Biogen

June 10, 2021

Dear Dr. Steve Pearson,

Thank you for the opportunity to comment on ICER's *Alzheimer's Disease, 2021: Draft Evidence Report.* Biogen values credible, reliable scientific and economic evidence based on valid assessment methods, and meaningful input from subject matter experts and patient communities. We recognize the unique challenges that an Alzheimer's disease value assessment brings and the complex task ICER had in drafting this assessment for the first Biologics License Application for the treatment of Alzheimer's disease. After careful review, we are deeply disappointed and fundamentally disagree with ICER's draft evidence report and press releases.

At this time, due to requirements under the FDA's Accelerated Approval regulatory pathway, we will not be making specific analytical recommendations on ICER's draft evidence report. We aim to supplement this letter with a more substantive response at a later date.

We would like to note the following with regards to best practices on biostatistical and pharmacoeconomic modeling methods for health technology assesments:

- When conducting comparative effectiveness analysis and economic modeling, data should be pooled only when adjustments are made for differences within the datasets.
    - In particular, to pool data from different trials without adjusting for known relevant differences such as duration of follow-up, exposure to the target treatment dose, etc may lead to biased results.
- All methodological assumptions in a cost effectiveness analysis need to be balanced and justified.
    - When assumptions are made, base assumptions should be realistic and tested in extensive scenario analysis.
- Technology assessments should incorporate unique societal considerations of the disease state being assessed.
- Appropriate disease-specific value thresholds should be utilized in the economic model.
    - For example, ICER's quality-adjusted life-year (QALY) thresholds ($100K-$150K) are too low for Alzheimer's disease and should be adjusted to capture the devastating disease burden, lack of treatments, and other contextual considerations.

This is an important and exciting time for Alzheimer's disease patients, families, and innovation. At Biogen, we look forward to continuing to bring our health economic and technology assessment experience, together with experts across the field, to advance the development of equitable value frameworks for new Alzheimer's disease treatments.

Sincerely,

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June 2, 2021

Lilly Response to ICER's Draft Evidence Report – Aducanumab for Alzheimer's Disease

ICER's review of aducanumab, as the first drug submitted to the FDA with the potential to modify the progression of Alzheimer's disease (AD), is of particular interest to the field given its potential to establish important precedents with respect to the evaluation of future disease-modifying agents for AD. We focus our comments on ways in which we believe ICER can improve its assessment of value, both within and outside of the traditional "cost per QALY" framework.

Inadequacy of Traditional Cost-Effectiveness Paradigm for Alzheimer's Disease

We were encouraged to see ICER include in the draft evidence report on aducamumab (Section 5) a short list of potential benefits and contextual considerations *beyond those captured in the traditional cost-effectiveness paradigm* that may affect overall judgments of long-term value for money provided by treatments for AD. A more comprehensive benefit list was articulated by a special ISPOR task force in 2018 and includes a number of additional value elements of particular relevance in AD.[1] These include: (1) "scientific spillover," the value of research and innovation in an area of high unmet medical need on future generations regardless of immediate health gains; (2) "insurance value," the benefit to healthy persons of physical and financial risk protection provided by effective new treatments; (3) "severity of disease," the greater value placed by society on treating more severe diseases; and (4) "distributional equity," addressing the disproportionate impact of disease on different groups and communities, including those defined by age, gender, race/ethnicity, socioeconomic status and educational level. These additional value elements are missing in the standard "cost per QALY" framework. Given the critical importance of many of these factors in AD, we disagree with ICER's approach of defaulting to the "frequently cited" willingness-to-pay thresholds of $50K, $100K and $150K per QALY gained for base-case analyses and in "fair price" calculations. AD, in particular, has been called out, along with metastatic cancers, as one of the most "severe" illnesses with high unmet need, for which use of a higher threshold would be appropriate.[2] While asking the members of the California Technology Assessment Forum (CTAF) voting body to consider additional contextual considerations when assessing the value of treatments for AD is appropriate, we feel that anchoring such judgments to traditional (and controversial) cost-per-QALY benchmarks is problematic.[3]

Comments on Long-Term Cost Effectiveness Analyses

We commend ICER for responding to several important points that were raised consistently by multiple stakeholders in response to the initial Scoping Document on aducanumab reported in

November 2020. In particular, we applaud the formal adoption of both health care system and societal perspectives as base-case comparative cost-effectiveness analyses and the consequent inclusion of costs and benefits from both patient and caregiver perspectives. On the other hand, we remain concerned that in its current form ICER's cost-effectiveness model may still significantly underestimate the full extent of the costs of AD from both of these perspectives. For example, ICER's current model does not include out-of-pocket expenditures paid by patients and family members for medical care, long-term care and formal care, which can be substantial, particularly in later stages of disease.[4-6] Furthermore, caregiver costs captured in ICER's model reflect only the opportunity cost of time spent caregiving and neglect other spill-over costs attributable to reduced health and well-being of the caregiver and other family members.[7-8]

A short-coming of many AD cost-effectiveness models, including the model used by ICER, is that they underestimate the complexity of the disease state, with only a small number of discrete states defined solely on the basis of cognitive status (i.e., MCI, mild, moderate, and severe AD and death). Given the steady, progressive and irreversible nature of AD, such models may fail to fully capture the value of disease modification that may accrue in smaller but meaningful cost-offset and quality-of-life increments over shorter time intervals. In contrast, a more granular model that is better able to capture treatment impacts across multiple dimensions (e.g., cognition, function, and dependency) and shorter time intervals may be preferable for this complex disease. Use of a more detailed approach is also more likely to permit modeling from intermediate trial endpoints and could help address the critique that benefits seen in trials are not "clinically meaningful."

Another concern with the current model is that it likely significantly underestimates the quality-of-life impact of AD on both patients and caregivers due to the choice of utilities used in modeling. The patient utility values used in ICER's model are derived from a study[9] using generic health-related quality-of-life instruments (i.e., EQ-5D and HUI3) that are broadly criticized as inappropriate in AD in that they are insensitive to changes in disease progression and having substantial ceiling effects and poor inter-rater reliability.[10-13] This same study was used for estimates of caregiver quality-of-life, despite the fact, as noted by the authors of the draft report, that these utilities "did not vary by AD disease severity" – a fact that demonstrates a lack of face validity for this use and further reinforces our concerns about the scores. Another recent study demonstrated that the EQ-5D, when used to assess caregiver quality-of-life, has a low sensitivity to change and fails to differentiate by patient AD dementia severity. The authors concluded that "the EQ-5D is not particularly effective for capturing the true impact on caregivers of caring for people with Alzheimer's disease."[14] We propose that using values derived from direct utility elicitation studies or, alternatively, mapping from more sensitive disease-specific measures such as the Quality of Life Alzheimer's Disease scale (QOL-AD) to utility scores could provide more reliable and credible estimates.[15-16]

As a final point, we note that ICER chose to conduct sensitivity analyses only from the *health care system* perspective. In light of the importance of and uncertainty around, both indirect costs of care and caregiver quality-of-life impacts as noted above, we suggest ICER include sensitivity analyses from the *societal* perspective in order to understand the effects of uncertainty on these and other caregiver-related variables on cost-effectiveness estimates.

Conclusion

Eli Lilly and Company applauds ICER's attention to the complexities of valuing disease-modifying treatments for Alzheimer's disease, as well as ICER's openness to input from other organizations on how to manage those complexities. We hope our comments contribute to a productive discussion for advancing and further refining ICER's approach. We welcome any additional follow-up questions or engagement.

Sincerely,

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Genentech
A Member of the Roche Group

June 02, 2021

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Dear ICER Review Panel:

Genentech, a member of the Roche Group, appreciates the opportunity to provide input on the *Aducanumab for Alzheimer's Disease (AD)* Draft Evidence Report [1]. We are dedicated to bringing innovative therapies to patients with unmet medical needs and developing evidence-driven solutions to support patient access. As part of an ongoing commitment to AD, Genentech has multiple research programs under development, including gantenerumab - an investigational, monoclonal antibody designed to bind to aggregated amyloid beta and remove amyloid beta plaques.

We provide the following recommendations to more accurately reflect the impact of AD on patients and caregivers, and describe the potential implications of AD therapies on health equity, thereby enhancing the patient-centricity of the report:

1. **Capture the holistic value of aducanumab by describing key secondary clinical endpoints from ENGAGE/EMERGE, in addition to primary endpoints, in the Comparative Clinical Effectiveness section.**
2. **Adopt a more comprehensive approach to estimating patient/caregiver burden in the societal perspective by adding scenarios that include health-related quality of life (HRQoL) beyond a single, primary caregiver and that reflect the broader productivity impacts for patients and their caregivers.**
3. **Leverage equity-informative value assessment methods to incorporate health equity considerations into the appraisal of aducanumab.**

We further expand on these recommendations with supporting rationale and implications below:

1. **Capture the holistic value of aducanumab by describing key secondary clinical endpoints from ENGAGE/EMERGE, in addition to primary endpoints, in the Comparative Clinical Effectiveness section.**

   Recommendation: The Comparative Clinical Effectiveness section should include a detailed discussion of secondary clinical endpoints from ENGAGE/EMERGE trials,

including Mini-Mental State Exam (MMSE), Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog 13), Alzheimer's Disease Cooperative Study Scale for Activities of Daily Living in Mild Cognitive Impairment (ADCS-ADL-MCI), and Neuropsychiatric Inventory 10 (NPI-10).

Rationale: The overall clinical benefit of aducanumab cannot be adequately appraised using Clinical Dementia Rating - Sum of Boxes (CDR-SB) and safety data alone. Secondary clinical endpoints in AD capture important value dimensions on behavioral, functional, and cognitive performance. While current data availability may mean incorporation of these endpoints into a more granular cost-effectiveness analysis (CEA) is not practical, these measures are both necessary and important to appraise the overall clinical benefit of any disease-modifying therapy (DMT) in AD [2,3]. Furthermore, they are of high patient relevance, as reflected by the key challenges of living with AD highlighted in the Patient and Caregiver Perspectives section of the report.

