that ICER's continuing use of a QALYs in its economic modeling discriminates against people with chronic conditions, including MS. Such flawed

analyses could lead insurance companies and other payers (including government programs) to use those analyses for actively denying payment or creating barriers that limit access to treatments recommended by their clinicians.

- Summarize and restate your thoughts, and provide overall recommendations for what ICER should do – or not do – particularly related to the harms access barriers that ICER's conclusions could cause. And specifically, note that ICER's comparisons that include a treatment that is not approved for treating MS is a perilous practice.

- Particularly note that access barriers to care can compound inequities in U.S. healthcare because overcoming them requires time and resources, which people with MS may find especially difficult as they are trying to confront the new challenges presented by the disease itself.