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**RE: Proposed National Coverage Determination for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease (CAG-00460N)**

Dear Ms. Syrek Jensen:

On behalf of the Alzheimer’s Disease Task Force (the “Task Force”), the 18 undersigned organizations and individuals appreciate the opportunity to offer comments to the Centers for Medicare & Medicaid Services (“CMS” or the “Agency”) regarding its proposed National Coverage Determination (“NCD”) requiring Coverage with Evidence Development (“CED”) for monoclonal antibodies (“mABs”) targeting amyloid for the treatment of Alzheimer’s disease (“AD”). Collectively, the Task Force represents people living with Alzheimer’s disease and related dementias (“ADRD”); family caregivers; healthcare providers; researchers; coalitions and advocacy organizations focused on chronic disease, aging, and minority and women’s health; private-sector leaders; and clinical trial sites. **Together, we strongly urge CMS to remove CED requirements in this NCD and allow coverage for Food and Drug Administration (“FDA”)-approved uses<sup>1</sup> of these Alzheimer’s disease drugs for Medicare beneficiaries nationwide. People living with Alzheimer’s disease, informed by their doctors, should have the option to use FDA-approved drugs; CMS should not use its coverage authority to take that option away.**

Alzheimer’s disease is a devastating and often fatal disease affecting over six million Americans, 80% of who are Medicare beneficiaries. The disease has long been a national priority, and the U.S. Department of Health and Human Services (“HHS”) 2021 National Plan to Address Alzheimer’s Disease has recognized that “the inability to access health care due to a lack of insurance is a major concern.”<sup>2</sup> Notwithstanding that explicit warning, CMS’ proposed coverage decision will create a lack of insurance for those who need it most. Medicare cannot claim to serve its beneficiaries if it will not afford access to, and coverage for, FDA-approved Alzheimer’s treatments.

If CMS finalizes the proposed coverage determination, it will set a dangerous precedent for rationing Medicare beneficiary access to current and future FDA-approved Alzheimer’s drugs, as well as current and future FDA-approved drugs for *other* serious and life-threatening conditions, especially those reviewed under the congressionally authorized Accelerated Approval (“AA”)

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<sup>1</sup> CMS’ proposed NCD applies to the entire class of mAB drugs, which includes the FDA-approved mAB drug, aducanumab, as well as several drugs in clinical development. Since drugs in the mAB class have varied target populations and may have different efficacy profiles, it is important for this Medicare coverage indication to remain flexible and harmonize with the FDA-approved indication (according to the FDA-approved label).

<sup>2</sup> U.S. Dep’t of Health & Human Servs. Off. of the Assistant Sec’y for Planning & Evaluation, National Plan to Address Alzheimer’s Disease: 2021 Update, Strategy 2.B (Dec 27, 2021), <https://aspe.hhs.gov/reports/national-plan-2021-update>.

Program.<sup>3</sup> CMS has never before: (1) refused to cover an FDA-approved drug for its medically accepted use; or (2) denied coverage for *an entire class* of drugs where final clinical trials are not completed and whose data are not yet reported, but are expected to be reported soon. The closest analogue was CMS' 2019 proposal to institute a CED requirement for FDA-approved (under AA) Chimeric Antigen Receptor (CAR) T-cell therapies in certain patients with relapsed or refractory cancers. However, CMS reversed that proposal and issued an NCD covering CAR-T treatment.

In its final decision memo, CMS acknowledges that FDA requires post-marketing studies of the therapy, which is used only in very specific cases where there are no other options, and that CAR-T treatment is an area of ongoing research.<sup>4</sup> The memo also recognizes that routine costs of clinical trials of newer CAR-T therapies being studied are to be covered under Medicare's existing policy on trials and noted that “[i]nformed decision making between a physician and patient remains key to determining the best treatment.”<sup>5</sup> The same patient-centered CMS coverage considerations should apply to mAB drugs targeting amyloid for the treatment of AD. Like CAR-T therapies, mAB drugs used in the treatment of AD must be covered for all of their FDA-approved uses, and the failure to do so would be arbitrary and capricious.<sup>6</sup>

Our comments below outline the specific reasons why we oppose CMS' current proposed draft NCD under CED for mAB therapies targeting amyloid for the treatment of Alzheimer's disease in people with mild cognitive impairment (“MCI”) due to AD or mild AD dementia. Our comments also summarize a number of the many reasons why CMS' use of CED for this drug class is arbitrary and capricious. Finally, we describe how new treatments for people with Alzheimer's disease are being exploited in the larger political drug pricing debate and underline the need for all those involved to restore focus on beneficiaries. Throughout our comment we include personal stories from people currently living with Alzheimer's disease and their family caregivers. They have reviewed this comment letter, we have de-identified the authors, and we request that CMS retain as much of their stories as possible under the requirements of the HHS Privacy Rule.

## I. Overview and Executive Summary

We urge CMS to modify the proposed NCD, which is a *de facto* non-coverage decision tied to an improper CED pathway. In its final decision, we urge CMS instead to authorize full Medicare coverage for all FDA approved uses of mAB drugs targeting amyloid for the treatment of Alzheimer's disease. We disagree with the proposal because it:

- **Denies Treatment Access to Patients with AD Absent Meaningful Alternatives and in a Medically Unethical Manner:** CMS' proposed NCD requiring CED will severely limit beneficiary access to FDA-approved mABs directed against amyloid for the

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<sup>3</sup> See 21 U.S.C. § 356(c) (as amended by Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, § 901(b), 126 Stat. 993, 1079, 1083-84 (2012)).

