PhRMA
RESEARCH • PROGRESS • HOPE

950 F STREET NW, SUITE 300, WASHINGTON, DC 20004 | 202.835.3400 | PhRMA.ORG

February 10, 2022

VIA ELECTRONIC DELIVERY

Tamara Syrek Jensen, JD
Director, Coverage and Analysis Group
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244-1850

Re: Proposed Decision Memo for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease

Dear Director Jensen:

The Pharmaceutical Research and Manufacturers of America (PhRMA) appreciates the opportunity to respond to the Centers for Medicare & Medicaid Services' (CMS') decision memo outlining a proposed National Coverage Determination (NCD) for Monoclonal Antibodies (mAbs) directed against amyloid for the treatment of Alzheimer's disease. PhRMA represents the country's leading innovative biopharmaceutical research companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives. Since 2000, PhRMA member companies have invested more than $1 trillion in the search for new treatments and cures, including $91.1 billion in 2020 alone.

PhRMA is deeply concerned about CMS' proposed coverage policy, which would employ a "Coverage with Evidence Development" (CED) paradigm to severely restrict patient access to important treatment options for Alzheimer's disease. As the proposal is fundamentally flawed, we urge CMS to withdraw the proposal and initiate a new process involving additional, meaningful input from patients, caregivers, physicians, and other stakeholders to determine how best to proceed.

CMS' proposal represents an inappropriate and largely unprecedented application of coverage policy that would have profoundly negative implications for patients with Alzheimer's disease and their caregivers, as well as patients with other serious diseases who are desperate for progress against significant unmet needs. We are equally concerned that, while CMS has expressed good intentions regarding improvement of health disparities, the proposal will have the effect of significantly undermining this stated priority of the agency by requiring beneficiaries to enroll in randomized clinical trials, involving a very limited subset of health care providers, in order to gain access to antiamyloid mAbs. Finally, we are troubled that CMS' proposal would impose a restrictive, CED-only coverage policy affecting multiple emerging medicines for Alzheimer's disease, several of which are currently undergoing review by the Food and Drug Administration (FDA) and may have significant differences in study designs, endpoints, and clinical results. In Section I of this letter, we outline our concerns in more detail.

CMS should not move forward with a CED-based coverage policy for antiamyloid mAbs. As CMS reassesses how

to proceed, we propose key principles in Section II of this letter that the agency should adhere to. First, CMS should preserve timely beneficiary access to FDA-approved drugs and biologics. Second, any further evidence generation must be the least burdensome approach available and ensure the policy aligns with FDA decisions, including those related to post-market confirmatory studies. Indeed, CMS' own CED guidance expressly states that CED "will not be used when less restricted coverage is justified by the available evidence."[1] Third, CMS should provide clear guidance on the particular additional evidence it seeks, and how it will determine when desired benchmarks have been met. We believe that these principles are essential to protect patient access and support development of further evidence in a way that is reinforcing and beneficial to patients, which can help to reduce (rather than exacerbate) health disparities and ensure clear alignment between CMS' and FDA's respective authorities.

I. CMS' FLAWED PROPOSAL WILL CREATE SIGNIFICANT ACCESS BARRIERS FOR PATIENTS WITH ALZHEIMER'S DISEASE, WHO FACE SIGNIFICANT UNMET NEED FOR NEW THERAPIES.

A. The agency's proposed NCD would create significant access barriers to current and future FDA-approved medicines for patients with substantial unmet medical need.

As CMS itself recognizes, Alzheimer's disease is a crisis for our country, and for Medicare beneficiaries specifically. An estimated 6.2 million Americans aged 65 and older are living with the disease and it is the sixth leading cause of death in the United States. One in three seniors will die from Alzheimer's disease or another form of dementia—more than breast cancer and prostate cancer combined. And though progress has been made in other disease areas, Alzheimer's disease remains a significant challenge. Between 2000 and 2019, deaths from heart disease have decreased by 7.3% while deaths from Alzheimer's disease increased 145%.[2]

As a result of the tremendous burden posed by Alzheimer's disease, the health care and long-term care costs associated with caring for patients with the disease make it one of the costliest to society and our health care system. Last year the total national cost of caring for individuals with Alzheimer's disease and other dementias reached $355 billion—including a $181 billion cost to Medicare. Those who care for a loved one with Alzheimer's disease also face crushing burdens—more than 11 million Americans provided unpaid care for people living with Alzheimer's disease or other dementias last year. These caregivers provided an estimated 15.3 billion hours of care valued at nearly $257 billion.[3]

Unfortunately, patients with Alzheimer's disease have very few treatment options. Prior to the approval of aducanumab, the first antiamyloid mAb, the only FDA-approved treatment options available to patients were medicines to partially manage symptoms by helping to maintain mental function and control behavioral changes.