Implications: Including a detailed discussion of secondary clinical endpoints in the Comparative Clinical Effectiveness section ensures that the full clinical benefit of aducanumab is presented, and that adequate consideration is given to endpoints that are important to patients and relevant in clinical practice. Only describing them in the supplementary materials, and not in the main report body, risks both underestimating the clinical benefit of aducanumab and undermining the importance of the patient- and clinical practice-relevant domains for decision making in AD.

2. **Adopt a more comprehensive approach to estimating patient/caregiver burden in the societal perspective by adding scenarios that include health-related quality of life (HRQoL) beyond a single, primary caregiver and that reflect the broader productivity impacts for patients and their caregivers.**

Recommendation: A scenario analysis should be added that incorporates additional caregiver utility decrements to reflect instances where an AD patient has more than one informal caregiver, including secondary caregivers. Additionally, the approach to modeling caregiver societal costs should be updated to include broader productivity impacts (e.g., absenteeism, presenteeism) and non-market productivity losses (e.g., volunteer activities, secondary childcare, and eldercare) for multiple caregivers per AD patient.

Rationale: We recognize that several data gaps exist when attempting to understand family spillover effects, especially in conditions with limited therapeutic options like AD. While ICER notably leverages information on caregiver HRQoL impacts and cost of unpaid carer time, there is an opportunity to further enhance ICER's assessment to better reflect the true burden of AD on patients and their carers by taking a more holistic approach to estimating societal impact.

Firstly, the current approach to estimating the HRQoL reduction from caregiving only models the impact on the primary caregiver. However, additional informal caregivers, such as secondary caregivers, may also experience clinically significant distress [4]. Furthermore, the caregiver disutility estimates rely on a study that leveraged the HUI-2

which - like most instruments that map to a QALY scale - commonly fail to capture important domains of how caregiving impacts HRQoL [5]. They are, therefore, likely to further underestimate the true caregiver HRQoL burden.

Given that up to 40% of caregiver burden is borne by secondary caregivers (in addition to primary carers), ICER should conduct a sensitivity analysis where utility decrements are increased to reflect how AD patients commonly rely on more than one informal caregiver [6]. The need for this change is supported by recent health technology assessment (HTA) methods reviews which highlight the importance of understanding the average number of informal carers per patient to ensure that any assessment reflects the relative contributions and HRQoL impacts of primary and secondary informal carers [7,8].

Secondly, while we commend ICER for including caregiver costs in the co-base case, the current approach to modeling societal impacts for both patients and caregivers is narrow and could be improved through more formal integration of non-market productivity and other indirect costs. In addition to lost time to care for AD patients, caregivers experience other forms of societal costs, including - but not limited to - increased absenteeism and presenteeism, and a reduction in non-market productivity [9,10]. As such, we recommend ICER incorporates these inputs into the model for both primary and secondary caregivers.

If detailed information on the impact of caregiving absenteeism, educational, career, and productivity loss in AD is missing, ICER may consider creating scenario analyses where market and non-productivity losses with age and gender-based US estimates [10] are utilized. We also propose that ICER includes productivity losses for patients aged ≥65 years given the growing recognition of societal losses in elderly populations [11,12].

Implications: Increased scenarios exploring the impact of multiple informal caregivers and a more comprehensive approach to modeling productivity losses for patients and caregivers are needed to ensure that the model appropriately captures the true burden of AD. Ignoring these effects risks underestimating the potential benefits of a DMT in AD for healthcare payers, patients, and their families.

3. **Leverage equity-informative value assessment methods to incorporate health equity considerations into the appraisal of aducanumab.**

Recommendation: Explore and apply formal health equity-informative methodology (e.g. distributional cost-effectiveness analysis [DCEA]) to the value assessment of aducanumab.

Rationale: Health inequity is a major challenge in the US generally and, in AD specifically, evidence suggests minority populations experience higher prevalence of disease [e.g., 13,14] and may achieve worse clinical outcomes [e.g., 15] vs. Caucasian populations. We commend ICER for recognizing the importance of considering health inequalities when assessing the relative value of new health technologies, and the important strides to discuss health equity considerations in their assessments and their CEPAC meetings. To enhance this effort, we encourage ICER to explore and apply

formal health equity-informative methodologies, such as DCEA [16] to this value assessment. DCEA is an extension of CEA that characterizes existing health inequalities and formally measures the impact of an intervention on such health inequalities, beyond the impact on overall population health.

If formal equity-informative methods of cost-effectiveness are not feasible for ICER at this time, we recommend that ICER conduct extensive scenario analyses to (1) benchmark the level of inequality in AD patients relative to the other diseases; and (2) consider how differences in timing of diagnosis across subgroups impacts treatment effect. Furthermore, ICER should describe the important variation in family spillover effects across key vulnerable subgroups based on race/ethnicity and other social determinants of health in the main body of the report.

Implications: Formal steps to characterize both the current state of health inequalities in the US and the expected impact of a new DMT for AD will provide decision makers with needed data-driven insights to understand the impact of their decisions on existing health disparities. Without information to better inform equity implications of value assessments, there is the risk of further hardwiring, and potentially increasing, existing underlying health inequalities.

Conclusion

We commend ICER for their efforts to incorporate important societal impacts of AD into the appraisal of aducanumab via their integration of institutional care information and caregiver HRQoL, and adopting a societal co-base case. The potential availability of a long-awaited DMT for AD is of great importance to society, and a robust appraisal of aducanumab's value should consider the full burden that AD imposes on patients, caregivers, and society. This is essential to help inform health care decision making and ensure optimal and equitable patient access to therapy. ICER therefore has a responsibility to ensure their appraisal considers the holistic value of aducanumab and continued innovation in AD, as well as health equity considerations and the needs of all relevant stakeholders. We believe that our recommendations will enhance the utility of the evidence report, optimize its patient centricity, and provide stakeholders with sufficient information to inform meaningful decisions. Genentech is committed to advancing methods to ensure equitable and patient-centric value assessments, and welcomes the opportunity to discuss these recommendations further.

Sincerely,

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June 28, 2021

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To Whom It May Concern,

On behalf of the Alliance for Aging Research (Alliance), and the millions of older adults whose health and access to care we advocate for, we appreciate the opportunity to provide comment on the Institute for Clinical and Economic Review (ICER)'s draft evidence report on aducanumab for the treatment of Alzheimer's disease (AD).

Do Not Ignore the Value of Alzheimer's Innovation

The development of effective therapies to prevent, delay, and better manage AD and related dementias is one of the most pressing and complex public health challenges facing our nation. Alzheimer's disease is the only top-ten cause of death in the United States without a cure. One in three older adults who die have ADRD, and over six million Americans suffer from AD. According to NIH-sponsored research, the total healthcare and caregiving costs for a person with probable dementia are $287,000 in the last five years of life, compared to $173,000 for someone with cancer and $175,000 for someone with heart disease. In 2020, Medicare and Medicaid spent $206 billion on the total cost of care for AD.

The human cost of not finding a cure for Alzheimer's disease is astronomical. An AD drug development program's total cost is estimated at $5.7 billion, with an expected study time of 13 years from preclinical studies to market approval. However, due to the clinical complexity of ADRD, the failure rate for test therapies in the clinical pipeline to treat AD is 98 percent**.** Between January 2008 and February 2019, 87 clinical programs investing and researching Alzheimer's disease closed. The clinical trial success rates for AD candidates are lower than observed for all other disease areas combined. Ensuring that assessments reflect the value of a treatment to patients and society is vital to support continued investment in treatments for AD.

ICER's Made-Up "Modified Societal Perspective" Does Not Cut It

In May 2021, the Alliance for Aging Research released a report, "Assessing the Value of Therapies in Alzheimer's Disease: Considerations to create a practical approach to value," which the Alliance

commissioned from the actuarial firm Milliman. The report outlines a new framework for assessing the value of Alzheimer's treatments and describes how the traditional approach to value assessment for therapeutics fails to address the challenges posed by AD and suggests principles to create an alternative, equitable value assessment framework.

To evaluate the effectiveness of established value assessment approaches in terms of a disease's true impact on family caregivers, communities, and social service needs, the report authors analyzed publicly available financial and public health data specific to AD. The authors explain that total costs for AD care exist disproportionately beyond medical costs, with an extensive burden on families and residential long-term care. In fact, the status quo of AD care consists of systems of care that depend on low-paid workers or family caregivers, create multi-generational family burdens, and exacerbate existing racial disparities. Available public health data show Alzheimer's has immeasurable and intangible effects on both the patient and caregiver, including unintended job loss, reduction in income, behavioral and psychiatric consequences, and much more.

However, ICER's method of disease burden analysis incorporates direct medical costs into its model and relegates the costs of health effects to family caregivers or work loss for family members related to care needs for loved ones with AD to its subjective "modified societal perspective" as a "co-base-case analysis." ICER states that the rationale for this additional analysis is due to "the large impact of AD on caregivers," which makes it seem as though it would better account for the caregiver perspective. Instead, the modified societal perspective that ICER invented *penalizes* the caregiver for the productivity and economic impacts of keeping a loved one at home, as captured in report summary and comment: "In addition, keeping a patient in earlier AD states longer, which delays the transition to long-term care, can increase productivity losses for the caregiver…This highlights the complexities of capturing caregiver perspectives in the modified societal perspective in that caregivers may prefer to keep loved ones at home, rather than in a long-term care facility, although doing so may increase the negative financial impact on the caregiver."

This statement illustrates the tension inherent in the assumptions underlying ICER's value assessment framework, even under the modified societal perspective proposal, illustrating its inherent weakness and inability to truly account for the family caregiver perspective. From a patient, family caregiver, and societal perspective, there is significant value to prolonging independence and identity that is not reflected in medical costs or solely captured in caregiving burden. Slowing the progression of AD means prolonging independence and identity, both lowering caregiver burden in earlier stages of the disease and providing immense intrinsic value to patients and their families that outweighs opportunity costs lost elsewhere. **If this value is not reflected in the value assessment, that is a shortcoming of the model in accurately capturing and incorporating value, not of patients and caregivers in valuing non-monetary outcomes.** If value assessment fails to accurately capture value to those who benefit from the therapeutic, then the exercise is incomplete.