<sup>4</sup> See generally Ctrs. for Medicare & Medicaid Servs., *Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers Decision Memo* (Aug. 7, 2019).

<sup>5</sup> *Id.*

<sup>6</sup> See *Bracco Diagnostics v. Shalala*, 963 F. Supp. 20, 27-28 (D.D.C. 1997) (“If an agency treats similarly situated parties differently, its action is arbitrary and capricious in violation of the APA.”).

treatment of AD (*i.e.*, aducanumab [alternatively referred to as “Aduhelm”] and other drugs under development) to only those few patients able to participate in ill-defined, CMS-approved randomized controlled trials (“RCTs”) that meet specified criteria.<sup>7</sup> As correctly noted by Dr. Stephen Salloway, a distinguished Professor of Psychiatry and Human Behavior and Neurology at Brown University and the Director of Neurology and the Memory and Aging Program at Butler Hospital, “[t]he proposed CMS NCD for anti-amyloid monoclonal antibodies is essentially a non-coverage decision that restricts access.”<sup>8</sup> Moreover, the proposal would do so in a medically unethical manner by requiring patients to risk taking a placebo when an approved treatment would be available but for the proposed coverage decision.

- **Creates Barriers to Access and Inclusion Rather than Meeting CMS’ Goal of Promoting Health Equity:** While we applaud CMS’ appropriate sensitivity to equity and inclusion in treatment for Alzheimer’s disease, we urge the Agency to make its coverage decision through a lens that *actually* prioritizes timely and appropriate access to mAB therapies for all eligible Medicare beneficiaries. Unfortunately, the proposed NCD with CED requirements will instead disproportionately *exclude* people of color, people with intellectual disabilities including Down syndrome, those living with multiple chronic conditions, and those living in rural areas from access to AD detection and treatment. In effect, this decision would restrict access to an FDA-approved treatment to only the limited number of beneficiaries that are able to self-pay or participate via eligible trial sites.
- **Effectively Reverses FDA’s Approval for Aducanumab and Contradicts the National Institute of Health’s Research Expertise:** The proposed NCD is contrary to FDA’s judgment of the scientific evidence that confirms aducanumab is safe and effective, which meets the CMS standard for items and services that are reasonable and necessary. It also contradicts an extensive body of clinical evidence generated by the National Institutes of Health (“NIH”).
- **Pre-Empts FDA Approval for, and Medicare Access to, the Entire Class of mAB Drugs:** The proposed NCD serves as a rush to judgement and restricts access to the entire class of anti-amyloid mABs—with three additional mABs expected to be under consideration for FDA approval within 18 months—without having evidence or data to reach such a conclusion. The proposal contradicts the scientific evidence development process.
- **Directly Competes with Clinical Trial Recruitment for FDA-Required Post-Market Studies and Will Ultimately Prolong Evidence Collection:** The proposed NCD imposes duplicative, unnecessary, and impracticable CED trial requirements that are contrary to prior coverage decisions for FDA-approved biologics. Redundant clinical trial requirements bifurcate the potential pool of participants for clinical trials, which will

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<sup>7</sup> See Ctrs. for Medicare & Medicaid Servs., *Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease Proposed Decision Memo* (“Proposed NCD Memo”) Sec. I (Jan. 11, 2022).

<sup>8</sup> Stephen Salloway, M.D., M.S., Comment, *CMS Plans to Limit Coverage to Clinical Trials*, ALZFORUM (Jan. 20, 2022), <https://www.alzforum.org/news/research-news/cms-plans-limit-aduhelm-coverage-clinical-trials>.

extend evidence collection and delay access to beneficiaries who would have otherwise benefitted but may progress beyond the point of FDA-label eligibility. This concern is compounded by the potential for three additional mABs to receive FDA approval in the near future. At best, the proposed clinical trials will delay Medicare beneficiary access to treatment (for all but the few thousand in the trials) for a decade or longer.

- **Extends Insufficient Coverage for Amyloid PET Scans:** The proposal offers to cover one amyloid PET scan, which restricts research and physician medical judgment regarding how many scans may be needed by a patient.
- **Uses CED in an Arbitrary and Capricious Manner:** The proposal is in violation of law, because the CED pathway is not authorized by statute and, even if it were authorized, it is being used in an arbitrary manner—the evidence does not support a CED here. Further, the proposal effectively nullifies FDA’s statutory authority to use accelerated approval.
- **Exploits Alzheimer’s Disease to Influence the Political Debate Over Drug Pricing:** The proposed CED is yet another step in misusing Alzheimer’s patients medication needs to seek to influence the current drug pricing debate.

For these reasons, explained in detail below, the Task Force encourages CMS to issue a final NCD for mAB therapies similar to its NCD for Chimeric Antigen Receptor (CAR) T-cell Therapy (110.24).<sup>9</sup> As explained in one organization’s previous comment dated August 11, 2021 to CMS’ National Coverage Analysis (“NCA”), the Task Force believes this approach reflects the flexibility needed when deciding coverage for multiple drugs in a class with varied target populations, different efficacy profiles, and distinct FDA label indications.<sup>10</sup> Accordingly, CMS should adopt a final NCD that states:

*Nationally Covered Indications:*

*Effective for services performed or items used on or after [DATE], the Centers for Medicare & Medicaid Services (CMS) covers monoclonal antibody treatment for Alzheimer’s disease when used for a medically accepted indication as defined at Social Security Act section 1861(t)(2) -i.e., is used for either an FDA-approved indication (according to the FDA-approved label for that product), or for other uses when the product has been FDA-approved and the use is supported in one or more CMS-approved compendia. CMS will also cover beta amyloid positron emission tomography (PET) scans associated with the covered treatment, and such coverage has been determined to meet the CED requirements included in the Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease NCD (220.6.20), amyloid PET imaging associated with monoclonal antibody diagnostic examinations treatment.*

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<sup>9</sup> See generally Ctrs. for Medicare & Medicaid Servs., *National Coverage Determination (NCD) for Chimeric Antigen Receptor (CAR) T-cell Therapy (110.24)* (Aug. 7, 2019).