Recent progress in treatment for Alzheimer's disease has been exceptionally hard-won—despite the critical unmet need, developing medicines to prevent, delay, slow, or cure Alzheimer's disease has proven remarkably difficult. Successful disease-modifying therapies have challenged researchers for many reasons, including limitations of preclinical models and clinical trial challenges.[4] As a result of these challenges, between 1998 and 2021 there were 198 unsuccessful medicines in clinical trials for Alzheimer's disease—and more than half of these failures occurred at Phase II or later and 35 occurred at Phase III or later, highlighting the tremendous risk associated with this work.[5]

Importantly, these setbacks underscore the immense complexity of research for Alzheimer's disease. But the 85 new potential medicines for the treatment of Alzheimer's disease also reflect the continued dedication of research to advance progress for patients with this devastating disease and to learn and build upon the many research setbacks along the way.

---

[1] CMS, Guidance for the Public, Industry, and CMS Staff: Coverage with Evidence Development (Nov. 20, 2014).
[2] Alzheimer's Association. "2021 Alzheimer's Disease Facts and Figures: Special Report—Race, Ethnicity and Alzheimer's in America." Available at: https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf
[3] Id.
[4] https://phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/A-C/AlzheimersSetbacksSteppingStones_FINAL_digital.pdf
[5] PhRMA Analysis of Adis R&D Insight Database. May 2021.

About 83% of medicines in development have the potential to be disease-modifying treatments, offering significant hope to the patients and caregivers living with Alzheimer's disease today and the many more who will be diagnosed in the future.[6]

This class of treatments marks a tremendous step forward for patients as the first therapies to target the fundamental underlying pathophysiology of the disease. CMS' decision to restrict coverage of these treatments will create significant hurdles for patient access. This would be devastating for patients as new treatments are desperately needed to curb this burdensome disease.

B. CMS' proposed CED-only paradigm creates significant access barriers by limiting coverage exclusively to patients who are able and willing to participate in CMS-approved or NIH-supported clinical trials, compounded by rigid research criteria.

CMS' proposed NCD would limit coverage of antiamyloid mAbs only to patients who participate in a CMS-approved or NIH-supported trial. To run a clinical trial, providers often require additional resources, such as ancillary staff and data collection infrastructure, in addition to required compliance with regulations and best practices. Requiring patients to enter randomized clinical trials in order to gain access to these important treatment options would meaningfully constrain access for patients, as not all patients are able or willing to enter a clinical trial, while many local health care providers are not adequately resourced to conduct intensive, complex clinical research.

In addition, the study design criteria CMS lists in the proposed decision memo will likely limit the number of clinical trials that will meet CMS approval and make it more challenging for beneficiaries to enroll. CMS proposes that trials must take place in the hospital outpatient setting, which means patients who would normally receive treatment from an independent physician practice or at an infusion center would have to change practitioners to be eligible. This requirement also creates serious risks for limiting available clinical trial sites given the significant staffing challenges hospitals are having related to clinical trials. In response to a recent survey of staff at trial investigator sites, 78% stated that the pandemic has impacted the initiation of new trials.[7]

The proposed framework for CED will likely create additional hardship for certain patients, such as those more reluctant to enter clinical trials or those who live further away from outpatient centers that are participating in CMS-approved studies. Millions of Medicare beneficiaries reside in rural parts of the country and many lack the resources to travel. As CMS itself has noted, "rural Americans often experience longer travel times to reach their health care practitioners and frequently lack access to public transportation, which can impede timely access to necessary care."[8]

Further, the eligibility criteria CMS proposes for clinical trials are likely to exacerbate existing access barriers. CMS has proposed excluding patients with comorbidities that may significantly contribute to cognitive decline or are likely to increase significant adverse events. This is likely to eliminate a significant number of patients with Alzheimer's disease from eligibility, as patients with dementia are more likely to have multiple health conditions. A 2019 study conducted in the United Kingdom showed that 22% of dementia patients had three or more comorbidities and 8% had four or more comorbidities, compared to 11% and 3% respectively in all patient groups. Between 17 and 20% of dementia patients had a diagnosis of stroke or depression, which could contribute to cognitive decline.[9] This criterion is also harmful to inclusive clinical trial design. Four in 10 Americans have two or more chronic conditions, conditions which also disproportionately impact communities of color.[10] We discuss the implications of this restriction for underserved and underrepresented communities in more detail in Subsection D.

---

[6] https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/trc2.12179

[7] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7538012/#:~:text=The%20survey%20results%20showed%20that,the%20initiation xf%20of%20new%20trials

[8] https://www.cms.gov/files/document/fy-21-improving-health-rural-communities508compliant.pdf

[9] https://www.gov.uk/government/publications/dementia-comorbidities-in-patients/dementia-comorbidities-in-patients-data-briefing#:~:text=Patients%20with%20dementia%20are%20more,in%20the%20all%20patient%20group.