ICER's Use of QALYs to Value Alzheimer's Disease Presents a Moral Quandary

The use of cost-effectiveness assessment to judge therapeutic value from a payer's perspective, and technical issues using quality-adjusted life years (QALYs) renders the approach problematic. The

QALY has significant limitations when dealing with complex diseases such as AD, as they do not recognize value driven by public health improvement, transformation, or even societal value. These issues are not unique to AD, although the characteristics of AD and the ecology of care around people with AD highlight these issues.

Use of QALY-based cost-effectiveness analysis is a significant issue for people with Alzheimer's disease since the majority of those with dementia are the oldest old—of the estimated 6 million people with Alzheimer's disease who are age 65 and older, 80 percent are 75 years or older, and more than a third are 85 years or older.[1] Also, people aged 65 years and older with Alzheimer's disease are likely to have a comorbid condition such as coronary artery disease (38 percent), diabetes (37 percent), chronic kidney disease (29 percent), congestive heart failure (28 percent), and chronic pulmonary disease (25 percent). When applied to healthcare decision-making by insurance companies, this can mean that treatments for these more vulnerable people are deemed "too expensive" and therefore "not cost-effective" to cover.

Objections about reliance upon QALY-based methodologies also extend to race. For example, Black Americans have an average life expectancy lower than whites. As such, treatments for conditions that disproportionately affect Black individuals may be assessed as lower value. Furthermore, Black and Latino communities experience Alzheimer's disease at higher rates than the general population. Data from the CHAP study shows that 18.6 percent of Black Americans and 14 percent of Hispanic Americans age 65 and older have Alzheimer's disease compared to 10 percent of White Americans.[2] ICER should not use measures that are unable to incorporate equity considerations, which may inadvertently promote structural discrimination.

ICER Pooled Clinical Trial Data with No Adjustments for Exposure

The Alliance for Aging Research is also the convening organization of the Accelerate Cures/Treatments for All Dementias (ACT-AD) coalition, which started in 2005 to be a point of advocacy to share updates and bring the perspectives of patients, family caregivers, health professionals, academic researchers, industry, and senior representatives from federal research and regulatory agencies with the Food and Drug Administration (FDA). In this role, we closely follow the clinical development paths of Alzheimer's disease and related dementia therapies.

ICER's evaluation of the cost-effectiveness of aducanumab in the draft evidence report inappropriately pooled the data of the ENGAGE and EMERGE trials without adjusting for the number of people titrated to a higher dose for the different time periods. Fewer trial participants had the opportunity in ENGAGE to receive high-dose treatment than the patients in EMERGE. By not adjusting, ICER's approach provides an inaccurate picture of the value of the treatment. In its July 2021 public meeting on aducanumab, we request that ICER address why it selected this approach instead of properly analyzing the updated sponsor data submitted to the FDA.

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[2] Ibid.

Next Steps Along a Better Path

To accurately assess the value of Alzheimer's disease treatments, Milliman's report outlines an alternative, equitable value assessment framework for use in AD that accounts for the ecosystem that surrounds people with AD, including the impact treatments may have on ameliorating social ills such as racial disparities. The principles include that such a framework should:

- utilize metrics that, when appropriate, apply the same standards regardless of age or socioeconomics,
- capture the health-related value of AD treatments not only for patients but also for their family caregivers, and
- appropriately account for changes in non-health outcomes and issues of community value related to AD patients and their caregivers.

Dr. Gillian Leng, the new chief executive for the UK's National Institute for Health and Care Excellence (NICE), recently wrote that dealing with COVID-19 has brought a new lens to the use of QALYs in cases where people are suffering from a life-threatening condition, but not yet dying. Her sentiments sound familiar. It is frustrating that ICER continues to espouse the QALY as other countries that have been using it for decades may be moving away from it.

The Alliance will be working in the coming months with leading experts in health economics to further expand upon an alternative value framework for Alzheimer's therapies. The question of whether ICER will modernize and take steps along a better path is in their hands.

If you have questions, please contact me at speschin@agingresearch.org. Thank you for considering our comment.

Sincerely,

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May 10, 2021

To Whom It May Concern,

On behalf of the Alzheimer's Association, all those living with Alzheimer's disease, their caregivers, and their families, we appreciate the opportunity to reiterate and expand upon comments we made in our external review on ICER's Aducanumab for Alzheimer's Disease: Effectiveness and Value Draft Evidence Report.

We fundamentally disagree with the methodology and conclusions of ICER's report. Throughout the report, ICER's analysis fails to take into account the totality of scientific evidence and a number of factors that an approved therapy may have on an individual with the disease and their caregivers. The impact of these methodological decisions could have the effect of limiting an individual's access to aducanumab--a drug that could add weeks, months, or even years of active life for those affected every day by the crushing realities of Alzheimer's. Our deep concerns are outlined below.

Inaccurate Characterization of Scientific Evidence

ENGAGE and EMERGE. In its effort to evaluate the cost effectiveness of aducanumab, ICER assumed blended efficacy of the ENGAGE and EMERGE trials. We dispute and question ICER's approach. EMERGE met its prespecified primary outcome and found in the high dose aducanumab group a 22% reduction in decline on the CDR-SB--an outcome that was evident even under the situation of early trial cessation.

The argument made by ICER 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 misconstrued. The 2013 version of the draft FDA guidance for "Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease" recommended the CDR-SB as one potential approach to evaluate cognitive and functional change in individuals with MCI. The outcome in CDR-SB was significant, and the test is an accepted measurement of both cognition and function as a primary outcome. While the scale of this test maintains a restricted range, small changes can reflect a clinically meaningful alteration for people living with MCI. In addition, EMERGE showed statistically significant differences between drug and placebo on all secondary outcome measures, including a 40% slowing of functional decline in the ADCS-ADL (a test that quantifies activities of daily living). The Neuropsychiatric Inventory (NPI), which was an exploratory outcome measure, assesses behavioral changes common in Alzheimer's. The NPI showed an 87% reduction from baseline, with a

corresponding 84% reduction of caregiver burden. All of this evidence should be the key to ICER's primary analysis. Further, the ICER analysis fails to consider the data in the context of the trial circumstances, instead only evaluating the pooled analysis. For instance, pooled analysis of the CDR-SB assessment across both studies has a treatment effect of 62%; however, when you include the key secondary outcomes in the analysis, this treatment effect is 99%, which better reflects the totality of evidence for high-dose aducanumab. When looking at the data from ENGAGE, similar benefits were observed in the ENGAGE participants who were treated with the high dose for longer periods of time. Lastly, when combined with PRIME data, the positive ENGAGE trial, supportive EMERGE and PRIME data, and additional data from other trials point to an efficacy signal. Per FDA guidance, approval of a drug can be based on a single positive study and supportive evidence.

Taken together, these results provide insight into not only the effects on cognition but also function and behavior that would be impactful for individuals living with Alzheimer's and their caregivers. They underscore our reasons to believe that aducanumab meets the standard of evidence for efficacy and should be what ICER uses for its cost-effectiveness analysis.

ARIA and Potential Harm. ICER has mis-characterized the ARIA-E and ARIA-H data and mis-interpreted the weight given to it compared with the potential benefits of the therapy. ICER notes that 41.3% of participants experienced ARIA-E and ARIA-H compared with 10.3% in the placebo arm; that 74.0% of ARIA-E cases in the high-dose aducanumab arm and 89.7% of cases in the placebo arm were asymptomatic; and that most ARIA-E symptoms and MRI findings were mild or moderate in severity and transient (98% resolved) in the high-dose aducanumab arm. These data simply do not support ICER's conclusion that taking aducanumab has a "high certainty of harm."

ARIA is a manageable side effect of treatment and is far less threatening than complications of many routinely used therapies for other conditions, including cancer. The FDA's rigorous review of any potential treatment significantly weights the safety but does so in the context of the full data package and in the context of expert guidance. This guidance, and the routine management of ARIA, has been adopted by multiple beta amyloid trials. The Alzheimer's Association Research Roundtable Workgroup developed recommendations[1] on detecting and monitoring amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials to protect participants, guide clinicians, and ensure that this research can continue. The FDA--whose mission is to protect public health--has adopted guidance, built upon these recommendations, for reasonable management of ARIA.

Furthermore, on behalf of the individuals living with and caring for those living with Alzheimer's, we take exception to the view that implementing ARIA monitoring and treatment is "challenging" as a sufficient reason to question approval or coverage of a therapy. Living with Alzheimer's without any disease-modifying therapy is far more challenging, and it is fatal.

Failure to Account for True Value

The misunderstanding and misrepresentation of the scientific evidence surrounding aducanumab has a dramatic effect on ICER's assumption of the value attributed to the drug, as measured by the assumed QALY gain. For example, using only the evidence from EMERGE rather than the blended data from

[1] Sperling RA, Jack CR, Black SE, Frosch MP, Greenberg SM, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: Recommendations from the Alzheimer's Association Research Roundtable Workgroup. *Alzheimers Dement* 2011;7(4):367-385.

both ENGAGE and EMERGE would result in a significantly higher assessed gain in QALY from aducanumab, resulting in a cost-effectiveness price about three times higher. Using the data for participants who received the highest dose of aducanumab in EMERGE, the QALY gain would likely be even greater. Such a dramatic difference underscores our concern about using blended data for this analysis, especially since it could have a profound effect on whether patients will have access to the drug.