<sup>10</sup> See Comment from Susan Peschin, President & CEO, Alliance for Aging Research, to CMS (Aug. 11, 2021), <https://www.cms.gov/medicare-coverage-database/view/ncacal-public-comments.aspx?ncaId=305&fromTracking=Y&>.

*Nationally Non-Covered:*

*Effective for services performed on or after [DATE], the use of non-FDA-approved monoclonal antibodies for the treatment of Alzheimer's disease is non-covered until such FDA approval. Effective for services performed on or after [DATE], routine costs in clinical trials that use monoclonal antibodies for the treatment of Alzheimer's disease and associated Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease as an investigational agent that meet the requirements listed in NCD 310.1 will be covered.*

## **II. Statement of Interest**

Many of the Task Force members will present their own responses to CMS and will actively advocate for those positions. The Task Force's comments are not intended to impact adversely the ability of individual Task Force members, alone or in combination, to pursue separate comments with respect to the proposed NCD for mABs directed against amyloid for the treatment of Alzheimer's disease.

## **III. The Proposed NCD Will Deny Treatment Access to Patients with AD for a Decade Absent Meaningful Alternatives, and Will Set Medically Unethical Requirements for the Clinical Trials**

*Personal Patient Story: I am 69 years old, and I want to continue contributing to society. I served as the Chancellor of the University of Denver, the President of Colgate University and the President of Swarthmore College. I am also a scholar in the fields of contemporary higher education in the field of religion and society. I have published or edited five books and authored over fifty articles. I loved my work because it was about serving people and contributing to America's common good. Three years ago, I went in for an annual physical. I got lost on the way, which had never happened before. I told my doctor I was sleeping a great deal. My astute physician gave me the first of many cognitive tests. I did not pass. Many tests and scans and consultations later, I was told the devastating news. I was in the early stages of Alzheimer's. To take care of my life and to make sure I didn't make mistakes as I was overseeing a large institution, my husband and I made the very difficult decision to resign. When we first received the news, we thought the end would come cruelly and swiftly. But it didn't, and now I work hard to follow my neurologist's prescription to "live with joy." But every day, I notice the changes – I miss appointments, read and reread. I stumble when I walk, I can't remember people's names. Every time such an incident like this happens, I am haunted by the thought "It's coming, I am getting worse." Behavior regimes like mine basically assure me that I am doing my part. I know they won't delay the onset of this disease. We need to make Aduhelm and other such drugs available so persons can also live well until this disease has a cure, and so rising medical costs for long term care can be curtailed. I don't have access to drug trials on Aduhelm, and I probably won't have access to any trial with drugs in this category. I live in Denver and there are no such trials anywhere near me. The current decision of CED to fund only those enrolled in research trials limits this drug to those who have the resources and the geographical access to the trials. And that means the continued research will be limited by geographical, social-economical*

*and racial factors. Not only is withholding the support for this drug to so many unfair, at the same TIME it limits continued research in this field. – (patient story, Jan. 2022).*

Alzheimer’s disease is a progressive, debilitating, and fatal neurological disease with no known cure. The vast majority of people with Alzheimer’s disease in the U.S. qualify for Medicare, which covers more than 60 million people, including those age 65 and older, and people with disabilities under 65. As CMS itself acknowledges, treating AD has been a national priority for decades. Given that background, CMS’ proposed NCD with CED is deeply troubling in that it undermines the decades of work by Congress and the Executive Branch, including the Secretary of HHS and its family of agencies, to address AD.

The significance of CMS’ proposed coverage determination for the AD community cannot be overstated. The timing is particularly critical given that aducanumab is the *first* novel therapy FDA has approved for AD in nearly 20 years.<sup>11</sup> More importantly, aducanumab is the *only* FDA-approved drug that targets amyloid plaques in the brain, a fundamental pathophysiology of the disease, which is expected to lead to an improvement in a patient’s condition.<sup>12</sup> The handful of existing therapies only treat symptoms of AD.<sup>13</sup> Yet, “FDA and CMS appear to be at odds regarding AD diagnosis and treatment, and patients are caught in the cross-hairs.”<sup>14</sup>

CMS must modify the proposed NCD because it is medically unethical to require patients to consent to an RCT with a placebo arm in the furnishing of anti-amyloid mABs in order to receive FDA-approved therapy treatment of AD. That basic fact might explain why the draft NCD has no precedent. It is further unethical to require patients to be subject to a placebo in place of a treatment already approved by FDA and determined to be safe and effective for this use, simply to secure coverage. CMS states that it will cover mABs for the treatment of AD in a CMS-approved RCT that meets specified patient inclusion and exclusion criteria.<sup>15</sup> This is commonly understood to mean an RCT that includes a control or placebo arm. **Yet, requiring patients to roll the dice on actually getting treatment as a predicate to having Medicare cover their (possible) care when FDA has already approved a treatment which is available independent of the CED RCT is a violation of basic medical ethics. It is further medically unethical for CMS to charge patients receiving a placebo a co-payment; to require those patients to undergo placebo IV administration in higher-risk hospital outpatient settings during an ongoing pandemic; to further be put at risk of potential infection from the placebo IV administration; and to pay out-of-pocket for transportation to, and parking at, the hospital. CMS cannot require coinsurance payments from beneficiaries in exchange for receiving a placebo in a CED trial, especially when the treatment is to slow the progression of a debilitating, fatal disease like AD.**

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<sup>11</sup> U.S. Food & Drug Admin., Press Release, *FDA Grants Accelerated Approval for Alzheimer’s Drug* (June 7, 2021), <https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug>.