[10] https://www.cdc.gov/pcd/issues/2020/20_0130.htm

Moreover, as listed in the proposed decision memo, the coverage criteria for CMS-approved trials are both restrictive and also described only superficially, leaving it unclear how some criteria might be operationalized. CMS does not explain how it will address the ethics of informed consent associated with asking patients with Alzheimer's disease to participate in a randomized clinical trial comparing a treatment to "standard of care," whether this would involve a placebo control and, if not, what trial designs might be acceptable. Before restricting Medicare beneficiaries' access to an FDA-approved drug or biologic to a small subset of patients who may be eligible to participate in a CMS-approved or NIH-supported clinical trial, these are significant issues that require further consideration and explanation that is not provided. The number of significant, unanswered questions in this coverage proposal—which would have substantial impact on access to an entire class of treatments for patients with Alzheimer's disease—reinforces the importance of withdrawing it and initiating a new process to gain more detailed input before proceeding. PhRMA strongly supports the development of robust clinical evidence to support health care decision-making, via both clinical trials and real-world evidence. However, we are gravely concerned about Medicare coverage policies that would impose severe access restrictions on FDA-approved drugs and biologics to achieve that objective. As we have stated in prior comments regarding CMS' CED guidance and NCDs on specific interventions, PhRMA believes that, in order to effectuate CMS' goals related to appropriate beneficiary access, CED generally should not be applied to drugs or biologics for indications that are supported in the FDA-approved label or supported in a CMS-recognized drug compendium, because underlying coverage policy already supports appropriate beneficiary access.[11] We continue to strongly urge CMS to reconsider its proposal for CED as a framework for coverage for this class of treatments, as it will unnecessarily impede beneficiary access.

C. CMS' proposal undercuts FDA's authority to determine whether treatments are safe and effective and should be made available as an option for patients and caregivers.

In addition to creating significant access barriers to antiamyloid mAbs, we are deeply concerned that CMS' proposal would undercut FDA's past and, potentially, future determinations regarding the safety and effectiveness of drugs and biologics. CMS' proposal creates significant tension by questioning FDA's judgment and, if finalized, would undermine the substantial, longstanding trust that patients and other stakeholders place in FDA. It also creates an untenable confusion regarding division of responsibilities among the agencies.

To date, CMS has generally recognized that FDA approval of a drug or biologic—grounded in prospective clinical trials evaluating the potential risks and benefits of the treatment—provides a robust basis for deeming the drug to be "reasonable and necessary" for at least some patients and ensuring it is covered and available to Medicare beneficiaries. This approach recognizes that, when treatments are evaluated and approved by FDA based on clinical evidence demonstrating safety and efficacy, patients and their physicians can and will evaluate their available options and make individualized decisions about the treatment approach that is best for them. Further, this approach reflects the reality that the optimal treatment regimen can vary among patients, based on their different clinical needs, preferences, risk-benefit considerations, and treatment objectives. In covering FDA-approved drugs and biologics, CMS has recognized the importance of supporting patients and physicians and has empowered them to make well-informed, individualized decisions about the treatment that is best for them.

CMS' general approach of providing timely coverage of FDA-approved medicines has served patients well in ensuring access to medically appropriate, evidence-based treatment options; supporting significant improvements in patient outcomes; and affording patients the ability to make important treatment decisions in consultation with their treating physicians. FDA's drug review program is the global gold standard for regulatory review and approval, involving a rigorous, science-based evaluation of safety and effectiveness before any new drug or biologic can be introduced. This approach has supported significant gains against serious diseases such as cancer, HIV/AIDS, Hepatitis C, and the recent advances against the COVID-19 pandemic. This success includes use of the accelerated approval pathway, through which aducanumab was approved. As recently noted by FDA officials, FDA's expedited regulatory approval pathways have resulted in earlier

[11] See, e.g., PhRMA Comments Re: Coverage with Evidence Development in the Context of Coverage Decisions: Draft Guidance for the Public, Industry and CMS Staff, submitted January 28, 2013.

availability of promising therapies for patients with cancer, a median of 3.4 years before completion of the confirmatory trials that would have been necessary for traditional approval.[12] CMS' policy of ensuring Medicare beneficiaries have timely access to new medicines has played an important role in achieving meaningful gains for patients.

CMS' proposal marks a departure from this approach, one that would have the effect of substituting the agency's own judgment not only for FDA's, but for that of a patient and physician about what is best for the individual. As is the case for any other serious disease or condition, patients facing a diagnosis of Alzheimer's disease rely on their physicians to discuss with them the available data on treatment options and which approach might be best for them based on their individual needs and preferences. The clinical, evidence-based approach taken by physicians in helping patients with Alzheimer's disease and caregivers choose the best course of care—including whether to prescribe antiamyloid mAbs—has been well-documented.[13] CMS has empowered patients and their physicians to make this judgement in the context of other therapies and disease states, such as oncology and rheumatology, among others. The current proposal suggests that CMS has decided that physicians who treat patients with Alzheimer's disease are less capable than other specialists of other disease states in assessing and deciding, with their patients and patients 'caregivers, what treatments are clinically appropriate. This proposed interference with the physician-patient relationship and clinical decision-making process is anomalous and, if finalized, would effectively remove an FDA-approved biologic (as well as future treatments), as an option entirely for all but a severely limited and restricted subset of Medicare beneficiaries.