It should be noted that this significant QALY difference is only over the interpretation of the scientific data. ICER's threshold analysis still relies on a rigid, inflexible, narrow--and in our view, outdated--formula that looks solely at direct patient costs instead of a valuation more appropriately suited to therapies for Alzheimer's disease and the long-term value of such a therapy. Alzheimer's disease presents unique issues and challenges to traditional cost-effectiveness analyses. While ICER acknowledges some of these challenges--and does attempt to include a broader "modified societal perspective" in the report--we are troubled that a more serious effort was not made to account for the full range of value that an Alzheimer's therapy would bring or the effect this failure might have on patient access to the drug.

What follows are several aspects of value that we believe should be taken into account in a cost-effectiveness analysis of Alzheimer's drugs. We strongly urge ICER to revise its analysis prior to the July 15 public meeting to incorporate this broader and more appropriate assessment of value. And we strongly recommend the appraisal committee vote to give these aspects a very high priority in judging the long-term value of an Alzheimer's treatment.

What Patients and Caregivers Value: ICER's formulation fails to take into account the value of what is truly important to those living with the disease and their caregivers. A systematic review of studies[2] found that patients and caregivers value outcomes such as maintaining an individual's independence and identity--that is, observable effects on their daily life. While ICER incorporates cognitive test scores from the clinical trials on aducanumab in determining cost-effective pricing, these scores can only be faint proxies for what individuals and caregivers truly value: the impact on how they are able to live on a day-to-day basis. ICER does not incorporate these values into the assessment.

Caregiver Burden. Alzheimer's places a huge burden on caregivers. If ever there was a disease or condition for which the value of a drug to caregivers must be taken into account, Alzheimer's disease is it. The care required of family and friends of those living with the disease is more intense and broader in scope than for caregivers of those with other conditions. Compared with other caregivers, dementia caregivers have twice as many substantial emotional, financial, and physical difficulties. Depression is significantly higher. They are twice as likely to say their health has worsened as a result of caregiving. And, those who contribute to the care of someone with dementia are 28% more likely than other adults to eat less or go hungry because they cannot afford food.

A drug therapy that slows the progression of Alzheimer's disease--extending the period of time when individuals with the disease remain in a stage where they have some level of independence and an ability to significantly contribute to their own care--provides an enormous value to caregivers, which

[2] Tochel C, Smith M, Baldwin H, Gustavsson A, Ly A, et al. What outcomes are important to patients with mild cognitive impairment or Alzheimer's disease, their caregivers, and health-care professionals? A systematic review. *Alzheimers Dement (Amst)* 2019;11:231-247.

must be taken into account in cost-effectiveness analyses. ICER's modified societal perspective includes medical and productivity costs of the primary caregiver--but does not fully account for what caregivers value and the value a drug would bring to caregivers, such as a reduction in distress and burden. In fact, the additional QALY gain under the modified societal perspective appears to be only about 0.005. Other analyses have found the QALY gain attributable to caregiver value significantly higher, indicating that ICER is not taking into account the full and true value to caregivers.

Unmet Need. The unmet need for those living with Alzheimer's and those who will develop Alzheimer's is critical. No disease modifying treatments exist, and for more than a decade there have been a series of initially promising but ultimately ineffective potential disease modifying therapies. Aducaumab represents a real advance for those affected by this devastating disease. It is not a cure, nor even the most successful possible therapy. But it would provide as many as several years of positive benefits for a devastating disease that places an enormous burden on caregivers--and for which there is no alternative. In other words, addressing an unmet need has value in and of itself and should be accounted for.

Innovation. The first-ever disease modifying therapy has value in another way: Innovation. Rarely is a first-of-its-kind treatment--for any condition--a panacea or cure-all. But it often does spur the research into and development of additional and better therapies. For example, approval and coverage of the first reductase inhibitor for lowering LDL cholesterol--and thus delaying the onset of heart disease, the leading cause of death in the United States--spurred the development of at least six additional therapies. There were questions surrounding the effectiveness of the first treatment for HIV, but AZT's approval and coverage stimulated the scientific community to develop additional treatments and combination therapies that have now resulted in a nearly two-thirds decline in the number of HIV deaths since 2000. Even with Alzheimer's disease, approval of the first symptomatic treatment (tacrine) led to the development and approval of better and safer symptomatic drugs.

This innovation value is crucial for people living with Alzheimer's and future generations of individuals who will develop Alzheimer's. Without the first, there cannot be the second or third or fourth, each improving on the earlier treatments. We recognize this value cannot be measured in terms of short-term patient costs, but we oppose the systematic exclusion of innovation from determinations of value.

Earlier Diagnosis: Even without a disease-modifying therapy, the benefits of an early diagnosis of Alzheimer's are well-known. Early diagnosis allows individuals with the disease and their caregivers to better manage medications, build a care team, manage comorbidities, receive counseling and other support services, create advance directives, and address driving and safety concerns. Studies have also shown that health and long-term care costs are lower among people diagnosed earlier.[3] Unfortunately, too many individuals with Alzheimer's are diagnosed too late--if they are diagnosed at all. Many primary care physicians say they doubt the value of diagnosing a condition for which there are no treatments, and nearly half of primary care physicians in one survey[4] say they sometimes choose not to even assess an individual's cognition because, if the individual is eventually diagnosed, treatment

[3] See, for example: Lin PJ, Zhon Y, Fillit HM, Chen E, Neumann PJ. Medicare expenditures of individuals with Alzheimer's disease and related dementias or mild cognitive impairment before and after diagnosis. *J Am Geriatr Soc* 2016;64(8):1549-1557; and Alzheimer's Association. 2018 Alzheimer's Disease Facts and Figures. *Alzheimers Dement* 2018;14(3):367-429.
[4] Alzheimer's Association. 2019 Alzheimer's Disease Facts and Figures. *Alzheimers Dement* 2019;15(3): 321-387.

options are limited. The approval and coverage of a disease-modifying therapy for Alzheimer's would drive earlier diagnosis and thus accrue benefits, even if the direct effect of the drug were limited.

This is of particular importance among diverse populations. Evidence suggests Blacks and Hispanics on average are diagnosed at a much later stage than Whites. This raises profound health equity concerns around access to care, quality of care, and financial burden. As the first-of-its-kind treatment, aducanumab's value in driving earlier diagnosis should not be ignored, and this value should be taken into account.

Equity Impact: In addition to the potentially greater value of an earlier diagnosis that the approval and coverage of aducanumab may have on traditionally underserved populations, the treatment itself could have tremendous value in addressing the disproportionate impact of Alzheimer's. Blacks are about twice as likely and Hispanics are about one and a half times as likely as Whites to develop Alzheimer's. In other words, relatively, this drug could have a greater value on the Black and Hispanic communities than the White population. ICER's formula does not take into account the value of reducing health disparities between those who are at higher risk of developing Alzheimer's and those who are not.

Conclusion

As indicated by our comments in the external review and this letter, the Alzheimer's Association believes ICER's analysis has deep flaws with respect to both the scientific evidence and the assessment of value. It dismisses or ignores the far-reaching effects of the disease and the wide-spread benefit aducanumab would have for millions of individuals and families. The consequences could be dire: it could serve to deny millions access to a necessary treatment and to a real advancement in the treatment of Alzheimer's. We strongly urge ICER to carefully consider the input contained in these comments and amend its analysis accordingly.

Thank you for the opportunity to comment. Please do not hesitate to contact Matthew Baumgart, Vice President of Health Policy, at mbaumgart@alz.org or 646.849.9978 if we can be of additional assistance.

Sincerely,

Joanne Pike, DrPH
Chief Strategy Officer

The Alzheimer's Association received 0.89% of its total 2020 contributed revenue from the biotechnology, pharmaceutical, diagnostics, and clinical research industry, including 0.15% from Biogen and Eisai. For more information, see alz.org/transparency.

June 1, 2021

Submitted electronically to: publiccomments@icer-review.org

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

Re: Draft Evidence Report for Aducanumab for Alzheimer's Disease, May 5, 2021

Dear Dr. Pearson:

On behalf of the Institute for Patient Access, I thank you for the opportunity to provide comments regarding ICER's draft evidence report, "Aducanumab for Alzheimer's Disease: Effectiveness and Value," dated May 5, 2021.

About the Institute for Patient Access

The Institute for Patient Access (IfPA) is a physician-led policy research organization dedicated to maintaining the primacy of the physician-patient relationship in the provision of quality health care. To further that mission, IfPA produces educational materials and programming designed to promote informed discussion about patient-centered care. IfPA was established in 2012 by the leadership of the Alliance for Patient Access, a national network of health care providers committed to shaping a patient-centered health care system. IfPA is a 501(c)(3) public charity nonprofit organization.

Draft Evidence Report Comments

As the draft evidence report notes, an estimated 6.2 million Americans aged 65 and older are living with Alzheimer's in 2021.[1] Due to the aging of the Baby Boom generation, this number is projected to more than double to 12.7 million Americans by 2050, and 13.8 million Americans by 2060.[2] Since the number of Americans living with this disease will increase significantly over the next three decades, Alzheimer's financial and health cost will become an even larger burden in the future without effective treatments.

Should cost-effectiveness assessments fail to account for all of the individual and societal costs imposed by these diseases, in addition to the direct health care costs, access to efficacious treatments for the millions of patients impacted by Alzheimer's and other forms of dementia will be jeopardized. Toward the goal of access, IfPA commends the inclusion of "a modified societal

[1] https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf.
[2] Rajan KB, Weuve J, Barnes LL, McAninch EA, Wilson RS, Evans DA. Population estimate of people with clinical AD and mild cognitive impairment in the United States (2020-2060).

perspective" as a co-base-case analysis in the draft evidence report. The modified societal perspective includes estimates for patient productivity impacts, caregiver time, caregiver quality of life and caregiver direct medical costs. As noted in the draft evidence report, it is important to include the non-health care costs associated with dementia when evaluating the cost-effectiveness of drugs that treat these diseases.

While the draft evidence report considers these societal costs, however, the coverage is incomplete and the cost estimates are low. Addressing these concerns is crucial for the final evidence report and any future reports that evaluate the cost-effectiveness of drugs designed to treat Alzheimer's or other forms of dementia. Unless these important considerations are incorporated, the results may undervalue the benefits of effective treatment.