<sup>12</sup> *Id.*

<sup>13</sup> *Id.*

<sup>14</sup> Salloway, *supra* note 8.

<sup>15</sup> Proposed NCD Memo, *supra* note 7, at Sec. I.C.

When confronted with this glaring issue, CMS has offered conflicting guidance on the need for an RCT with a placebo arm. For example, during a stakeholder teleconference on January 13, 2022, CMS suggested that RCTs may not need to be randomized or placebo controlled after all.<sup>16</sup> But this is directly at odds with the plain meaning of the proposed NCD decision memorandum. If CMS wants to arrogate FDA’s decision-making, it will only be able to demonstrate whether the “benefits outweigh the risks” if the CED trial(s) has a control group against which it can measure treatment outcomes (both adverse events and efficacy). If the CED trial(s) is to be conducted and ever finish, there must be clinical endpoints and a control group to be measured. For CMS to suggest after publishing its draft that no placebo group will be required—particularly when the draft CED is so explicit on the point—is contradictory and exacerbates confusion across the stakeholder community.

Beyond the significant bioethics concerns, the proposed NCD with CED would indefinitely and effectively prevent hundreds of thousands of Medicare beneficiaries from having access to a potentially disease-modifying therapy. Coverage would be restricted only to those few Medicare beneficiaries who are fortunate enough to be able to participate in CMS-approved clinical trials, which will be small in number and available in only limited geographic areas.<sup>17</sup> CMS is explicit on this point: anti-amyloid mABs for the treatment of AD “provided outside of the CMS approved randomized controlled trials and trials supported by the NIH are nationally non-covered.”<sup>18</sup>

As CMS knows, approximately 80% of AD patients are Medicare beneficiaries.<sup>19</sup> Further, if finalized, CMS’ proposed decision will have far-reaching consequences beyond Medicare. Private payers are unlikely to provide coverage more broadly than the Medicare program.<sup>20</sup> As a result, only a few thousand patients with AD enrolled in post-market clinical trials will be able to access anti-amyloid mABs for the treatment of AD for the estimated 10 or more years it will take to design, enroll, and conduct these trials, even though an FDA-approved treatment is already available and other treatments may soon be approved and available to those with sufficient private resources to access treatment.<sup>21</sup>

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<sup>16</sup> Cathy Kelly, *Medicare’s Final Coverage Decision on Alzheimer’s Drugs: Thoughts from a Former CMS Chief*, PINK SHEET (Jan. 21, 2022), <https://pink.pharmaintelligence.informa.com/PS145562/Medicares-Final-Coverage-Decision-On-Alzheimers-Drugs-Thoughts-From-A-Former-CMS-Chief> (quoting Mark McClellan, former CMS Administrator).

<sup>17</sup> The proposal also puts at risk Medicaid beneficiaries, as state Medicaid programs are also seeking waivers to ban coverage until the proposed CED trials are concluded. See Gabrielle Wanneh, *Medicaid Directors Want Power To Impose CED Restrictions On Aduhelm*, INSIDE HEALTH POLICY (Jan. 27, 2022), at <https://insidehealthpolicy.com/inside-drug-pricing-daily-news/medicaid-directors-want-power-impose-ced-restrictions-aduhelm>.

<sup>18</sup> Proposed NCD Memo, *supra* note 7, at Sec. I.D.

<sup>19</sup> Alzheimer’s Association Facts and Figures, available at [https://www.alz.org/alzheimers-dementia/facts-figures?utm\\_source=google&utm\\_medium=paidsearch&utm\\_campaign=google\\_grants&utm\\_content=alzheimers&gclid=EAAlQobChMIwfupjert9QIVjYzICh0BvQZkEAAAYASAAEgKx3\\_D\\_BwE](https://www.alz.org/alzheimers-dementia/facts-figures?utm_source=google&utm_medium=paidsearch&utm_campaign=google_grants&utm_content=alzheimers&gclid=EAAlQobChMIwfupjert9QIVjYzICh0BvQZkEAAAYASAAEgKx3_D_BwE)

<sup>20</sup> See Jeffrey Clemens & Joshua D. Gottlieb, *In the Shadow of a Giant: Medicare’s Influence on Private Physician Payments*, 125(1) J. POL. ECON. 1, 1–39 (Dec. 2016), available at <https://pubmed.ncbi.nlm.nih.gov/28713176/>.

<sup>21</sup> UsAgainstAlzheimer’s, *Myth vs. Fact: CMS Draft Decision on Alzheimer’s Drugs* (Jan. 19, 2022), <https://www.usagainstalzheimer.org/press/myth-vs-fact-cms-draft-decision-alzheimers-drugs>.