CMS itself has recognized the importance of FDA's regulatory responsibility and ensuring that Medicare policy does not duplicate or second-guess it. In its own principles governing application of CED, CMS states that "CED will not duplicate or replace the FDA's authority in assuring the safety, efficacy, and security of drugs, biological products, and devices."[14] Despite this, CMS appears to question the safety and efficacy of aducanumab at several points throughout the proposed decision memo. CMS states, for example: "Due to the lack of a clear clinical benefit and the frequency of adverse events like [Amyloid-Related Imaging Abnormalities], the evidence does not support that the benefits outweigh the harms for mAbs directed against amyloid for the treatment of [Alzheimer's disease]." CMS makes this statement despite FDA having already determined that the potential risks of taking aducanumab are outweighed by the potential benefits.[15] CMS fails to explain how it reconciles its conclusions with FDA's decision to approve aducanumab. As noted by the Director of FDA's Center for Drug Evaluation and Research, FDA concluded that the "benefits of Aduhelm for patients with Alzheimer's disease outweighed the risks of the therapy."[16] These two statements are in direct contradiction to each other, a disconcerting dynamic for two federal agencies whose roles should be complementary, indeed two federal agencies whose statutory authority is delegated to the HHS Secretary.

D. CMS' proposal ignores important differences in individual treatments, including those not yet approved by the FDA.

PhRMA is concerned that CMS' decision would apply a highly restrictive coverage policy to an entire class of new and emerging medicines, several of which have not been approved or submitted to the FDA for review. This approach would prove particularly problematic in this therapeutic area. CMS' proposal would foreclose the ability to consider important potential differences in individual treatments, study designs, and patient outcomes by applying a blanket policy to a class of medicines, most of which are currently under development, in an emerging therapeutic area. Aducanumab, as well as the additional antiamyloid mAbs that are currently under development, may have structural distinctions that could lead to differences in dosing regimens, clinical outcomes, or side-effect profiles. FDA reviews individual drugs for safety and efficacy,

---

[12] Mehta GU, de Claro RA, Pazdur R. Accelerated Approval Is Not Conditional Approval: Insights From International Expedited Approval Programs. JAMA Oncol. Published online January 20, 2022. doi:10.1001/jamaoncol.2021.6854

[13] https://www.healio.com/news/neurology/20211118/aan-neurologists-must-discuss-aduhelm-risks-with-patients-families

[14] https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=27

[15] See 21 USC 355(d), F.D.C.A. 505(c) (outlining required finding for approval of drugs); 21 USC 356(h)(8), F.D.C.A. 506(h)(8) (confirming accelerated approval provisions do not alter "the standards of evidence and applicable conditions for approval" under Federal Food, Drug, and Cosmetic Act or Public Health Service Act); 42 USC 262(a), P.H.S.A. 361(a) (governing approval of biologics).

[16] https://www.fda.gov/drugs/news-events-human-drugs/fdas-decision-approve-new-treatment-alzheimers-disease

based on controlled clinical trials that are designed in consultation with the agency. Just as it would be inappropriate for FDA to apply the same regulatory review to approve the entire class of antiamyloid mAbs, it is inappropriate for CMS to rely on data from one treatment to render judgments across the class for the purposes of coverage policy.

In preemptively restricting access to an entire class of treatments, CMS could also stunt innovation and inadvertently limit the potential range of future treatment options for patients and physicians by discouraging other biopharmaceutical research manufacturers exploring antiamyloid mAbs from entering the market. If CMS preemptively restricts Medicare coverage for the entire class of treatments, including those that are not yet approved by the FDA, it will eliminate the incentive for the industry to develop new treatments for Alzheimer's disease, knowing that the drug will likely face significant restrictions on coverage if it is approved. As noted previously in this letter, treatment options within a class are critically important for patients, as responses to medicines can differ considerably among patients.

Science is iterative and not all treatments in a class are the same. As researchers continue to accumulate data across the various development programs our understanding of Alzheimer's disease pathology and the causal pathway of amyloid in Alzheimer's disease will continue to grow. New treatments may clear amyloid plaque more efficiently or may be tolerated at higher doses. It is important to incentivize further research in this space so that new medicines are developed for the benefit of a subset, or entire population, of patients.

In addition to applying to an entire class of treatments, CMS' proposed NCD applies to treatments that have not yet been submitted to or approved by FDA, and for which clinical trials are still ongoing. Consistent with CMS' general approach of recognizing FDA approval for purposes of Medicare coverage of drugs and biologics, the agency should not render a coverage decision before FDA has rendered a judgment about whether it is safe and effective for a particular use. For treatments that remain in development, CMS does not have sufficient information to make a judgment about whether a treatment is "reasonable and necessary." CMS claims that it has conducted a "thorough review of the evidence to consider coverage of antiamyloid mAbs." In fact, CMS has primarily examined data for one treatment, aducanumab, and extrapolated that data to consider coverage for an entire class of treatments.