Alzheimer's Costs Are Significantly Higher Than the Values in the Draft Evidence Report

The draft evidence report cites the total costs of Alzheimer's to be at least $500 billion annually, which is likely an understatement of the actual costs. According to the Alzheimer's Association,[3] the direct health care costs alone are projected to be $355 billion in 2021. A study in the AJMC confirms this estimate, finding that the direct health care costs for treating Alzheimer's in 2020 were $305 billion.[4] A substantial share of these costs, 49% according to a May 2021 Milliman report, are related to long-term residential nursing care.[5] These costs impose significant financial burdens on families but also on state governments, as Medicaid will ultimately bear a large share.

In addition to these costs, caregivers provide nearly $257 billion in unpaid care to people living with Alzheimer's and other dementias as of 2020.[6] These costs are based on the 15.3 billion hours of unpaid assistance that caregivers must provide patients every year and imply total annual costs in excess of $600 billion – 20% larger than the number cited in the report. And even this cost estimate is incomplete because it does not account for the many costs of the disease that are difficult to quantify.

Alzheimer's Imposes a Tremendous Burden on Caregivers

These cost estimates do not account for the emotional burden on caregivers. According to a 2017 survey from the Alzheimer's Association, 64% of those caring for someone with Alzheimer's or dementia felt "'isolated or alone" in the task. More than four in every five (84%) said they needed "more help with caregiving, especially from other family members."[7] These stresses ultimately impact caregiver's health, with surveys showing that caregivers experience higher

[3] https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf.
[4] https://nccd.cdc.gov/BRFSSPrevalence/rdPage.aspx?rdReport=DPH_BRFSS.ExploreByTopic&irbLocationType=StatesAndMMSA&islClass=CLASS17&islTopic=TOPIC15&islYear=2019&rdRnd=24372.
[5] https://www.agingresearch.org/app/uploads/2021/05/Assessing-the-Value-of-Therapies-in-Alzheimer%E2%80%99s-Disease_FINAL.pdf.
[6] https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf.
[7] https://alzheimersnewstoday.com/2017/06/01/alzheimers-dementia-caregivers-emotional-toll-need-support-surveys/.

rates of physical and emotional stress and depression. They even report declines in cognition themselves.

Importantly, Alzheimer's caregivers are enduring a larger burden compared to caregivers for other diseases. According to a survey by Home Care Assistance, "dementia caregivers were seven times more likely to experience daily physical, emotional and mental exhaustion from caregiving than non-dementia caregivers. The survey also found that dementia caregivers were three times more likely to feel extreme stress from their caregiving responsibilities than other types of caregivers." As documented by the $257 billion in costs referenced above, there are also substantial financial and economic consequences that, as with the formal costs of care, are expected to grow significantly over the next several decades.

As Alzheimer's patients often have multiple caregivers,[8] these caregiver burdens significantly expand the number of people experiencing negative consequences from this disease. The severity and pervasiveness of these burdens demonstrates that it is essential for a cost-effectiveness model to incorporate the full costs borne by caregivers even if it is challenging to quantify them. Without an accurate assessment of these burdens, the model will significantly undervalue the benefits of any efficacious treatment.

The Lifetime Burden from Alzheimer's Disease Should Be Considered

The cost estimates reviewed above look at the disease's cost from an annual basis. When discussing the financial burden of a degenerative disease, however, it is important to explicitly recognize that the costs are incurred for many years and will increase over time as the degeneration worsens. In short, an estimation of costs is incomplete if it does not incorporate the lifetime burden of the disease (appropriately discounted into the present value).

According to Jutkowitz et al. (2017), over each patient's lifetime, "the discounted cost of care for a person with dementia was $321,780 (2015 dollars)".[9] The Alzheimer's Association estimates that in 2020 dollars, these lifetime costs, which reflect only the direct care expenditures, equate to $373,527.

It is also important to note that a disproportionate share of the financial burden from this disease will be directly borne by families. According to Jutkowitz et al. (2017), families will incur 70% of the total cost burden ($225,140), compared to Medicaid, which will incur 14% ($44,090), and Medicare, which will incur 16% ($52,540).[10]

[8] As evidence to this reality, the CDC estimates there are more than "16 million Americans providing unpaid care" to patients with Alzheimer's and other dementia (https://www.cdc.gov/aging/caregiving/alzheimer.htm) compared to 6.2 million living with the disease.

[9] Jutkowitz E, Kane RL, Gaugler JE, MacLehose RF, Dowd B, Kuntz KM. Societal and family lifetime cost of dementia: Implications for policy. J Am Geriatr Soc 2017;65(10):2169-75.

[10] Jutkowitz E, Kane RL, Gaugler JE, MacLehose RF, Dowd B, Kuntz KM. Societal and family lifetime cost of dementia: Implications for policy. J Am Geriatr Soc 2017;65(10):2169-75.

In light of these costs, the $500 billion cost estimate cited in the report may be an inaccurate basis from which to judge the benefits of effective treatments.

Accounting for Patients' "Loss of Self" and Alzheimer's Less Tangible Costs

Loss of identity is one of the more devastating and terrifying aspects of Alzheimer's and other forms of dementia. Patients struggle to maintain their self-worth while having to accept the inevitable cognitive decline and realization that they will become a burden on loved ones.

According to the aforementioned 2017 survey by the Alzheimer's Association, 70% of participants feared being unable to care for themselves and live independently as they aged. Only 24% were planning financially for their future care needs, and only 20% reported talking with a family member about care preferences. [11] Alzheimer's patients also commonly experience depression, have thoughts of suicide, and generally experience a poorer quality of life even before the disease's progression robs them of their memories.[12] [13]

Here, as with many of Alzheimer's burdens on patients and caregivers, the methodologies to quantify impact are underdeveloped. Nevertheless, when it comes to Alzheimer's and dementia, not incorporating these impacts will lead to a vast underestimation of the benefits provided by an efficacious treatment.

It Is Essential to Explicitly Account for Alzheimer's Impact on Communities of Color

As the draft evidence report mentions, Alzheimer's imposes a disproportionate impact on communities of color. According to the Alzheimer's Association, "African Americans are about two times more likely than whites to have Alzheimer's and other dementias, [but] they are only 34% more likely to have a diagnosis. Hispanics are about one and one-half times more likely than whites to have Alzheimer's and other dementias, but they are only 18% more likely to be diagnosed."[14]

Thus, communities of color have a higher risk of developing this devastating disease and, because it is discovered later, have higher average medical costs. The disproportionate impact on communities of color also means that an efficacious treatment will be particularly valuable for these demographic groups.

Conclusion

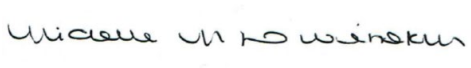
Alzheimer's and dementia already afflict too many people, yet their prevalence is expected to more than double in the coming decades. Effective Alzheimer's treatments will reduce the

[11] https://alzheimersnewstoday.com/2017/06/01/alzheimers-dementia-caregivers-emotional-toll-need-support-surveys/.
[12] https://www.webmd.com/alzheimers/alzheimers-depression.
[13] https://bmcgeriatr.biomedcentral.com/articles/10.1186/s12877-018-0831-2.
[14] https://www.alz.org/aaic/downloads2020/2020_Race_and_Ethnicity_Fact_Sheet.pdf.

disease's economic costs today and will significantly decrease the expected cost burdens of the disease in the future.

If IfPA can provide further detail or aid the Institute for Clinical and Economic Review in incorporating any of the above recommendations into its analysis, please contact us at 202-499-4114.

Sincerely,



Michelle M. D. Winokur, DrPH
Executive Director

From the President's Desk
National Alliance for Caregiving
1730 Rhode Island Ave., Suite 812
Washington, DC 20036

VIA ELECTRONIC DELIVERY

June 2, 2021

David Rind, MD, Chief Medical Officer
Institute for Clinical and Economic Review (ICER)
Two Liberty Square, Ninth Floor
Boston, MA 02109

RE: Public Comment on ICER Draft Evidence Report, Voting Questions – Aducanumab for Alzheimer's Disease: Effectiveness and Value[1]

Dear Dr. Rind:

Thank you for the opportunity to provide input on the new Draft Evidence Report and Draft Questions for Deliberation and Voting on Aducanumab for Alzheimer's Disease ("Draft Report"). First, we would like to commend ICER for recognizing the vital role of the unpaid friend and family caregivers who support people living with dementia.[2] We also greatly appreciate the opportunity to provide feedback on the role of the family caregiver, based on NAC's national and global work in building partnerships in research, advocacy, and innovation to make life better for the more than 53 million Americans who care for someone with a health care need or disability.

In this letter, please find:

1. **Background on the National Alliance for Caregiving and Disclosures**
2. **Comment 1: Innovative Care Payment Models Trend Toward a Whole-Family Approach**
3. **Comment 2: The Role of Caregivers in the Assessment of Alzheimer's Disease and Dementia Therapies**
4. **Comment 3: Additional Considerations and Response to Questionnaire**

I. Background on the National Alliance for Caregiving and Disclosures

NAC aims to support a society that values, supports and empowers family caregivers to thrive at home, work, and life. As a 501(c)(3) charitable non-profit organization based in Washington, D.C., we represent a coalition of more than 60 non-profit, corporate, and academic organizations; nearly 40 family support researchers with expertise in pediatric care, adult care, and geriatric care; and more than

[1] https://icer.org/news-insights/press-releases/icer-releases-draft-evidence-report-on-aducanumab-for-alzheimers-disease
[2] We were encouraged to see that the term "caregiver" and "caregiving" appeared more than 130 times in this report, as compared to seventeen mentions in the final report on Multiple Myeloma (2021) and seventeen in the Lupus Nephritis report (2021). We would contend that most advanced illnesses, including but not limited to neurodegenerative disorders such as dementia, often impact the person with the illness and family caregivers. See, *Caregiving in the U.S. 2020*, AARP and National Alliance for Caregiving, https://www.caregiving.org/caregiving-in-the-us-2020/.