In addition, even if the proposed CED trials may be accessed by a small subset of Medicare beneficiaries, such trials would exclude countless other Medicare beneficiaries with AD because they will not satisfy the CMS enrollment criteria at the start of the proposed clinical trial(s). Assuming (optimistically) the trials begin in 2023, hundreds of thousands of Medicare beneficiaries will be diagnosed with AD after the clinical trials begin and/or hit their enrollment limits. It is estimated that nearly 500,000 Americans develop new cases of AD each year.<sup>22</sup> Clinical trials generally enroll no more than 1,500 participants. At best, clinical trials of 10,000 individuals could be expected in response to the proposed NCD.<sup>23</sup> Meanwhile, 1.2 million Americans living with either MCI due to AD or mild stage AD could potentially benefit from this class of drugs today.<sup>24</sup> CMS' CED trial requirement will inevitably deny an FDA-approved treatment to hundreds of thousands of U.S. patients facing cognitive and functional decline from the progression of AD. These patients have no other recourse and will lose their memories, face discrimination, require growing caregiving requirements, and die from the disease—all because of factors that they cannot control. CMS should not in good conscience deny access to safe and effective therapies that FDA approves for modifying or delaying the course of this horrific disease.

Millions of Medicare beneficiaries' conditions will worsen so long as CMS precludes coverage as the Agency has proposed to do. It is unclear when these CED trials purport to enroll patients and begin treatment, nor the degree of evidence that CMS will decree as adequate to cease the CED trials. Indeed, some clinical trial experts predict that the proposed NCD would delay these patients access to aducanumab and other anti-amyloid mABs targeting AD for 10 or more years, all while recognizing the reality that these treatments are most effective in the early stages of AD.<sup>25</sup> Tragically, each day an estimated 1,000 individuals progress from mild to moderate AD dementia.<sup>26</sup> Over 10 years, that means that 1,000 individuals each day for 365 days for each of 10 years will move past the disease window at which these drugs are targeted, effectively a death sentence during the decade in which CMS awaits the results of its CED trials. **Patients cannot wait.** Any delay means it will be too late for millions of patients to counteract a currently irreversible, progressive and always fatal brain disorder.

#### **IV. The Proposed NCD Creates Barriers to Access and Inclusion Rather than Meeting CMS' Goal of Promoting Health Equity**

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<sup>22</sup> Bright Focus Foundation, *Alzheimer's Disease: Facts & Figures* (July 14, 2021), <https://www.brightfocus.org/alzheimers/article/alzheimers-disease-facts-figures#:~:text=It%20is%20estimated%20that%20nearly,most%20common%20form%20of%20dementia.>

<sup>23</sup> There is also a significant question regarding who would undertake and pay for such a trial. While typically manufacturers pay for such trials in the clinical development process, Biogen is already pursuing its Phase IV trial, and we understand it has already received approval from FDA on its trial design, which would not satisfy the CED requirements. Similarly, ongoing NIH trials would not meet the CED study criteria. We urge CMS to consider that there may not be an available sponsor for the CED trial(s) it proposes.

<sup>24</sup> UsAgainstAlzheimer's, *Myth vs. Fact: CMS Draft Decision on Alzheimer's Drugs* (Jan. 19, 2022), [https://www.usagainstalzheimer.org/press/myth-vs-fact-cms-draft-decision-alzheimers-drugs.](https://www.usagainstalzheimer.org/press/myth-vs-fact-cms-draft-decision-alzheimers-drugs)

<sup>25</sup> *Id.*

<sup>26</sup> Cai Gillis et al., *Urgency to Treat Before It's Too Late: Daily Transitions to Mild or Moderate AD Dementia in the US and Europe*, J. OF PREVENTION OF ALZHEIMER'S DISEASE S73, S146 (Nov. 2021), available at <https://www.ctad-alzheimer.com/files/files/CTAD21%20Posters.pdf>.



*Personal Patient Story: I am married and a mother of 3 daughters. I received my Bachelor of Arts degree in Human Resource Management at Judson University in Elgin, IL. My working career of 38 years included human resource management, customer service, accounting, sales, human services and entrepreneurship. I left the workforce in 2015, after being diagnosed with Early Onset Alzheimer's Disease at the age of 58. I could not remember passwords, lost my Passport and driver's license within the same year, and was becoming more disorganized. "Dementia does NOT discriminate or exclude anyone." The same is applicable to those that are marginalized. That would include people like me, fellow African Americans and people of color. Moreover, many of us are ignored: no clinical trials available in our neighborhoods and hospitals are far away. Myself and others KNOW how to make a decision to want to continue to live and receive adequate care. Often, we may desire to participate in a study only to discover it is NOT within reach to be able to participate. A Clinical study – it is NOT for everyone. It is for someone that has MORE than I, not people of color that are ignored/or denied the privilege to apply. How can Clinical Trials help in making progress when it's NOT available to the millions of people living with the disease DO NOT get a chance! Do YOU think this is fair? Are there 2 classes? I plead with you to open coverage to ALL, NOT some! – (patient story, Jan. 2022).*

Notwithstanding CMS' numerous statements emphasizing health equity, both generally and in the draft NCD, the Task Force has deep concerns that the proposed NCD will disproportionately harm diverse and already underrepresented communities of color, particularly women of color. The Task Force is also concerned about whether it is even possible to recruit and undertake an adequate number of trials that meet CMS' proposed goals, especially in a timely fashion. Many members of this Task Force are actively engaged in grassroots efforts to improve the representativeness of clinical trials, including direct recruitment of participants. While some sponsors have expressed enrollment goals aligned with or in excess of CMS' stated goals, the reality is more daunting.

Underrepresented beneficiaries are often not located near clinical trial sites CMS has designated as fit, making geography a major barrier to enrollment. CMS' own CED trials have historically proven to fail at enrolling minority and rural populations, resulting in prolonged CED decisions that last for a decade or more. This proposal will only make this problem worse (notwithstanding CMS' aspirational goals to the contrary) by limiting patient enrollment (and, consequently, access to mABs) only to the hospital-based outpatient setting.<sup>27</sup> As evidenced in both NIH's current AD trials and in CMS' prior CED trial experience (addressed below), participating eligible hospitals are principally found in large, urban areas, connected to academic research centers. Rural and private clinics, along with smaller hospitals, are proposed to be shut out from participating in the CMS trials. This has significant implications for minority groups, who more often receive healthcare services from essential providers. The proposed CED trials will deny them access to care.

