

February 10, 2022

Chiquita Brooks-LaSure
Administrator
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

Re: Proposed National Coverage Determination for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease

Dear Administrator Brooks-LaSure:

The American Geriatrics Society (AGS) appreciates the opportunity to comment on the Centers for Medicare and Medicaid Services' (CMS) Proposed National Coverage Determination (NCD) for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (MAs for the treatment of AD). The AGS recognizes the heavy toll of Alzheimer's disease and other dementias on patients, caregivers, and their families and we appreciate the careful attention to evidence development in the proposed NCD with a focus on ensuring that study populations reflect the diversity of Medicare beneficiaries who are living with Alzheimer's disease.

The AGS is a nationwide, not-for-profit society of geriatrics healthcare professionals dedicated to improving the health, independence, and quality of life of older people. Our 6,000+ members include geriatricians, geriatrics nurse practitioners, social workers, family practitioners, physician assistants, pharmacists, and internists who are pioneers in advanced-illness care for older individuals, with a focus on championing interprofessional teams, eliciting personal care goals, and treating older people as whole persons. The AGS believes in a just society, one where we all are supported by and able to contribute to communities where ageism, ableism, classism, homophobia, racism, sexism, xenophobia, and other forms of bias and discrimination no longer impact healthcare access, quality, and outcomes for older adults and their caregivers. The AGS advocates for policies and programs that support the health, independence, and quality of life of all of us as we age.

SUPPORT FOR COVERAGE WITH EVIDENCE DEVELOPMENT

The AGS believes that the CMS decision to only cover MAs for the treatment of AD for Medicare beneficiaries with evidence development is the right decision for the class. We support the requirement for randomized trials given that a registry or other designs that are largely observational and do not use randomization would not address the outstanding questions that still remain. We particularly appreciate the attention to requiring diversity in CMS-approved trials given that trials¹ and research² for AD often

¹ Franzen S, Smith JE, van den Berg E, Rivera Mindt M, van Bruchem-Visser RL, Abner EL, Schneider LS, Prins ND, Babulal GM, Pappa JM. Diversity in Alzheimer's disease drug trials: The importance of eligibility criteria. *Alzheimers Dement*. 2021. [doi:10.1002/alz.12433](https://doi.org/10.1002/alz.12433). [Epub ahead of print].

² Jack CR, Bennett DA, Blennow K, et al. NIA-AA research framework: towards a biological definition of Alzheimer's disease. Published September 19, 2017. Accessed 2022. Available at <https://www.alz.org/aaic/downloads/draft-nia-aa-9-19-17.pdf>.

lack diversity. Below we have outlined our specific observations and recommendations in further detail. Please note that given the information that is available on aducanumab, we have framed some of our comments through the lens of what is known about the U.S. Food and Drug Administration (FDA) process and deficiencies in the evidence submitted by Biogen. However, we intend our comments to serve as a general guide to CMS as other drugs in the class are approved by the FDA. We encourage CMS to review a recently published article in the *Journal of the American Geriatrics Society (JAGS)* outlining the findings of a survey to gather public opinion around the approval of aducanumab.³

NCD for All Monoclonal Antibodies Directed Against Amyloid for the Treatment of AD

We appreciate that CMS wrote the NCD for the class in order to be transparent about how it intends to treat all MAs for the treatment of AD and to make manufacturers aware of the specific health outcomes that need to be met for full coverage. The AGS supports the need to gather additional data through coverage with evidence development (CED) for drugs that have been approved by the FDA's accelerated pathway, including aducanumab, which is currently the only approved therapy in this class. However, there are multiple drugs in the class that are in various stages of discovery with some submitted for approval. As with aducanumab, the evidence of effectiveness and safety are still unknown for the drugs in the pipeline. For that reason, we urge CMS to consider that it may need a review process for drugs in this class that are approved by the FDA through its regular pathway given that these drugs—unlike aducanumab—would potentially have generated sufficient data on safety and clinical benefit in the study population. As we noted in our prior comment letter to CMS,⁴ we believe that CMS can play an integral role in ensuring that the diversity of study populations reflects the diversity of people who are living with AD.⁵ We support CMS in making its own independent determination as to whether additional evidence is needed before covering any individual drug or a class of drugs.