50 advocates who work on national, state and local platforms to support caregivers across the United States. In addition to our national work, NAC leads and participates in several global meetings on caregiving and long-term care. To learn more, visit www.caregiving.org.

This letter is not intended to endorse, support, or advocate for the approval of any specific medication, including (BLA) 761178, the aducanumab solution for intravenous infusion submitted by Biogen Inc. to treat Alzheimer's disease, currently under review at the Food and Drug Administration. Likewise, this letter does not take a position on the reimbursement rate for any such medication if approved.

As a 501(c)(3) organization, NAC receives funding through corporate grants and sponsorships, corporate membership dues, non-profit membership dues, and foundation grants from charitable foundations. Biogen is a current NAC member and contributed $25,000 in FY2019 on a total budget of $1,238,403 (approximately 2% of total revenue). For FY2020, we anticipate Biogen will renew its membership at the $25,000 level, contributing to total expected revenue of $1,572,645, representing less than 2% of total revenue (approximately 1.6%).

II. Comment 1: Innovative Care Payment Models Trend Toward a Whole-Family Approach

Response to: 4.2 Key Model Assumptions and Inputs (page 23 – 25)

We support the need for cost-effectiveness research under the general framework of the Triple Aim[3] that a change process – including interventions such as medicine – should aim to reduce the per capita cost of health care in alignment with better quality care for individuals and better population health outcomes. While cutting all health care services might lower per capita costs, it would not improve patient or population health. Likewise, an intervention that may significantly improve individual patient health may not meet the Triple Aim if the cost is exorbitant and population health is not improved.

The Triple Aim is relevant in calculating cost-effectiveness because family caregivers for people living with dementia can help health systems achieve better care, better quality at lower costs. As described in the Draft Report, the model's current assumption assumed no benefit of reducing disease progression. This assumption ignores two critical realities in the management of Alzheimer's disease: (1) increased costs in households where caregivers are managing dementia; and (2) data that demonstrates a "ripple effect" on the cognition of people caring for someone with dementia.

To the first point, a recent BlueCross BlueShield study[4] identified how caregiving could impact the health of the caregiver – this is particularly relevant for families where both the person needing care and the caregiver are on the same insurance plan. While the study is not exclusive to dementia caregiving, the study features caregivers of people with dementia. The health impact of caregiving among commercially insured beneficiaries was higher than average, with worse overall health and a higher prevalence of cost-driving health conditions including anxiety, major depression, adjustment disorder, and hypertension. Caregivers were also more likely to engage in behaviors that increase care costs over time, including increased tobacco use, coping with alcohol or food, and coping with medication.

[3] See Institute for Healthcare Improvement, "IHI Triple Aim Initiative," Last accessed (5/25/21), at http://www.ihi.org/Engage/Initiatives/TripleAim/Pages/default.aspx.
[4] See BlueCross BlueShield. The Impact of Caregiving on Mental and Physical Health (9/9/20), last accessed 5/25/21, https://www.bcbs.com/the-health-of-america/reports/the-impact-of-caregiving-on-mental-and-physical-health.

Family-centered care models that assess whether a potential medicine can offset disease strain may offer additional value than a patient-only approach. For example, behavioral health interventions for family caregivers, such as the Resources for Enhancing Alzheimer's Caregivers Health (REACH) intervention, have demonstrated a reduction in overall healthcare costs within the Veterans Administration.[5] Drug sponsors who capture data on how a particular medicine impacts the family would have a unique opportunity: they could potentially assess both the caregiver's health and the caregiver's capacity to provide care to someone with dementia. For payers such as BlueCross BlueShield, this may mean additional cost savings if an intervention offsets strain and stabilizes or even improves the caregiver's health where both the caregiver and the person are on the same insurance plan. A study on Parkinson's caregiving, for example, revealed that safe and effective medicines could improve the caregiver's ability to partner in care and improve patient outcomes by reducing the strain of disease on the family unit.[6]

Response to: Supplement B, Patient Perspectives: Supplemental Information

ICER should note in the Draft Report when reviewers lack the information needed to assess caregiver strain and quality of life, caregiver health impact, and the caregiver's ability to provide care. Noting limitations more clearly will assist advocates and sponsors in understanding the opportunities to collect additional, meaningful evidence in the ongoing monitoring of existing treatments. This may also incentivize sponsors to collect and identify this data in the development of future clinical trials.

III. Comment 2: The Role of Caregivers in the Assessment of Alzheimer's Disease and Dementia Therapies

Response to: 4.1 Methods Overview (page 33)

In the last year, researchers and public health agencies including the FDA and CDC reiterated the need to collect better data, including more robust data on people with diverse backgrounds, experiences, and abilities in public health research and practice.[7,8,9] Yet the tools and models used to assess the value of health technologies have been slow to align their methodologies with a person-centered and health equity lens. This is especially detrimental in the evaluation of treatments for conditions such as

[5] See, e.g., Nichols LO, Martindale-Adams J, Zhu CW, Kaplan EK, Zuber JK, Waters TM. Impact of the REACH II and REACH VA Dementia Caregiver Interventions on Healthcare Costs. *J Am Geriatr Soc*. 2017;65(5):931-936. doi:10.1111/jgs.14716.

[6] See, e.g., Michalowsky B, Xie F, Eichler T, Hertel J, et al. Cost-effectiveness of a collaborative dementia care management—Results of a cluster-randomized controlled trial. *Alzheimer's & Dementia 2019; 15 (10): 1296-1308*,https://doi.org/10.1016/j.jalz.2019.05.008; see also, Cummings J, Isaacson S, Mills R, et al., Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. Lancet. 2014 Feb 8;383(9916):533-40. doi: 10.1016/S0140-6736(13)62106-6., at https://www.sciencedirect.com/science/article/abs/pii/S0140673613621066 (suggesting that reduced caregiver strain may provide Parkinson's caregivers with additional capacity for caregiving activities, and thereby improve patient health).

[7] Spinner J, Araojo RR. FDA's Strategies to Close the Health Equity Gap among Diverse Populations. *Journal of Primary Care & Community Health*. January 2021. doi:10.1177/21501327211000232

[8] U.S. Department of Health and Human Services Office of Minority Health. *Improving Data Collection to Reduce Health Disparities*. 2019. Available at https://minorityhealth.hhs.gov/assets/pdf/checked/1/Fact_Sheet_Section_4302.pdf

[9] Liburd, Leandris C. PhD, MPH; Ehlinger, Ed MD, MSPH; Liao, Youlian MD; Lichtveld, Maureen MD, MPH Strengthening the Science and Practice of Health Equity in Public Health, Journal of Public Health Management and Practice: January/February 2016 - Volume 22 - Issue - p S1-S4 doi: 10.1097/PHH.0000000000000379

Alzheimer's and dementia where the impact on the family caregiver is extensive[10]. Among other methodological limitations, the QALY[11] does not include the essential caregiver perspective.

Family caregiving dynamics are best understood as a constellation, rather than a dyad and increasingly involves a system of family, friends and neighbors providing medical and social support to a recipient.[12] In its 2021 report, the Alzheimer's Association found that as many as 30% of older adults with dementia had three or more unpaid caregivers.[13] In evaluating treatment for certain diseases, such as Alzheimer's Disease, where the impact on the family is significant, the base case modeled should accurately count the number of involved caregivers, and be inclusive of the caregiver time spent caregiving, caregiver quality of life and caregiver direct medical costs.

Value assessors such as ICER need more nuanced models and measures that can incorporate novel aspects of value essential to patients and caregivers, especially in complex, progressive, and not yet curable conditions and where treatment could provide value other than the extension of life.

IV. Comment 3: Additional Considerations and Response to Questionnaire

Response to: Comment Period for Draft Evidence Reports

The timing and duration of ICER's Draft Report public comment period disincentivizes stakeholders from participating. The current period is limited to four or five weeks and ends before a treatment's Prescription Drug User Fee Act (PDUFA) action date. Key stakeholders such as caregiver advocates, patient advocates, and researchers with relevant input may lack resources to mobilize their networks and provide useful comments in this short timeframe. The current timeframe asks stakeholders to provide input despite uncertainty around whether or not a drug will be approved for use and what indication.

Effectiveness and safety of a medicine are essential inputs in the determination of its value. Stakeholders, including family caregivers who are concerned about the safety and efficacy of a particular medicine for their loved one, are asked to comment without the benefit of knowing the FDA's decision and therefore cannot respond to the reality of a treatment's actual approved use. Extension of ICER's public comment period on Draft Reports would engender trust with patient and caregiver advocates by creating a genuine dialogue wherein stakeholders can incorporate additional understandings gained from the FDA's determination.

Response to: Draft Questions for Deliberation and Voting

[10] National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Care Services; Board on Health Sciences Policy; Committee on Care Interventions for Individuals with Dementia and Their Caregivers; Stroud C, Larson EB, editors. Meeting the Challenge of Caring for Persons Living with Dementia and Their Care Partners and Caregivers: A Way Forward. Washington (DC): National Academies Press (US); 2021 Feb 23. 6, A BLUEPRINT FOR FUTURE RESEARCH. Available from: https://www.ncbi.nlm.nih.gov/books/NBK570076/

[11] While QALYs are a well-established economic tool and are widely used to measure in value assessment by ICER and across Europe including the UK, they have several limitations that undervalue the lives of older adults and people with disabilities. Notably, QALYs do not account for individual treatment goals and rely on data collected from able-bodied persons that is subject to bias (the "disability paradox":). See, e.g., National Council on Disability. Quality-Adjusted Life Years and the Devaluation of Life with Disability: Part of the Bioethics and Disability Series. Nov 6 2019, https://ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf. In fact, the federal National Council on Disability (NCD) recommends a ban on using QALYs in the Medicare and Medicaid programs.

[12] About half (53 percent) of caregivers say there are others who provide unpaid help to their care recipient. See National Alliance for Caregiving. *Caregiving in the U.S. 2020*. 2020, available at https://www.caregiving.org/caregiving-in-the-us-2020/.