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<sup>27</sup> Proposed NCD Memo, *supra* note 7, at Sec. I.A.

The disproportionate impact of AD and other dementias falls upon older Black and Hispanic Americans, as compared to older white Americans,<sup>28</sup> and is not explained by genetic factors. CMS' proposal, however, turns a blind eye to the known disparity being caused by negative social determinants of health for older Black and Hispanic populations compared with older white populations. Chronic health conditions associated with higher dementia risk, such as cardiovascular disease and diabetes, disproportionately affect Black and Hispanic populations.<sup>29</sup> Social and environmental disparities, including lower levels and quality of education, higher rates of poverty, and greater exposure to adversity and discrimination, increase the risk for these chronic conditions and risk for dementia in Black and Hispanic populations.<sup>30</sup> Yet, in setting up its proposed trials, CMS ignores this reality and perpetuates guidelines that create an unharmonized set of diversity requirements and constraints that make it impossible to obtain diverse enrollment.

Neither can the CED trials achieve the diversity benchmark set by CMS. CMS requires the randomized controlled trials to include a diversity of patients that are representative of the national population diagnosed with AD. While laudable in principle, the treatment of underrepresented populations “is window-dressing and unrealistic as currently proposed.”<sup>31</sup> CMS must learn from the equity and inclusion failures of past CED trials that such trials are a wholly inappropriate methodology to address equity and inclusion. For example, the Amyloid PET Alzheimer's Prevention Through Exercise (“APEX”) CED trial enrolled 117 participants, 112 of whom were white and 5 of whom were Black. The Cognitive Training and Practice Effects in Mild Cognitive Impairment CED trial enrolled 197 participants. Of those that completed the trial, 111 participants were white, zero were Black or Latino, and only 2 were Asian.

This disparity is not unique to the prior Alzheimer's CED trial. The Cochlear Implantation CED trial, Cochlear Implantation in Adults With Asymmetric Hearing Loss Clinical Trial, studied 40 participants: 33 white, 4 not reported, 2 Asian, and 1 Black. And the TAVR CED, which remains ongoing, Safety and Efficacy Study of Lotus Valve for Transcatheter Aortic Valve Replacement (REPRISE III) had 1,425 participants: 1,172 White, 45 Black, 43 Not Reported, 30 Hispanic, 9 Asian, 9 American Indian, 8 Other, and 3 Native Hawaiian/Pac. Islander. Given these results, it is not surprising that Professor Lon Schneider of the University of Southern California concluded that the proposed CED trial's racial equity requirements are “flatly unattainable, because our national health systems aren't structured to give equitable care to begin with.”<sup>32</sup>

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<sup>28</sup> Alexander Chin et al., *Diversity and Disparity in Dementia: The Impact of Ethnoracial Differences in Alzheimer's Disease*, 25(3) ALZHEIMER'S DISEASE & ASSOCIATED DISORDERS 187, 187–88 (July–Sept. 2011).

<sup>29</sup> Lisa Lines & Joshua Wiener, *Racial and Ethnic Disparities in Alzheimer's Disease: A Literature Review*, U.S. DEP'T OF HEALTH & HUMAN SERVS. OFF. OF THE ASSISTANT SEC'Y FOR PLANNING & EVALUATION (Feb. 2014), <https://aspe.hhs.gov/reports/racial-ethnic-disparities-alzheimers-disease-literature-review-0>.

<sup>30</sup> Jennifer Weuve et al., *Cognitive Aging in Black and White Americans: Cognition, Cognitive Decline, and Incidence of Alzheimer Disease Dementia*, 29(1) EPIDEMIOLOGY 151, 154 (Jan. 2018).

<sup>31</sup> Salloway, *supra* note 8.

<sup>32</sup> AlzForum, *CMS Plans to Limit Coverage to Clinical Trials* (Jan. 20, 2022), <https://www.alzforum.org/news/research-news/cms-plans-limit-aduhelm-coverage-clinical-trials>.

These conclusions also apply with equal force to NIH-conducted trials, which are a core part of the proposed CED here. Although the NIH for decades has had explicit policies mandating inclusion of minority populations in NIH-sponsored clinical trials,<sup>33</sup> it has proven impossible for NIH to meet these objectives in its own trials. Notably, NIH's Alzheimer's disease clinical trials have consistently been unable to enroll minorities at the contemplated rates because of insurmountable systemic barriers. NIH's most recent published data indicates that its Alzheimer's disease clinical trial participants include only 6% of blacks or African Americans, and that its Alzheimer's Disease Related Dementia trials include only 3% of blacks or African Americans.<sup>34</sup> The results for other minority groups is even worse, with less than 1% of Asians and less than 1% of Hispanics being included. While again, CMS' goal is laudable, it is simply not realistic when measured against the very NIH trials that are proposed to be used as part of the CED process.