Evidence Development

The AGS supports CMS's proposal for CED of FDA-approved monoclonal antibodies directed against amyloid for the treatment of AD. We believe CED is required to ensure that CMS understands how these treatments are prescribed, administered, including who is receiving treatment, and whether the treatments fall within the defined benefit categories under 1861(s)(2)(A) or 1861(s)(2)(B) of the Social Security Act. Particularly as the FDA approval for aducanumab was invoked through the accelerated approval pathway based on beta amyloid levels as a surrogate endpoint of reasonably likely clinical benefit, it is unclear whether the drug produces meaningful clinical benefits. Concomitantly, the heterogeneity of AD (i.e., the underlying biology) is a primary impediment that is not typically taken into consideration in trial designs.⁶ We urge CMS to distinguish between drugs approved as part of FDA's accelerated pathway versus drugs that have met the criteria for full approval. We also request CMS to clarify whether the CED would be revised as more evidence about the MAs for the treatment of AD becomes available.

³ DiStefano, MJ, Alexander, GC, Polsky, D, Anderson, GF. Public opinion regarding U.S. Food and Drug Administration approval of aducanumab and potential policy responses: A nationally representative survey. *J Am Geriatr Soc.* 2022;1-10. [doi:10.1111/jgs.17692](https://doi.org/10.1111/jgs.17692).

⁴ Comments on National Coverage Analysis for Aducanumab for Treatment of Alzheimer's Disease. August 11, 2021. Available at https://www.americangeriatrics.org/sites/default/files/inline-files/American%20Geriatrics%20Society%20Aducanumab%20NCD%20Comments%208%2011%2021_Final_0.pdf.

⁵ Manly JJ, Glymour MM. What the Aducanumab Approval Reveals About Alzheimer Disease Research. *JAMA Neurol.* 2021;78(11):1305–1306. [doi:10.1001/jamaneurol.2021.3404](https://doi.org/10.1001/jamaneurol.2021.3404).

⁶ Devi G, Scheltens P. Heterogeneity of Alzheimer's disease: consequence for drug trials?. *Alz Res Therapy.* 2018;10(122):1-3. [doi:10.1186/s13195-018-0455-y](https://doi.org/10.1186/s13195-018-0455-y).

Representativeness

The AGS is appreciative of CMS's efforts to address health disparities and advance equity. We agree that underrepresented, disproportionately affected, and understudied populations should be engaged, recruited, and retained in the clinical trials for these treatments to ensure that the diversity of participants is representative of the population diagnosed with AD. The ENGAGE and EMERGE clinical trials for aducanumab that were the basis of FDA approval only included 0.6 percent participants identifying as Black and only six of these participants were randomized to the treatment dose that was eventually approved by FDA under its accelerated pathway.⁷ Considering the racial and ethnic diversity of people living with Alzheimer's disease and related dementias (ADRD) among subpopulations,⁸ we support CMS's efforts to ensure a diverse study population so that the evidence generated from the study populations is reflective of the people who are diagnosed with this disease.

The AGS also recommends representative inclusion of those excluded from the ENGAGE and EMERGE trials, including patients in the older age subgroup (85 and older), on anticoagulation therapy, or with other concurrent or previous neurologic pathophysiology (e.g., psychiatric disorders, neurodegenerative disorders, history of stroke) to evaluate the clinical evidence of treatments and their safety and efficacy in these populations. More than 92 percent of Medicare beneficiaries with ADRDs, including 85 percent of beneficiaries with mild cognitive impairment (MCI), would have met one of the Phase 3 trial exclusion criteria with 64.4 percent of patients meeting multiple criteria for exclusion. Particularly worrisome is that the risk of vascular edema and hemorrhages seen in the clinical trials is likely to be higher in populations that were not eligible, particularly patients with prior stroke or chronic conditions treated with antiplatelets or anticoagulants.⁹

Due to the level of potential harms and lack of evidence that aducanumab is an effective intervention for the treatment of AD, the AGS recommends ensuring disclosure of the absence of safety and efficacy data in the populations that were underrepresented in the clinical trials during informed consent conversations for patients in these groups.¹⁰