[13] Alzheimer's Association. *2021 Alzheimer's Disease Facts and Figures.* Alzheimers Dement 2021;17(3), https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf

For the first question on making judgments of overall long-term value for money, consider the addition of the following:

- Add "Magnitude of the lifetime impact on caregivers' capacity to partner in care for the individual patients of the condition being treated"
- Add "Magnitude of the lifetime impact on caregivers' own health as a result of their care of individual patients of the condition being treated"

For the question on the relative effects of aducanumab plus supportive care versus supportive care alone, the Draft Question offers "Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life" as consideration. Caregiver quality of life and ability to achieve major life goals should not be presented together as these measure different items. We would recommend focusing on evidence-based considerations that can be measured through validated clinical outcome assessment tools and that speak to the caregiver's ability to partner in care. This may include:

- Caregivers' strain related to intensity of care[14]
- Caregiver's health and wellness
- Caregiver's quality of life

Thank You and Contact Information

We appreciate the opportunity to provide input and are available to provide additional information as needed. Thank you again for your consideration of our comments.

Kind regards,

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[14] For example, the Zarit Burden Interview is a validated and widely used tool that could be used to interpret the impact of the disease on a family caregiver. From the American Psychological Association, https://www.apa.org/pi/about/publications/caregivers/practice-settings/assessment/tools/zarit.

PIPC Partnership to Improve Patient Care

June 2, 2021

Dr. Steven D. Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson,

The Partnership to Improve Patient Care (PIPC) appreciates this opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft evidence report regarding treatments for Alzheimer's Disease. More than six million Americans are living with Alzheimer's Disease and over eleven million Americans provide unpaid care for people with Alzheimer's Disease.[1] Given the huge toll that Alzheimer's Disease takes on patients, caregivers, and society writ large, treatments that improve quality of life and mitigate higher levels of care would mark a huge medical milestone. As we see more treatments in development and coming to market, there is a great responsibility to approach their assessment in a responsible and reliable manner using methods that capture outcomes that matter to patients. For this reason, we strongly urge ICER to postpone this assessment until after FDA approval of this drug. Should ICER choose to move forward at this premature phase, we submit to ICER the following comments on its current model.

ICER is conducting this assessment far too early to produce accurate and useful results.

A consistent concern PIPC and many others have presented to ICER is that it conducts assessments at too early a juncture to have accurate inputs for its models, and, as a result its results are often incomplete or incorrect. This assessment is particularly worrisome, as ICER's timeline is so condensed that it is requiring commenters to submit feedback prior to aducanumab being approved by the FDA. ICER already delayed the assessment once to align with FDA's changing timeline, and it would be prudent to delay the comment deadline until after approval. Conducting the assessment prior to approval, and requiring stakeholders to comment prior to the approval, forced both ICER and stakeholders to make inferences and deal in conjecture. This puts an undue burden on stakeholders and undermines the credibility of the assessment that will be referenced by payers.

In this case specifically, it is also very likely that we will have additional reliable data about this drug upon the conclusion of additional trials. Cognitive decline in mild

[1] https://www.alz.org/alzheimers-dementia/facts-figures

cognitive impairment (MCI) and mild Alzheimer's Disease generally occurs over years. Because of this, longer-term follow-up data from patients enrolled in the ENGAGE and EMERGE trials are currently being collected in an open-label study, EMBARK, which is scheduled to be completed in 2023. The results from EMBARK will provide additional information about the longer-term efficacy and safety of aducanumab.

Therefore, we strongly suggest ICER delay this study, at a minimum until after FDA approval, and ideally until the conclusion of the EMBARK trial.

ICER significantly underestimated the impact on caregiver burden in evaluating treatments for Alzheimer's Disease.

Alzheimer's disease puts a particularly large burden on caregivers and accrues a multitude of societal care costs. The National Institute for Health and Care Excellence, NICE, which ICER leans heavily on for its approach to value assessment, has already included caregiver utility in its cost-effectiveness models for diseases such as Alzheimer's Disease, multiple sclerosis and Parkinson's disease.[2]

When ICER does look at caregiver burden, it appears to drastically underestimate it. More than 11 million family members and other caregivers provided an estimated 15.3 billion hours of unpaid care to patients with Alzheimer's Disease or other dementias, putting these caregivers at risk for negative mental, physical, and emotional outcomes.[3] For example, as patients moved from mild to severe Alzheimer's Disease, the financial, physical, psychosocial, social, and personal strain as measured by the Modified Caregiver Strain Index (MCSI) increased from an average score of 9.0 to 17.5, indicating a substantial increase in caregiver impact.[4] Despite this data, ICER assumes a very marginal impact on caregivers' utility.

Given the huge burden Alzheimer's Disease places on families and the assumption that ICER will continue to use this model to assess new treatments for Alzheimer's drugs as they come to market, we strongly encourage ICER to update its caregiver utilities.

ICER continues to rely on the Quality-Adjusted Life Year (QALY), which is known to devalue the lives of older adults.

As PIPC has consistently stated – the use of the QALY in ICER's models is inappropriate, as the QALY discriminates against older adults, patients,[5] and people

[2] Afentou N, Jarl J, Gerdtham UG, Saha S. Economic evaluation of interventions in Parkinson's disease: a systematic literature review. Movement disorders clinical practice. 2019 Apr;6(4):282-90.
[3] Deb A, Thornton JD, Sambamoorthi U, Innes K. Direct and indirect cost of managing alzheimer's disease and related dementias in the United States. Expert Rev Pharmacoecon Outcomes Res. 2017;17(2):189-202
[4] UsAgainstAlzheimer's. AD PACE. usagainstalzheimers.org: UsAgainstAlzheimer's; 7/29/2020 2020.
[5] Paulden M. Recent amendments to NICE's value-based assessment of health technologies: implicitly inequitable?. Expert review of pharmacoeconomics & outcomes research. 2017 May 4;17(3):239-42.

with disabilities.[6] This is widely recognized as a problem with the QALY. In fact, in 2019, the National Council on Disability, an independent federal agency, published a report finding that the use of the QALY would be contrary to United States civil rights laws and disability policy.[7] The use of this metric is particularly concerning in an assessment of treatments for Alzheimer's disease, as it is a condition that generally impacts older adults.

In recognition of the fact that QALYs are innately discriminatory, health economists have begun investigating ways to repair this problem and have been actively developing new metrics, from healthy year totals[8] to risk-adjusted QALYs.[9] The most recent work shows that due to diminishing returns, traditional cost utility methods overvalue treatments for mild illnesses and undervalue treatments for highly severe illnesses, like Alzheimer's disease. ICER should be evolving away from use of the QALY, toward use of outcome measures based on the most up to date science.

ICER's model underestimates the probability of patients being admitted to long-term care facilities, which is a major driver of costs and burden related to Alzheimer's Disease.

Transition into long-term care facilities is a very common outcome for patients and people with disabilities with Alzheimer's Disease. The set of probabilities used in the ICER model seems quite conservative compared to other data points. As ICER's source is over twenty years old, we would posit it is now out of date. A more recent study suggests that the probability of transitioning to long-term care is much higher than those estimates used in the ICER model. Examples of this discrepancy include 16% a year in moderate Alzheimer's Disease as compared to 11% used in ICER's model and over 32% in severe Alzheimer's Disease as compared to just 23% used in the ICER model.[10] Since admission into long-term care facilities is such a large driver of costs and burden of this disease, updating these numbers is essential for the model to accurately describe the long-term cost savings of an effective treatment for Alzheimer's Disease.

Conclusion

We highly encourage ICER to postpone this assessment until after FDA approval. If ICER does move forward, we encourage it to fix some of the obvious shortcomings in

[6] Nord E, Pinto JL, Richardson J, Menzel P, Ubel P. Incorporating societal concerns for fairness in numerical valuations of health programmes. Health economics. 1999 Feb;8(1):25-39.
[7] https://www.ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf
[8] Basu A, Carlson J, Veenstra D. Health years in total: a new health objective function for cost-effectiveness analysis. Value in Health. 2020 Jan 1;23(1):96-103.
[9] Lakdawalla DN, Phelps CE. Health Technology Assessment With Diminishing Returns to Health: The Generalized Risk-Adjusted Cost-Effectiveness (GRACE) Approach. Value in Health. 2021 Feb 1;24(2):244-9.
[10] Davis M, O'Connell T, Johnson S, Cline S, Merikle E, Martenyi F, Simpson K. Estimating Alzheimer's disease progression rates from Normal cognition through mild cognitive impairment and stages of dementia. Current Alzheimer Research. 2018 Jul 1;15(8):777-88.

its model to paint a more accurate picture of Alzheimer's disease and the individuals impacted by it.

Sincerely,

Tony Coelho
Chairman
Partnership to Improve Patient Care

Society for Women's Health Research

June 2, 2021

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

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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 that 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

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Submitted via email: publiccomments@icer-review.org

RE: Response to Aducanumab for Alzheimer's Disease: Effectiveness and Value; Draft Evidence Report.

Dear Colleagues,

This letter is being submitted by UsAgainstAlzheimer's (UsA2) in response to ICER's Draft Evidence Report for Aducanumab for Alzheimer's Disease, released on May 5, 2021. UsA2 is a patient-driven, non-profit organization that exists to conquer Alzheimer's disease (Alzheimer's, AD). Driven by the suffering of millions of families, UsA2 presses for greater urgency from government, industry and the scientific community in the quest to end Alzheimer's disease and related dementias (ADRD).

UsA2 appreciates ICER's willingness to engage with the Alzheimer's community and consider the experiences of those living with AD. We would like specifically to commend ICER for acknowledging and incorporating the quality of life, health, and productivity of the caregiver in its base case analyses. We were also pleased to see that ICER had considered the Alzheimer's Disease Patient and Caregiver Engagement (AD PACE) data and findings of What Matters Most in its report, as well as our research on caregiver burden, when compiling its report.

