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June 2, 2021

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Steven D. Pearson, MD, MSc, President
Institute for Clinical and Economic Review (ICER)
Two Liberty Square
Ninth Floor
Boston, MA 02109

**Re: Aducanumab for Alzheimer's Disease: Effectiveness and Value
Draft Evidence Report**

Submitted electronically to: publiccomments@icer.org

Dear Dr. Pearson:

On behalf of the Society for Women's Health Research, we appreciate the opportunity to provide comments on ICER's Aducanumab for Alzheimer's Disease: Effectiveness and Value Draft Evidence Report.

For over 30 years, SWHR has dedicated itself to promoting research on biological sex differences in disease, and to improving women's health through science, policy and education. We continue to serve as a resource to ICER on key aspects of value assessment that have implications for women and their health. SWHR's Alzheimer's Disease network raises awareness about biological sex differences in AD and has created recommendations for future research and policies in this field.

In October 2020, we provided [comment](#) on ICER's Alzheimer's Disease Update: Open Input, encouraging ICER to analyze data on Alzheimer's Disease (AD) sex and gender differences and account for them in its model analysis plan. We also suggested that ICER should consider for comparison all available evidence-based options, including behavioral therapies and lifestyle interventions. Finally, we asked that ICER quantitatively account for the public health burden of AD and its cost-effectiveness methodologies, and that burden of illness factors that impact women disproportionately (like caregiver burden) should be included in ICER's model analysis plan.

SWHR is concerned about the methodology and conclusions of the Draft Evidence Report, which we believe fails to take into account the totality of scientific evidence and factors that an approved therapy might have on an individual with AD, as well as their caregivers. Specifically, the use of the methodology could limit a

person's access to medications that could add years of active life. For women in particular, methodologies must take into account the burden of AD on women as both patients and caregivers, and recognize the burden that could be assuaged by new therapies that have the potential to lengthen and improve quality of life. We offer the following comments:

Inaccurate Characterization of Scientific Evidence.

ICER assumed blended efficacy of the ENGAGE and EMERGE trials when working to evaluate cost effectiveness of aducanumab. Further, ICER's [argument](#) that "the primary outcome of CDR-SB, while a validated scale, is not used frequently in clinical practice and thus the minimal clinically important difference has not been established" is not accurate. FDA's guidance on the development of drugs for the treatment of early-stage disease specific to AD [recommends](#) CDR-SB as just one potential approach to evaluate cognitive and functional change in individuals with MCI. We reiterate that even small changes can be clinically meaningful for patients and their caregivers, and must be taken into account.

EMERGE specifically showed statistically significant differences between drug and placebo on all secondary outcome measures, with the Neuropsychiatric Inventory (NPI), which assesses behavioral changes common in AD, showing an 87% reduction from baseline with an 84% reduction of caregiver burden. These types of data and evidence should be incorporated into the methodology so as to evaluate value and reduction in burden.

ICER's characterization that taking aducanumab has a "high certainty of harm" is not aligned with the evidence related to the ARIA-E and ARIA-H data, particularly as it relates to the benefits of the therapy. As the Alzheimer's Association points out, "ARIA is a manageable side effect of treatment and far less threatening than complications of many routinely used therapies for other conditions, including cancer." Given the FDA guidance and work of the [Alzheimer's Association's Research Roundtable Workgroup](#) recommendations on the matter, management of ARIA is possible, with the benefits of treatment outweighing the risks.

Account of Value, Need and Innovation

Because ICER assumed blended efficacy of ENGAGE and EMERGE, the calculation of quality of life years (QALY) was skewed inappropriately. Had ICER used only evidence from EMERGE, a higher assessed QALY would have resulted- with the Alzheimer's Association [indicating](#) that it would result "in a cost-effectiveness price about three times higher."

Further, QALY should incorporate a more flexible formula that appropriately values quality of life years, beyond direct patient costs. SWHR would have liked to have seen a broader range of value that this therapy would bring to a patient and their caregiver. Given this, we reiterate our [Value Assessment Principles](#) for consideration: Value assessments should account for diversity in patients, including sex and genders; in addition to measuring clinical outcomes, value assessment frameworks should account for what matters most to patients, caregivers, and society, while recognizing that these values vary and change across patient populations; value assessments should take into consideration the long-term benefits of a therapy; and value assessments should use a range of high-quality evidence to demonstrate improvement in outcomes.

Unfortunately, it does not appear that ICER incorporated these principles broadly into its draft evidence report for aducanumab. We are specifically concerned that this was not the case related to the burden of caregiving. Nearly half of all caregivers (48 percent) who provide help to older adults do so for someone with AD or another dementia. In 2017, caregivers of people with AD or other dementias

provided an estimated 18.4 billion hours of unpaid assistance, a contribution to the nation valued at \$232.1 billion.

The responsibilities of caring for someone with dementia frequently fall to women, with daughters comprising over one-third of dementia caregivers. Female caregivers report a twofold higher level of caregiver burden compared to male caregivers. While men also provide assistance, women tend to spend more time providing care than men (21.9 v 17.4 hours per week). Further, women are likely to assist with more difficult caregiving tasks, such as toileting and bathing, while men are more likely to assist with finances or arrange for other care.

Caregiving generally is associated with elevated levels of cortisol and impaired attention and executive function. Dementia caregivers in particular are broadly at risk for a variety of health difficulties, including increased rates of chronic conditions, more frequent interactions with the health care system, decreased engagement in healthy preventative behaviors, and increase behavioral health concerns, such as smoking. Caregivers also demonstrate poorer immune responses to vaccines, slowed healing time, and reduce overall immunity to disease. Spousal caregivers may be at higher risk of cognitive impairment of dementia than non-caregiver spouses in response to several psychosocial, behavioral and physiological variables.

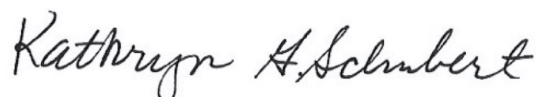
Any therapy that would slow progression of AD – extending the period of time when those with the disease may remain in a stage where they have some level of independence and ability to contribute to their own care – provides a huge value to caregivers, which must be taken into account in value analyses. ICER did not fully account for the reduction of this burden as well as the sheer level of burden experienced by those caring for individuals with AD in its draft evidence report.

Beyond this, there is significant unmet need for those living with AD. Currently no disease-modifying treatments exist, and aducanumab signifies the potential for those affected by AD, as well as opens the doors to additional, new therapies that might alter the progression of disease. The lack of current treatments like this should be incorporated into the methodology both because of its potential to meet unmet need and for its innovation.

Conclusion

We appreciate the opportunity to provide comment on ICER's Aducanumab for Alzheimer's Disease: Effectiveness and Value Draft Evidence Report. We believe that innovative treatments that impact both disease progression and caregiver burden have great value to a patient population, and that any methodology to assess value should include these factors, and those above. Please do not hesitate to contact me at kathryn@swhr.org or (202) 297-5122 if we can provide additional information or be of assistance.

Sincerely,



Kathryn G. Schubert, MPP
President and Chief Executive Officer
Society for Women's Health Research