INPUT ON PROPOSED TRIALS

Recruitment into Trials

The AGS believes it is important for all of us to own the work of addressing the impact that structural racism continues to have on the biomedical research enterprise and urges inclusivity in research. It may be helpful for researchers to allocate funding to create and share resources, such as translation of materials into other languages, that would ensure they have the appropriate tools when working with

⁷ US Food and Drug Administration Center for Drug and Evaluation and Research. FDA clinical review of Aduhelm: application number: 761178Orig1s000. Published June 6, 2021. Accessed February 1, 2022. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000MedR_Redacted.pdf.

⁸ Matthews KA, Xu W, Gaglioti AH, et al. Racial and Ethnic Estimates of Alzheimer's Disease and Related Dementias in the United States (2015-2060) in Adults Aged ≥65 Years. *Alzheimers Dement*. 2019;15(1):17-24. [doi:10.1016/j.jalz.2018.06.3063](https://doi.org/10.1016/j.jalz.2018.06.3063).

⁹ Anderson TS, Ayanian JZ, Souza J, Landon BE. Representativeness of Participants Eligible to Be Enrolled in Clinical Trials of Aducanumab for Alzheimer Disease Compared With Medicare Beneficiaries With Alzheimer Disease and Mild Cognitive Impairment. *JAMA*. 2021;326(16):1627-1629. [doi:10.1001/jama.2021.15286](https://doi.org/10.1001/jama.2021.15286).

¹⁰ Chiong W, et al. Decisions With Patients and Families Regarding Aducanumab in Alzheimer Disease With Recommendations for Consent. *Neurology*. 2022;98(4):154-159. [doi:10.1212/WNL.0000000000013053](https://doi.org/10.1212/WNL.0000000000013053).

diverse populations. To achieve diversity in enrollment for clinical studies, attention to diversity in the recruitment plan for proposed trials will be critically important.¹¹ Moving beyond only academic institutions enhance the potential for a full range of translational and pragmatic research.¹² An example of the consequences of a lack of community-based research infrastructures in 2020 was the lack of access to COVID-19 trials and therapeutics beyond large hospitals and academic medical centers.¹³

Strategies for recruiting underrepresented and understudied communities will require prioritizing partnerships and building trust within communities where people live, work, pray, and age. Partnerships should prioritize enabling and building an infrastructure that centers around community-based entities and ensure that research is designed to address access and other limitations. Partnerships must create a nexus of connection points that truly link representative aspects of underserved and vulnerable communities, including highly disadvantaged areas, nursing homes, and rural communities. This will require establishing trust with community leaders (i.e., religious, senior centers, senior housing). Building relationships with underrepresented groups require a long-term commitment to engaging communities. A major impediment to this is the lack of infrastructure funding for developing and sustaining those relationships. For research outside academia, other forms of federal and non-federal partnerships will be essential as will ensuring that partners are fully engaged and funded to participate in this work.

Among the barriers for patients in accessing diagnosis and treatment of and clinical trials for AD—particularly for people who are socioeconomically disadvantaged—is transportation to appointments. Individuals still working or their family caregivers may need to take time off from their jobs, often lack paid family and medical leave, and are paid hourly. One solution is the distribution of waivers to assure paid-time off and transportation supports access to diagnosis and treatment as well as clinical trials. We recommend that CMS require that proposed clinical trials align with the National Institutes of Health (NIH) standards, including the Guiding Principles for Ethical Research¹⁴ and Ethics in Clinical Research.¹⁵

The AGS believes that new data from CMS-approved randomized controlled trials (RCT) would help to evaluate the clinical evidence for safety and efficacy of these treatments as the prior trials for aducanumab, the only currently FDA-approved monoclonal antibody direct against amyloid, did not have sufficient data on clinical efficacy in addition to the lack of generalizability to the affected populations. Though the gold standard is a placebo-controlled RCT, we ask CMS to consider pragmatic clinical trials (PCT) given they would not require a placebo arm and ameliorate the concerns around recruitment into a placebo-controlled trial for the treatment of AD. Two pragmatic trials that hold particular promise for accomplishing CMS’s objectives are a randomized, wait-list lottery or stepped

¹¹ American Geriatrics Society. Letter to Rep. Eshoo on the DEPICT Act Discussion Draft. September 29, 2021. Available at <https://www.americangeriatrics.org/sites/default/files/inline-files/AGS%20Comments%20on%20the%20DEPICT%20Act%20Discussion%20Draft%20%289%2029%2021%29%20%28FINAL%29.pdf>.