E. The proposed CED paradigm would worsen existing disparities in access to care by significantly restricting where and to whom the treatments are available.

Last year, the Administration outlined goals to mitigate "potential barriers that underserved communities and individuals may face" in access to health care in an Executive Order[17] on Equity. Additionally, when it initiated the National Coverage Analysis (NCA) for antiamyloid mAbs, CMS indicated a strong interest in addressing issues of equity and inclusion in its coverage policy development process. Despite this interest from CMS and the Administration broadly, the CED-only coverage policy CMS has proposed is certain to have the opposite effect—it will worsen health disparities by significantly limiting access, more so for vulnerable communities. This approach is especially devastating as applied to treatments for Alzheimer's disease, because, as CMS itself acknowledges in the proposed decision memo, some racial and ethnic community groups are disproportionately impacted—one in three Native Americans is impacted by Alzheimer's disease, and Black Americans and Hispanic Americans are at least two times more likely to develop Alzheimer's disease than non-Hispanic white Americans.[18] The LGBTQ community is similarly impacted.[19]

The framework CMS proposes, including rigid study design criteria, systematically undervalues the preferences, priorities and health care needs of diverse populations that make up the United States. It is widely acknowledged that

[17] https://www.whitehouse.gov/briefing-room/presidential-actions/2021/01/20/executive-order-advancing-racial-equity-and-support-for-underserved-communities-through-the-federal-government/
[18] https://www.alz.org/aaic/downloads2020/2020_Race_and_Ethnicity_Fact_Sheet.pdf
[19] https://www.alz.org/aaic/releases_2019/sunLGBT-jul14.asp#:~:text=LOS%20ANGELES%2C%20JULY%2014%2C%202019,to%20their%20cisgender*%20heterosexual%20counterparts.

although underrepresented populations may be equally willing as the general population to participate in a clinical trial,[20] there are still challenges in recruitment of a diverse population.

Specifically, CMS' exclusion of patients with comorbidities that may significantly contribute to cognitive decline or are likely to increase significant adverse events is harmful to inclusive clinical trial design, particularly given that chronic conditions disproportionately impact communities of color. Researchers have specifically pointed to co-morbidities as a factor that may contribute to lack of diversity in clinical trials for Alzheimer's disease. A recent study showed that in a review of clinical trials for Alzheimer's disease, eligibility criteria such as exclusion of people with psychiatric illness and cerebrovascular disease may have led to a disproportionate exclusion of ethnoracially diverse individuals.[21] The criteria also disadvantage patients with certain disabilities, such as those with Down Syndrome, about 50% of whom are diagnosed with Alzheimer's disease by their sixties.[22]

The restriction on coverage to clinical trial sites will acutely impact disadvantaged and socioeconomically deprived communities, as identification, enrollment and participation in a clinical trial will likely require significant resources. Disparities in income and access to care are important determinants of health that have bearing on families navigating treatment for Alzheimer's disease. These disparities have widened significantly since the start of the COVID-19 pandemic. Due to concerns about the pandemic, 41 percent of adults have avoided or delayed routine or emergency/urgent care.[23] The prevalence of delaying or avoiding care is higher among Black (60 percent higher) and Hispanic (50 percent higher) adults than non-Hispanic white adults. These disparities demonstrate that the pandemic has had harmful effects on social, economic, and health care-related outcomes among lower-income and race/ethnic-diverse groups. Indeed, the projected life expectancy of communities of color has dropped sharply since the pandemic's onset, a development that also affects patients with Alzheimer's disease and their families.[24]

The proposed clinical trial requirements also do not appear to take into consideration the lived experiences of patients and patient barriers to health care when restricting where and to whom treatments are made available. CMS' proposed requirement that clinical trials take place only in hospital settings could further widen health disparity instead of closing a health care access gap for patients with Alzheimer's disease. A study from the University of South Carolina finds that hospital closures and resulting health care provider shortages have left 4.4 million residents in rural areas living in a county without a hospital.[25] Similarly, half of the trips made by Black Americans for medical care take more than a half-hour compared with 25 percent of the trips white Americans make.[26]

The noted lack of equitable access to hospital sites and exclusion of those with co-morbidities, and the pervasiveness of chronic disease within diverse populations, will draw marked distinction between those with means and opportunity to access the kind of potentially transformational effect of aducanumab (as well as future treatments) and those who cannot. We encourage CMS to go directly to impacted patients with Alzheimer's disease and encompassing communities and work directly with them to ensure that the concerns of diverse communities are recognized and addressed to mitigate the effect of this proposed decision.