Ironically, at the same time CMS emphasizes the importance of diverse, representative AD CED study populations, the Agency's draft NCD also excludes patients with "medical conditions, other than AD, likely to increase significant adverse events."<sup>35</sup> This limits participation significantly because 96% of Medicare beneficiaries with Alzheimer's disease or other dementias have at least one other chronic condition.<sup>36</sup> According to the Alzheimer's Association, in 2014 (the latest year for which information is available), 38% of Medicare beneficiaries age 65 and older with dementia also had coronary artery disease, 37% had diabetes, 29% had chronic kidney disease, 28% had congestive heart failure, and 25% had chronic obstructive pulmonary disease.<sup>37</sup>

Additionally, CMS proposes to further exclude AD patients with "[a]ny neurological or other medical condition (other than AD) that may significantly contribute to cognitive decline,"<sup>38</sup> which would likely include people with Down syndrome or other persons with intellectual disabilities. As they age, individuals affected by Down syndrome have a greatly increased risk of developing a type of dementia that is either the same as or very similar to Alzheimer's disease. According to the National Down Syndrome Society, about 30% of people with Down syndrome who are in their 50s have Alzheimer's disease, and about 50% of people with Down syndrome in their 60s have Alzheimer's disease.<sup>39</sup> These statistics likely underestimate the frequency of AD because diagnosing dementia in a person with Down syndrome (or other intellectual disability) involves challenges with assessing cognitive changes.

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<sup>33</sup> See Nat'l Inst. of Health, *Inclusion of Women and Minorities as Participants in Research Involving Human Subjects* (Oct. 2017), <https://grants.nih.gov/policy/inclusion/women-and-minorities.htm>. This policy is the latest update to a series of NIH policies on inclusion since the 1980s.

<sup>34</sup> Nat'l Inst. of Health, *NIH RCDC Inclusion Statistics Report* (accessed Feb. 6, 2022), <https://report.nih.gov/RISR/#/home?facet=Race>.

<sup>35</sup> Proposed NCD Memo, *supra* note 7, at Sec. I.C.

<sup>36</sup> Ctrs. for Medicare & Medicaid Servs., *Chronic Conditions Charts: 2018*, tbl. 15 (2018), [https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Chronic-Conditions/Chartbook\\_Charts](https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Chronic-Conditions/Chartbook_Charts).

<sup>37</sup> Alzheimer's Ass'n, 2021 ALZHEIMER'S DISEASE FACTS AND FIGURES: RACE, ETHNICITY, AND ALZHEIMER'S IN AMERICA 74 (Mar. 2021), available at <https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf>.

<sup>38</sup> Proposed NCD Memo, *supra* note 7, at Sec. I.C.

<sup>39</sup> Gert de Graaf et al., *Estimation of the number of people with Down syndrome in the United States*, 19(4) *Genet Med.* 439, 439–47 (Apr. 2017), available at <https://pubmed.ncbi.nlm.nih.gov/27608174/>.

The Task Force pleads with CMS not to contribute to and exacerbate the massive inequities for people of color, people with intellectual disabilities, those living with multiple chronic conditions, and those living in rural areas in regard to access to AD detection and treatment by imposing any type of CED requirement. Unfortunately, the proposed NCD under CED cannot be cured by modifying the clinical study or hospital-based outpatient setting requirements, or by replacing them with required participation in a CMS-approved registry. For the additional reasons explained below, CMS must *remove the CED coverage requirements* from the proposed NCD and issue a final NCD that allows coverage for FDA-approved uses of these Alzheimer’s disease drugs for Medicare beneficiaries nationwide. Such coverage would enable the collection of evidence in real world populations as opposed to the strictly limited and defined populations in CMS-driven RCT’s.

There is a troubling history of CMS allowing the policy objectives underlying CED equity standards to be subverted, such that the use of CEDs ultimately condemns millions of Medicare beneficiaries to waiting a decade or more for access—which, in turn, only exacerbates the inability of underrepresented communities to *actually* obtain timely access to the therapies that they need to treat their serious medical conditions. CMS has two CEDs in effect today that are under extension for precisely this reason: the amyloid PET CED and the TAVR CED, both of which have been ongoing for 9 years and are expected to continue for at least several more years. In the 2019 reconsideration of the TAVR CED, CMS acknowledged its first TAVR trial resulted in “evidence [that] is insufficient for minority populations. We also await reports on longer-term outcomes for benefits and harms, including quality of life, for our beneficiaries. We continue to believe that the current coverage under CED offers the appropriate balance of quality and access, while simultaneously stimulating innovation of devices, procedural techniques, and indications for use (for subpopulations and patients with various comorbidities), and so we are continuing coverage with evidence development.”<sup>40</sup> The amyloid PET CED and the new IDEAS study will restrict beneficiary coverage of amyloid PET scans for a similar extended duration as well.

Beneficiaries cannot wait another decade or longer for the CED to conclude so that Medicare can cover aducanumab and the other mAB treatments expected to receive review by FDA in the coming months. CMS’ failure to remove CED requirements will only delay access for all beneficiaries and compound existing disparities that disproportionately impact patients with AD who belong to underrepresented communities.

## **V. The Proposed NCD Challenges Both FDA and NIH Research Expertise**

At its core, the CMS proposal to deny coverage outside of a CED clinical trial demonstrates a lack of belief in the “amyloid hypothesis”, the well-understood scientific finding that the imbalance between production and clearance of beta amyloid peptides is a key factor in Alzheimer’s disease.<sup>41</sup> CMS’ failure to recognize the role of amyloid in the Alzheimer’s cascade

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<sup>40</sup> Ctrs. for Medicare & Medicaid Servs., *Transcatheter Aortic Valve Replacement (TAVR) Decision Memo* (June 21, 2019).