¹² American Geriatrics Society. AGS Comments in Response to NIH Request for Input on Diversity and Inclusion in Biomedical Research. April 9, 2021. Available at [https://www.americangeriatrics.org/sites/default/files/inline-files/AGS Comments response NIH RFI Diversity Inclusion Biomedical Research 04092021.pdf](https://www.americangeriatrics.org/sites/default/files/inline-files/AGS%20Comments%20in%20Response%20to%20NIH%20Request%20for%20Input%20on%20Diversity%20and%20Inclusion%20in%20Biomedical%20Research%2004092021.pdf).

¹³ Gilmore B, Ndejjo R, Tchetchia A, et al. Community engagement for COVID-19 prevention and control: a rapid evidence synthesis. *BMJ Global Health*. 2020;5(10):e003188. doi:10.1136/bmjgh-2020-003188.

¹⁴ Guiding Principles for Ethical Research. Nih.gov. Published March 16, 2016. Accessed February 7, 2022. Available at <https://www.nih.gov/health-information/nih-clinical-research-trials-you/guiding-principles-ethical-research>.

¹⁵ Patient Recruitment: Ethics in Clinical Research. Cc.nih.gov. Published October 21, 2021. Accessed February 7, 2022. Available at <https://www.cc.nih.gov/recruit/ethics.html>.

wedge design as described in this recent commentary published in *JAGS*.¹⁶ In a recent public opinion survey also published in *JAGS*, 71 percent of respondents said they would be willing to enroll a family member with mild AD in a “waitlist”-style trial where participants are randomized to early versus late treatment and serve as their own controls, while 60 percent indicated they would be willing to enroll a family member in a randomized placebo-controlled trial.³

The AGS agrees with CMS that in order to provide the evidence that is needed, randomized trials with a control group are needed in order to fully understand whether MAs for the treatment of AD have clinical benefit. The AGS believes that a registry or other designs that are largely observational and do not use randomization would not address the outstanding questions that still remain. We recommend that CMS fine-tune the language to clarify what its expectations are in terms of the approximate length of the trial to achieve the desired result of being able to evaluate potential safety and benefit of these treatments. CMS should also clarify how individuals randomized into the control group would be treated should evidence indicate clinical efficacy. To evaluate such potential evidence, support for biomarker assessments as part of the trials would be valuable. One resource to look to would be the study designs for the recent trials of COVID-19 vaccines considering the speed at which evidence was developed and commitment to ensuring access to vaccines for study participants who were randomized into the control groups of those trials.¹⁷

In 2021, the National Institute on Aging (NIA) convened a small working group to consider how trial design could be modified to allow for more inclusion of older people with multiple chronic conditions with a focus on serious adverse events (SAEs) and adverse events (AEs). The convening process, funded by the NIA, was led by a planning group at the Icahn School of Medicine at Mount Sinai’s Claude D. Pepper Older Americans Independence Center (OAIC), the OAIC Coordinating Center at Wake Forest School of Medicine, and the National Palliative Care Research Center. The work of that group is being presented at the American Academy of Hospice and Palliative Medicine (AAHPM) 2022 State of the Science with a paper forthcoming.¹⁸ The aims of this workgroup were to: 1) systematically elaborate upon challenges in defining, classifying, and monitoring SAE/AEs in seriously ill older adults; and 2) establish an alternative approach building upon existing regulations. We encourage CMS to consider the following principles emanating from this work when reviewing proposed clinical trials with the goal of ensuring that there is great inclusion of older adults with multiple chronic conditions in the required trials: “Consider the intervention; Favor routine and aggregate over expedited reporting; Prioritize relatedness; Subsume expectedness into relatedness determinations; Factor in patient-centered care goals; Assess seriousness after other criteria.”¹⁸ We believe that reporting plans and decisions should follow an algorithm underpinned by these principles.