II. CMS' POLICY SHOULD ENSURE TIMELY ACCESS TO EXISTING AND FUTURE FDA-APPROVED TREATMENTS FOR ALZHEIMER'S DISEASE.

In view of the significant flaws and unanswered questions in CMS' proposed NCD, PhRMA urges the agency to withdraw it and re-engage stakeholders in a transparent and deliberative process to determine how best to approach coverage

---

[20] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1298944/
[21] https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1002/alz.12433
[22] https://www.alz.org/alzheimers-dementia/what-is-dementia/types-of-dementia/down-syndrome
[23] Czeisler MÉ, Marynak K, Clarke KE, et al. Delay or Avoidance of Medical Careylo Because of COVID-19–Related Concerns — United States, June 2020. MMWR Morb Mortal Wkly Rep 2020;69:1250–1257. DOI: http://dx.doi.org/10.15585/mmwr.mm6936a4
[24] https://www.pnas.org/content/118/5/e2014746118
[25] https://www.healthaffairs.org/doi/pdf/10.1377/hlthaff.2019.00914
[26] https://bmchealthservres.biomedcentral.com/articles/10.1186/1472-6963-7-40

for antiamyloid mAbs. As CMS proceeds, it should meaningfully address the issues raised above in these comments, consistent with the following principles.

A. CMS should provide broad coverage for new FDA-approved drugs and biologics; any requirements for additional research should represent a supplement to, and not a restriction of coverage.

As described above, it is critically important for CMS to continue ensuring that Medicare beneficiaries obtain timely access to FDA-approved drugs and biologics under Medicare Part B based on a recognition that FDA approval is generally a sufficient basis for deeming a drug "reasonable and necessary". We also note the significant tension and unfairness inherent in a CMS decision that an FDA-approved therapy would not be "reasonable and necessary" for any Medicare patient under any circumstance other than further research in a CMS-approved or NIH-sponsored clinical trial. Restricting coverage of this entire class of therapies to a CED-only framework is not necessary and is inconsistent with CMS historical reliance on FDA approval as a basis for making new medicines available in a timely manner under Medicare Part B.

As we have stated in prior comments to CMS, CED should never apply in cases where an FDA-approved drug or biologic's use is supported by FDA labeling or is recognized as a medically appropriate use under the Medicare statute and existing policy, which provide for coverage of unapproved uses that are included in recognized drug compendia or by peer-reviewed literature from an appropriate medical journal. CMS' own principles governing the application of CED also expressly state that "CED will not be used when less restricted coverage is justified by the available evidence." CMS' principles further reflect the agency's commitment that "CED will generally expand access to medical technologies for beneficiaries."[27]

Additionally, CMS should specify the particular evidence CMS is seeking and should articulate a clear benchmark when CMS would consider post-approval data collection requirements met for the relevant treatments. We have particularly strong concerns about the proposed NCD's lack of clarity in this regard, in light of past experiences with CED which demonstrate the access issues for patients, the uncertainty for innovators and researchers, and the perpetuation of unduly restrictive coverage conditions that result from a failure to specify clear criteria and standards for when the evidence will be sufficient in CMS' view to transition from a CED-only paradigm to a less restrictive policy.

B. CMS should ensure any coverage determination reduces health disparities, rather than exacerbating them.

CMS' proposal to restrict coverage of antiamyloid mAbs represents a new access barrier for historically disadvantaged communities that have faced historical barriers to care due to inadequate insurance coverage. While PhRMA strongly believes that CMS should generally cover physician-administered FDA-approved drugs and biologics under Medicare Part B, regardless of how CMS moves forward, it should ensure that its coverage determination reduces, rather than exacerbates, health disparities. CMS should consider the aggregate impact of the proposed decision and how it might undermine stated goals to reduce health disparities, particularly in communities touched by Alzheimer's disease and other neurodegenerative disorders. This proposed decision could be detrimental to access to other current and future therapies of benefit to diverse communities that might also serve to improve health care outcomes.

CMS should clarify how it will ensure any required post-market research or evidence generation is inclusive of underrepresented and underserved populations. PhRMA supports policies and practices to help drive durable, systemic change including improving clinical trial diversity and has made a concerted effort to better understand industry practice and ongoing efforts among member companies, health care providers, and community stakeholders to enhance clinical trial diversity. The biopharmaceutical industry sees furthering clinical trial diversity as a critical component of helping to ensure health equity for all communities and helping study populations better reflect intended treatment populations.

Documented research and real-world experiences point to several specific challenges:

- Real mistrust from experiments like the Tuskegee Syphilis Study, the use of Henrietta Lacks' cells, and current interactions with the health system have led many to be wary of clinical trials

[27] CMS, Guidance for the Public, Industry, and CMS Staff: Coverage with Evidence Development (Nov. 20, 2014).

- Limited awareness of trial opportunities among potential participants
- Barriers preventing patient access to trials, like inconsistent transportation, lack of access to broadband/internet, or lack of childcare
- A lack of existing clinical trial sites in underrepresented communities

These challenges only reinforce the problematic nature of CMS' proposal to restrict coverage for antiamyloid mAbs to clinical trials for underrepresented communities.