While we feel that the inclusion of the patient perspective and caregiver burden is trending in the right direction, we believe that ICER could have gone further to appropriately quantify the enormous impact a disease-slowing therapy would have on those living with AD and their care partners.

Please find the following specific recommendations for ICER's consideration.

Missing Costs. In our review of ICER's evidence report, it appears that several relevant costs were omitted, including: out-of-pocket costs incurred by the patient or caregiver for medical care, transportation, home adaptations, in-home paid caregiving, and adult day care services. Additionally, the model framework assumes a single primary caregiver. We know that AD takes a toll on the entire family and that often times there are many caregivers, including working-age and school-aged caregivers involved who may miss out on career opportunities, earned wages, and/or education.[1] Our colleagues at the Alzheimer's Association estimate that there are, on average, nearly two caregivers for every person living with the disease.[2] Including more comprehensive costs for the primary caregiver as well as costs for the secondary and tertiary caregiver(s) would provide in a more accurate reflection of the true burden of AD.

Population Healthcare Cost Estimates. The source selected for this important model cost input has several limitations. Quoting the study authors directly "Study limitations include that estimates are for a single geographic population, which in 2010 was 86% white. Olmsted County age- sex- and racial-distributions are also similar to these [Minnesota/Upper Midwest] geographic regions; however, Olmsted County residents exhibit higher income and education… While no single geographic area is representative of all others, the under-representation of minorities and the fact that essentially all medical care is delivered by few providers compromises the generalizability of our study findings to different racial and socio-economic groups and different health care environments." The County of Olmstead has a population with less racial and ethnic diversity than the nation, as well as a higher-than-average mean education level. It is also worth noting that the Mayo Clinic health system is located in this county and provides a different type of healthcare than the majority of the US experiences. Simply stated, Olmstead County, MN is not nationally representative and costs data from this county should not be the sole source for these critical model cost inputs.

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6226821/
[2] https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf

In addition to concerns that this study is not nationally representative, the cost estimates from this study also appear to be very low. For example, in another study by Aigbogun et. al. published in 2019, in individuals with Dementia and AD per person, per year medical costs ranged from $32,640 (no behavioral disturbance) to $42,284 (with behavioral disturbance).[3] In contrast, the Olmstead Country study reported costs in the prevalent population (most severe group) as only $11,678 per year. The lower cost estimates from Leibson et. al. are in part due to not including pharmacy costs. ICER only minimally accounted for these costs by adding costs of anti-dementia treatments into the model. In the same study, Aigbogun et. al. reported pharmacy costs ranging from $4,105 to $4,447 per year with high rates of several classes of medications not accounted for in the current ICER model. Utilization of several classes of medications have been shown to increase with disease severity including anti-depressants, anti-psychotics, and opioids as rates of symptoms and associated diagnoses increases.

Finally, accurate accounting of costs by disease stage is particularly important when you have a treatment with a smaller relative treatment effect over a longer period of time. It is also worth noting that the Olmstead County study also was only for people with dementia and did not break down costs into moderate or severe AD. The approach used by ICER to leverage the data from Leibson et. al. to assist in estimating direct medical cost multipliers by model disease stages is not unreasonable in the absence of another study. If a source of costs with each model defined disease stage is not available, it would be reasonable to use these costs multipliers developed from Leibson et. al.. However, if used, these cost multipliers should be applied to more nationally representative and complete medical costs data.

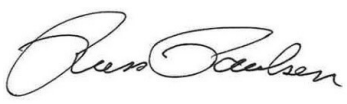
For all these reasons, we strongly recommend finding additional sources for calculating the inputs for Population Healthcare Cost.

Impact of delaying progression of Alzheimer's. UsAgainstAlzheimer's would like to reiterate that the importance of delaying progression and maintaining outcomes most important to people living with the disease, including not feeling as if they are a burden to others, not feel anxious, worried, down or depressed, cannot be understated.[4] While there is no complete cure on the horizon at this time, incremental steps or slowing progression would be of tremendous value to those living with AD and the people who care for them. We ask ICER to continue to consider the enormity of slowing this devastating disease when modeling the potential benefits of a therapy that would slow progression.

Voting Questions. In regards to the voting questions, UsAgainstAlzheimer's finds issue with the premise of Question 1 which asks: "Is the available evidence adequate to demonstrate that the net health benefit of aducanumab plus supportive care is superior to that provided by supportive care alone." We believe this is not an appropriate question to ask prior to FDA review as the FDA alone is tasked with assessing the efficacy (and safety) of a potential treatment and is the only organization with all of the information needed to make this assessment. Should the FDA approve the drug, and thus conclude the drug provides clinically meaningful benefit, then there is no need to even ask Question 1. We recommend removing this question.

Thank you for considering these recommendations. UsAgainstAlzheimer's is happy to continue engaging with ICER as you finalize your Evidence Report.

Sincerely,



Russ Paulsen
Chief Operating Officer
UsAgainstAlzheimer's

[3] Aigbogun MS, Stellhorn R, Hartry A, Baker RA, Fillit H. Treatment patterns and burden of behavioral disturbances in patients with dementia in the United States: a claims database analysis. BMC Neurol. 2019 Feb 28;19(1):33.
[4] Quantifying What Matters Most to Patients and Care Partners in Alzheimer's Disease

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27 May 2021

PUBLIC COMMENT FOR REVIEW OF ALZHEIMER'S DISEASE TREATMENT

I refer to your recently released Draft Evidence Report for Aducanumab in Alzheimer's disease[1].

As you will no doubt recall, you are aware of my concerns that the ICER reference case framework for value assessment fails to meet the standards of normal science [2] . That is, your reports lack credibility in the claims made for the value of products; they cannot be evaluated empirically nor can the claims be replicated. Your models also violate the fundamental axioms of measurement theory in confusing ordinal scales with interval and ratio scales. While you might view these reports and the application of lifetime incremental cost-per-QALY calculations and the application of cost-per-QALY thresholds as the state of the art in health technology assessment, the problem is that the entire exercise is essentially a waste of time. The QALY, as you have been informed on a number of occasions, is a mathematically impossible construct with a paper in *F1000Research* and a letter to *Value in Health* pointing this out [3] [4]. As noted in the latter, we have now experienced 30 wasted years in health technology assessment, with ICER perpetuating this charade. The key point is that in the case of Aducanumab we have too little data to make even a reasoned, and scientifically valid, claim for pricing and budget impact. This should be put on hold until more data become available instead of rushing in to invent modelled claims.

When pointing out the deficiencies of the QALY you have a standard response, couched in a series of unsubstantiated assertions. I quote from your response to my criticisms in your lupus nephritis evidence report:

> *As we have expressed before we (and most health economists) are confident that changes in the EQ-5D (and other multiattribute utility instruments) do have ratio properties. The EQ-5D value sets are based on time trade-off assessments (which are interval level), with preference weights assigned to different attributes. We fail to see why this should be considered an ordinal (ranked) scale. The dead state represents a natural zero point on a health related quality of life. Negative utility values on the EQ-5D scale represent states worse than dead. We do not find this lacks face validity* [5].

I would like to draw to your attention the assertion above that multiattribute utility instruments have ratio measurement properties. I think you misunderstand what ratio property means particularly as all direct and indirect preference instruments can produce negative responses or states worse than death. We have known this for at least 30 years and I would refer you to the classic paper by Patrick et al published in 1994 where he and colleagues considered preferences for health states worse than death for three direct preference instruments: category scaling (CS), time trade off (TTO) and standard gamble (SG) [6]. A more recent study of the EQ-5D-5L (which you have used in your imaginary simulations) has also emphasized the values of states worse than death [7]. In a five country evaluation states worse than death accounted for between 9% and 33% of responses.

You need to be clear on what a ratio scale actually means. Belief in the QALY as a mathematical construct must rest on a belief that any preference scale, for either direct or indirect values or utilities, has a true zero. If this condition is not met, under any circumstance, then the preference scale is, at best, an interval scale although this has to be proved. As the default then, we must assume that the preference scale is ordinal. They also yield negative preferences. This does not mean that certain health state descriptions will necessarily yield a negative value or utility, but that there is the likelihood that at least one respondent will attach a negative preference to one health state. This decision does not reflect just the description but can include attitudes to risk, cognitive understanding, possible interdependence between symptoms and other personal and environmental factors. Of course, the instrument rule makers may try to set negative lower bounds and even resort to continual tweaking of regression models to get a better 'fit' to their data and hopefully eliminate the likelihood of the pesky negative score. Unfortunately, this is a wasted effort: what needs to be proved is that under no circumstance can any respondent to the instrument return a negative preference score. Such a proof is impossible. However remote, the likelihood exists; there is no universal constant defining the true zero. There can be no true zero and hence a ratio scale argument for either direct or indirect preference elicitation is untenable.

The overarching criticism, however, is that your modelling and subsequent recommendations for pricing and patient uptake are entirely imaginary constructs. In short, the proposed 'evidence' you bring to the table to evaluate Aducanumab is invented through assumption driven lifetime simulations that fail the standards of normal science. Your standard defense of these criticisms is that this methodology is the one everyone else has pursued for the past 30 years in health technology assessments. This is hardly a defense, merely an excuse. Why persist in following a failed methodology? It would have been appropriate to inform Biogen, and other companies that have 'engaged' with you, on criticisms of your approach that have been published over the past six years, notably in the University of Minnesota journal *Innovations in Pharmacy* [8] [9]. The QALY, which is central to your cost-per-QALY claims and thresholds is, as you have been informed on a number of occasions, mathematically impossible [10]. But yet you deny it.

If you wish to consider the limitations of your reference case I refer you to my recently published commentary which provides a detailed deconstruction of the ICER approach to technology assessment:

Langley P. Peter Rabbit is a Badger in Disguise: Deconstructing the Belief System of the Institute for Clinical and Economic Review in Health Technology Assessment. *InovPharm*. 2021;12(2):No. 20
https://pubs.lib.umn.edu/index.php/innovations/article/view/3992/2855

Yours sincerely

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