Ideally, trial designs will include access to an interprofessional care team who will support the patients in accessing the services and supports that they will need as they move through the stages of AD. At minimum, this team would revisit the care plan at least annually and there should be an ongoing discussion of what matters to the person.

¹⁶ Glymour MM, Mor V. A Large Pragmatic Trial is the Right Solution for Testing Anti-Amyloid Therapies for Alzheimer’s Disease. *J Am Geriatr Soc*. doi:10.1111/jgs.17695. [Epub ahead of print].

¹⁷ World Health Organization. COVID-19 vaccine trial designs in the context of authorized COVID-19 vaccines and expanding global access: ethical considerations. Published November 29, 2021. Accessed February 10, 2022. Available at <https://apps.who.int/iris/rest/bitstreams/1396234/retrieve>.

¹⁸ Baim-Lance A, Ferreira K, Kitzman D, Archer A, Siu A, Morrison RS. Addressing Challenges in the Definition, Classification, and Monitoring of Adverse Events in Clinical Trials Involving Older Adults with Serious Illness. Rapid Poster 516. American Academy of Hospice and Palliative Medicine, State of the Science in Hospice and Palliative Care. February 12-13, 2022.

In the case of aducanumab, both the ENGAGE and EMERGE trials were terminated early so there is no data on when treatment should be discontinued. One strategy would be to randomize subjects to different treatment end dates and follow them to see if there are differences in rate of decline following termination of treatment. Another strategy is to pick a point of disease advancement to stop treatment. A natural concern for treatments that show clinical efficacy during treatment will be to consider what to do after treatment is terminated if cognitive decline starts including how soon after termination of treatment and the rate of decline. Biomarker assessments would also help determine when treatment should be discontinued.

CMS should also consider the potential high cost to patients for participating in a trial for a drug with known risks and the possibility that high out-of-pocket costs may lend itself to a patient population that is not representative of those with AD. The AGS believes that CMS should address how to limit financial barriers to participation for patients and consider the challenges associated with Medicare cost-sharing, especially if a decision is made to include placebo arms in the trial design.

Diagnostic Testing

In order to benefit from aducanumab as observed in the trials or other monoclonal antibody directed against amyloid, patients must have beta amyloid present in their brains. Therefore, AGS believes that CMS should cover the diagnostic tests as part of these trials that are needed to confirm the presence of beta amyloid in the brain. Beta amyloid positron emission tomography (PET) scans are currently covered only as part of a clinical trial that meets the requirements for CED with a lifetime limit of one such scan per participant (NCD 220.6.20). The AGS is concerned that limiting coverage will create access and equity issues for Medicare beneficiaries desiring to participate in the proposed CMS trials for this class of drugs. Therefore, patients without access to amyloid PET scans may otherwise be treated with aducanumab even though there is no evidence that they will benefit from the treatment. Although the CED requirements included in NCD 220.6.20 would be met for CMS-approved trials for MAs for the treatment of AD, the AGS is concerned that each beneficiary would be limited to one beta amyloid PET scan for these trials and only eligible for that scan if they had not previously received a beta amyloid PET scan. Furthermore, treating patients without the biomarker evidence of beta amyloid in their brains or with moderate or advanced dementia due to AD, may result in harm since aducanumab therapy carries a risk of significant side effects.

The AGS also believes that CMS should cover the diagnostic tests needed to confirm reduction in amyloid plaque to replicate the secondary endpoint that was the basis for FDA approval of aducanumab. This is important given the FDA's reliance on a correlation between reduction in beta amyloid and improvement or stagnation in cognitive and functional decline in its accelerated approval. These diagnostic tests are in addition to cognitive testing that confirms a diagnosis of MCI or mild stage AD, magnetic resonance imaging (MRIs) to monitor for Amyloid-Related Imaging Abnormalities (ARIA), and any additional assessments that are proposed to increase our understanding of whether MAs for the treatment of AD leads to meaningful outcomes for people living with AD such as slowing cognitive decline and being able to remain active and engaged in their communities longer.