Although there is no silver bullet, PhRMA is actively driving towards a solution. PhRMA's efforts over the last 18 months have not only helped us clearly identify and articulate external barriers to clinical trial participation, but create opportunities to build community awareness, remove access and participation barriers, increase access to ready clinical trial sites in underserved communities, train investigators and clinical support staff, and build trust. Industry has taken a stakeholder partnership in a community-driven approach to this effort, including issuing racial justice principles to show our commitment to address systemic issues that deter Black and Brown communities from participating in clinical trials[28] and our voluntary member company commitment to Principles on Clinical Trial Diversity,[29] which addresses building trust, reducing patient barriers to clinical trial access, and using real-world data to enhance information on diverse populations beyond product approval. As part of this effort, PhRMA recently convened over 150 organizations to address key barriers to participation and solutions that might increase involvement across diverse populations.

PhRMA also believes that a sustainable community-based clinical trial infrastructure focused on broader access to clinical trials for all patients wanting to participate would be a meaningful way to make the research enterprise both more robust and more equitable, and we are working toward a vision for how best to establish such an infrastructure. We would welcome the opportunity to further discuss with CMS how its coverage policy can narrow and eliminate health disparity gaps and improve patient quality of life.

C. Consistent with our position on access to antiamyloid mAbs, CMS should revise the existing NCD for the amyloid beta PET imaging scans to ensure appropriate access to this important diagnostic and facilitate the appropriate targeting of treatments.

In addition to urging CMS to ensure appropriate access to FDA-approved antiamyloid mAbs, we similarly urge CMS to facilitate appropriate access for Medicare beneficiaries to the diagnostic tools necessary to appropriately target these treatments. Regardless of how CMS chooses to cover the biologics that are the subject of the NCD, if Medicare beneficiaries do not have access to Positron Emission Tomography (PET) beta amyloid imaging, patients with Alzheimer's disease will continue to struggle to access the treatments, as physicians may be reticent to prescribe the latter without a positive diagnosis based on the former. However, the current coverage paradigm for PET beta amyloid imaging is significantly impeding access and appropriate diagnosis.

PET beta amyloid imaging is an important tool for physicians in detecting the presence and level of amyloid plaques, which result from the accumulation of the peptide amyloid-β, which many researchers believe is a cause of Alzheimer's disease. Research supported by CMS indicates that use of PET beta amyloid imaging significantly increases clinician confidence in diagnosing Alzheimer's disease—prior to PET imaging, clinicians reported diagnostic confidence in the uncertain range in 72.4% of patients, and this proportion was reduced to 16.2% at the post-PET visit.[30] The current restrictions

---

[28] PhRMA's Racial Justice Principles. PhRMA. Available at: https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/DEI/DEI_PrintAd_FINAL.pdf

[29] Principles on Conduct of Clinical Trials Communication of Clinical Trial Results. PhRMA. https://phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/P-R/PhRMAPrinciples-of-Clinical-Trials-FINAL.pdf?_gl=1*1bli4xc*_gcl_aw*R0NMLjE2MzE1NDYzMzYuRUFJYUlRb2JDaE1JdlllRzNKXzg4Z0lWcWZfSUNoMF93QU5SRUFBWUFTQUFFZ0tmUFBEX0J3RQ..

[30] Rabinovici GD, et al. Association of Amyloid Positron Emission Tomography with Subsequent Change in Clinical Management Among Medicare Beneficiaries with Mild Cognitive Impairment or Dementia. JAMA. 2019; Supplement 4, efigure 2. doi:10.1001/jama.2019.2000, https://jamanetwork.com/journals/jama/article-abstract/2729371

on access to beta amyloid PET imaging significantly undermine the ability to identify which patients are appropriate candidates for potentially receiving treatment with antiamyloid mAbs.

Obtaining an accurate diagnosis is a challenge for many patients, but it can be particularly challenging for patients in rural and underserved communities. In one study, Black, Hispanic, and Asian patients were found to be less likely than white patients to receive a comprehensive evaluation for dementia.[31] Patients in these communities have limited access to diagnostic tools and specialists confident in administering tests and interpreting results. Even if the diagnostic tools are physically accessible, barriers in terms of coverage and cost may prohibit the most vulnerable patient populations from accessing them.