In order to ensure equitable access to testing and ongoing monitoring, CMS should approve an expanded list of validated tests and other modalities for determining presence of beta amyloid plaque in

the brain (e.g., beta amyloid PET scan, tau PET scan, CSF testing). We also urge CMS to maintain flexibility on testing for presence of amyloid as knowledge and available tools evolve.

Sites of Service

The AGS is concerned that access would be limited for patients if clinical trials are conducted only in a hospital-based outpatient setting. This limitation may create more barriers for individuals to access clinical trials and in turn treatment for AD. We suggest that clinical trials be conducted in qualified sites. The requirements to be a qualified site should be meaningful and may include neuropsychology services, social support services, or partnership with an entity to provide such services. Sites should have access to expertise in ARIA and other adverse events that may emerge in response to the treatment provided.¹⁹ Patients who are actively receiving monthly aducanumab infusions will require close follow-up care to monitor for ARIA-related symptoms and FDA-prescribed follow-up MRI scans that are obtained and read by radiologists with expertise in ARIA.

The treatment setting should be inclusive of the treatment team capacity. Particularly for patients receiving aducanumab, the treatment setting should monitor the patient's status closely—including for drug side effects—and will require appropriate monitoring of cognitive and everyday function at specified intervals to assist in determining whether the patient is benefitting from treatment and, if not, to help decide whether to terminate treatment using shared decision-making. At a minimum, the ordering clinician(s) must be competent in dementia care. Ideally, the patient's care team will be interprofessional, inclusive of cognitive specialists and clinicians with geriatrics expertise, so that the patient receives whole person care that is focused on what matters to them. The clinicians involved should be familiar with the patient and involved in their routine health care needs and social supports.

A recently published commentary in *JAGS* suggested leveraging Alzheimer's Disease Research Centers (ADRCs) and other major care delivery networks that have the appropriate clinical infrastructure for infusion capacity, MRIs for safety monitoring, and amyloid PET scans or other biomarkers.¹⁶ Utilizing ADRCs takes advantage of patients already enrolled in research, however recruitment of diverse study populations into ADRCs is a challenge. We share the authors' belief that proposed trials should have comprehensive recruitment plans, including accountability for pre-specified recruitment targets, that reflect engagement with community-based organizations.

MEANINGFUL OUTCOMES

The AGS prioritizes what matters most to patients, their families, and other care partners who want to know whether a treatment provides clear and important benefits to cognitive and functional ability and other key outcomes. The AGS believes that the health outcome goals of treatment and care for patients with AD are to achieve and maintain cognitive and functional stability to the maximum extent possible for the longest period possible. Older persons with cognitive impairment—MCI or early-stage dementia—are most often managing a number of concurrent chronic medical conditions.²⁰ While their cognitive impairment may be the dominant comorbidity, treatment outcomes need to consider the

¹⁹ Salloway S, Chalkias S, Barkhof F, et al. Amyloid-Related Imaging Abnormalities in 2 Phase 3 Studies Evaluating Aducanumab in Patients with Early Alzheimer Disease. *JAMA Neurol.* 2022;79(1):13-21. [doi:10.1001/jamaneurol.2021.4161](https://doi.org/10.1001/jamaneurol.2021.4161).

²⁰ Clague F, Mercer SW, McLean G, Reynish E, Guthrie B. Comorbidity and Polypharmacy in People with Dementia: Insights from a Large, Population-Based Cross-Sectional Analysis of Primary Care Data. *Age and Ageing.* 2016;46(1):33-39. [doi:10.1093/ageing/afw176](https://doi.org/10.1093/ageing/afw176).

whole person, not isolated disease outcomes. Geriatrics health professionals focus on the **5Ms** of geriatrics: **M**ultimorbidity, **W**hat **M**atters, **M**edication, **M**entation (cognitive function), and **M**obility (physical function).²¹ Multimorbidity describes the older person who has more complex needs often due to multiple chronic conditions, frailty, and/or complex psychosocial needs. What Matters, Medication, Mentation, and Mobility describe the four main areas where geriatrics health professionals focus their clinical attention and form the basis for the age-friendly health systems framework that is focused on ensuring that all older people have access to this type of coordinated care, while also making sure personal needs, values, and preferences are at the heart of that care.²² In order to have meaningful improvement for patients, crucial health outcomes to consider include reduced symptom burden, effects on cognition and physical function, and sustained health-related quality of life.

Cognitive and physical function are especially important to older adults as reflected in conceptual models for what matters most to older adults such as the 5Ms.²³ Measuring daily function at baseline or better using standardized instrumental activities of daily living (IADL) and activities of daily living (ADL) scales would provide objective measures that improve our understanding of whether MAs for the treatment of AD are supporting people living with AD to remain active in their communities. Meaningful measures in the very early stages of neurodegenerative disease should include both qualitative experience measures and N of 1 approaches (participant, family, and research clinician) and tools capable of teasing apart subtle cognitive and behavioral changes (e.g., a variety of artificial intelligence (AI)-enhanced and digital tools). AI-enhanced and digital tools are part of a rapidly evolving field with many currently in development. As with testing for presence of amyloid plaque in the brain, we urge CMS to monitor these and other tools in development and maintain flexibility as to testing modalities so that trialists can draw on the full range of available validated tools in their proposed studies. Due to heterogeneity in course of decline, a long pre-treatment measurement phase to define individual trajectories would also help to identify meaningful outcomes. There is also value in being able to evaluate long-term outcomes to determine the impact of amyloid removal on cognition in 5-10 years following completion of treatment.

A recent viewpoint in the *Journal of the American Medical Association (JAMA)* hit the mark when the authors said that “Patients’ lived experience can also help contextualize clinical trial data when risks and benefits are not easily compared.” The authors commented that, “with aducanumab, patients could have been asked to offer insight into whether a small change in the Clinical Dementia Rating Scale Sum of Boxes, a score used to stage dementia severity, would translate to meaningful improvement in daily life—and how that benefit would compare with the risk of adverse events.”²⁴

We suggest that spouses, family members, and/or caregivers—in addition to patients—be considered so that the level of anxiety regarding their concern over the loss of memory and/or function in the patient is reduced. It would be important to sufficiently manage co-occurring medical conditions and ensure

²¹ Adapted by the American Geriatrics Society (AGS) with permission from “The public launch of the Geriatric 5Ms” [on-line] by F. Molnar and available from the Canadian Geriatrics Society (CGS) at <https://canadiangeriatrics.ca/2017/04/update-the-public-launch-of-the-geriatric-5ms/>.

²² Institute for Healthcare Improvement. Age-Friendly Health Systems: Guide to Using the 4Ms in the Care of Older Adults. Published July 2020. Available at https://www.ih.org/Engage/Initiatives/Age-Friendly-Health-Systems/Documents/IHAgeFriendlyHealthSystems_GuidetoUsing4MsCare.pdf.

²³ Tinetti M, Huang A, Molnar F. The Geriatrics 5M’s: A New Way of Communicating What We Do. *J Am Geriatr Soc*. 2017;65(9):2115. doi:10.1111/jgs.14979.

²⁴ Largent EA, Peterson A, Lynch HF. FDA Drug Approval and the Ethics of Desperation. *JAMA Intern Med*. 2021;181(12):1555-1556. doi:10.1001/jamainternmed.2021.6045

there is no increased risk of unscheduled acute health care needs. The AGS recommends the review of “Dementia prevention, intervention, and care: 2020 report of the Lancet Commission,” a report of individual and policy changes to delay the onset of and provide better ways to support and treat people with cognitive impairment and dementia and their families to improve their quality of life.²⁵

Thank you for taking the time to review our feedback and recommendations. For additional information or if you have any questions, please do not hesitate to contact, Anna Kim at akim@americangeriatrics.org.

Sincerely,



Peter Hollmann, MD
President



Nancy E. Lundebjerg, MPA
Chief Executive Officer

²⁵ Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission. *The Lancet*. 2020;396(10248):413-446. [doi:10.1016/S0140-6736\(20\)30367-6](https://doi.org/10.1016/S0140-6736(20)30367-6).