We agree with the comments articulated by a number of stakeholders during the CMS Listening Sessions for the NCA preceding this proposed NCD, which urged CMS to revisit its current coverage policy for diagnostic imaging tests that can play a key role in targeting available treatments to appropriate patients. In particular, we share the concern that CMS' existing CED policy for PET beta amyloid imaging in dementia and neurodegenerative disease has created—and continues to perpetuate and exacerbate—significant and harmful access barriers to important PET diagnostic imaging for patients with Alzheimer's disease and other dementias. Since 2013, Medicare has severely restricted coverage of PET beta amyloid imaging through a CED policy that limits coverage of this important diagnostic to an extremely narrow subset of Medicare beneficiaries who happen to be eligible for and able to enroll in a CMS-approved clinical study that meets specific criteria.[32] PET amyloid imaging is a critical tool that can assist health care providers in appropriately targeting aducanumab and other emerging treatments to patients most likely to benefit. Indeed, as noted by the FDA, the clinical trials for aducanumab used PET amyloid imaging to identify and quantify the presence of amyloid beta plaque.[33] Because aducanumab and other pipeline therapies in the class of medications within the scope of this proposed NCD are specifically "directed against amyloid for the treatment of Alzheimer's disease," it is critically important to ensure access to this FDA-approved diagnostic that identifies whether beta amyloid plaques are present.

To resolve these access barriers, PhRMA strongly urges CMS to rescind the PET beta amyloid imaging NCD under subsection 220.6.20 of the Medicare NCD Manual.[34] The current coverage policy for PET beta amyloid imaging has been in place since 2013, providing CMS with ample time and evidence to determine its effectiveness and its importance in the Alzheimer's disease treatment paradigm. Available evidence strongly supports providing robust and timely access to this important diagnostic tool for Medicare beneficiaries—that, in turn, will help facilitate appropriate targeting of and access to antiamyloid mAbs.

D. CMS should start a new process that involves additional meaningful input from patients, caregivers, and other stakeholders.

CMS should withdraw its proposal and undertake further deliberations and stakeholder discussions to assess appropriate coverage policy for these treatments. At the outset, CMS must seek additional meaningful input from key stakeholders and ensure critical patient access protections are in place. CMS itself emphasizes the importance of a deliberative, transparent NCD process in its 2014 guidance document, stating that "CED will occur within the coverage determination process, which is transparent and open to public comment."[35]

As we urge CMS to withdraw the proposed NCD and conduct further analysis following a different approach, we recognize that it will likely create further uncertainty for physicians who wish to treat their patients with aducanumab, or

---

[31] Tsoy E, et al., Assessment of Racial/Ethnic Disparities in Timeliness and Comprehensiveness of Dementia Diagnosis in California. JAMA Neurol. 2021;78(6):657-665. doi:10.1001/jamaneurol.2021.0399.

[32] Centers for Medicare & Medicaid Services. "National Coverage Determination (NCD) for Beta Amyloid Positron Tomography in Dementia and Neurodegenerative Disease (220.6.20)." Medicare Coverage Database. Available at: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=356&ncdver=1&bc=AAAAEAAAAAAA&.

[33] U.S. Food and Drug Administration. "FDA Grants Accelerated Approval for Alzheimer's Drug." June 7, 2021. Available at: https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug.

[34] https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=356&ncdver=1

[35] https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=27

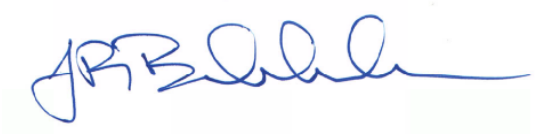
subsequent treatments approved by the FDA. CMS has already created significant uncertainty for physicians and patients (whose claims for aducanumab must be processed by Medicare Administrative Contractors on a case-by-case basis) by opening a NCA.[36] We urge CMS to provide clear direction to carriers to allow coverage for Medicare beneficiaries as it restarts the coverage determination process for antiamyloid mAbs. Patients with Alzheimer's disease don't have time to wait under a cloud of uncertainty or thicket of access barriers for access to treatment options while CMS sort out the very limited circumstances in which they may gain coverage.

* * *

As CMS considers its options for potentially moving forward with this NCD, we urge the agency to do so in ways that will facilitate, rather than impede, the goal of expanding beneficiary access to current and future therapies. We are concerned that the proposed NCD would, if finalized, create unnecessary barriers for Medicare beneficiaries to access FDA-approved treatments, and would exacerbate harmful disparities and inequities in the diagnosis and treatment of Alzheimer's disease. Accordingly, we urge CMS to withdraw the proposed NCD due to its fundamental flaws, and seek further input from patients, caregivers, and other stakeholders before proceeding with any new proposal. In addition, we urge CMS to revisit and revise its current coverage policy for PET beta amyloid imaging, as access to this diagnostic is important to help ensure that appropriate patients for potential treatment with this class of therapies can be identified.

Thank you again for this opportunity to provide input in response to CMS' proposed decision memo. We appreciate the agency's consideration of the concerns and recommendations discussed above.

Sincerely,



-----s-------

Randy Burkholder
Vice President, Policy & Research

Sylvia Yu
Vice President, Law

Lauren Neves
Deputy Vice President, Policy & Research

Amanda Pezalla
Assistant General Counsel, Law

[36] https://www.reuters.com/world/us/biogen-provides-free-aduhelm-us-clinics-await-medicare-payment-2021-08-30/