<sup>41</sup> See Dennis J. Selkoe & John Hardy, *The Amyloid Hypothesis of Alzheimer’s*, 8(6) *EMBO MOLECULAR MED.* 595, 595 (2016), available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4888851/>.

runs counter to FDA’s findings, which conclude that the reduction of amyloid is reasonably likely to predict clinical benefit.<sup>42</sup>

CMS’ decision to limit coverage to aducanumab and future drugs that clear amyloid plaques also runs contrary to the NIH’s continued focus on AD trials targeting beta amyloid, including the majority of the National Institute on Aging’s late-stage trials.<sup>43</sup> According to the National Institute on Aging (“NIA”), a meta-analysis supported by the institute and published in *Ageing Research Reviews* in July 2021, found that “[a]ntibody drugs that target a protein called beta-amyloid may slightly improve memory and thinking in people with Alzheimer’s disease.”<sup>44</sup> In its published discussion, the NIA meta-analysis found “[r]obust data syntheses of all included studies (12,585 participants) showed statistical improvements for monoclonal antibodies on cognitive outcomes (ADAS-Cog and MMSE) and a trend towards improvement on CDR-SOB, a measure that assesses both cognition and function.”<sup>45</sup> This review was widely cited in the CMS draft determination and was submitted for publication in November 2020, several months before additional studies on mABs were published showing clinical efficacy<sup>46</sup> and also prior to FDA’s June 2021 accelerated approval decision on aducanumab. CMS is overweighing outdated data while failing to give appropriate consideration to more recent data supporting clinical effectiveness.

As noted by Professor Dennis Selkoe of Harvard Medical School and Co-Director of the Center for Neurological Diseases at Brigham and Women’s Hospital, “there are numerous other inaccuracies and misunderstandings among the statements and references [CMS] cite[s]. For example, it is untrue that the ability to make a ‘clinical diagnosis of AD is poor.’ Early non-amnestic symptoms in clinical AD are not ‘rare.’ ASCVD/diabetes/obesity are not major risk factors for AD *per se*. The fact that A $\beta$  [beta-amyloid] monomers are normally produced is not a reason to conclude that lowering amyloid plaques and oligomers interferes with a critical normal function and could be hazardous. And citing that ‘A $\beta$  protects the brain from infections [and] repairs leaks in the blood–brain barrier’ is not widely validated and not a reason to avoid clearing oligomeric A $\beta$  assemblies that have been shown in myriad reports to result from mutant

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<sup>42</sup> See U.S. Food & Drug Admin., *Summary Memorandum: Aduhelm (aducanumab-avwa)* (June 7, 2021), available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2021/Aducanumab\\_BLA761178\\_Dunn\\_2021\\_06\\_07.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/Aducanumab_BLA761178_Dunn_2021_06_07.pdf).

<sup>43</sup> Of 72 current NIA-funded pharmaceutical trials, 20 trials (27%) target amyloid. U.S. Dep’t of Health & Human Servs. Nat’l Inst. on Aging, *NIA-Funded Active Alzheimer’s and Related Dementias Clinical Trials and Studies* (accessed Feb. 6, 2022), [https://www.nia.nih.gov/research/ongoing-AD-trials?utm\\_source=healthinfocptg&utm\\_medium=arrow&utm\\_campaign=link](https://www.nia.nih.gov/research/ongoing-AD-trials?utm_source=healthinfocptg&utm_medium=arrow&utm_campaign=link).

<sup>44</sup> U.S. Dep’t of Health & Human Servs. Nat’l Inst. on Aging, *NIA researchers Comprehensively Analyze Clinical Trial Data on Antibody Treatments for Alzheimer’s* (Sept. 28, 2021), <https://www.nia.nih.gov/news/nia-researchers-comprehensively-analyze-clinical-trial-data-antibody-treatments-alzheimers>.

<sup>45</sup> Konstantinos I. Avgerinos et al., *Effects of monoclonal antibodies against amyloid- $\beta$  on clinical and biomarker outcomes and adverse event risks: A systematic review and meta-analysis of phase III RCTs in Alzheimer’s disease*, 68 AGEING RES. REV. (July 2021), available at <https://pubmed.ncbi.nlm.nih.gov/33831607/>.

<sup>46</sup> Published data from a Phase 2 study of donanemab showed a statistically significant drug effect on the iADRS, a clinical composite scale that incorporates both cognition and function. See Mark A. Mintun et al., *Donanemab in Early Alzheimer’s Disease*, 384(18) N. ENGL. J. MED. 1691, 1691–1704 (May 2021), available at <https://www.nejm.org/doi/full/10.1056/NEJMoa2100708>. Similarly, Phase 2 data from lecanemab showed consistent dose-dependent effects on clinical measures. See Chad J. Swanson et al., *A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer’s disease with lecanemab, an anti-A $\beta$  protofibril antibody*, 13(1) ALZHEIMER’S RES. & THERAPY 80, 80–94 (Apr. 2021), available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8053280/>.

presenilins or mutant APP or Down's syndrome or ApoE4 and induce progressive synaptic dysfunction. All amyloids arise from normal proteins; clearing those amyloids helps patients."<sup>47</sup>

Professor Selkoe also notes that CMS is proposing to repeat both of Biogen's expensive Phase 3 RCTs already undertaken, but this time using federal funds for "hospital outpatient" clinicians to run the trials.<sup>48</sup> He notes that this repeat trial is "enormously costly, labor-intensive, ... complex [and] impractical," and instead calls for federal funds to be focused on novel approaches rather than proving the amyloid hypothesis again after NIH has already done so.<sup>49</sup> CMS should take these comments to heart.

## VI. The Proposed NCD Effectively Reverses FDA's Approval for Aducanumab

*Personal Patient Story: I've been living with Alzheimer's for nine years. In the past two years my communication skills have declined significantly, and [my spouse] will share my story.*

*As told by [spouse and caregiver]: [my spouse] could not afford to go to college but was able to get her nursing degree at Mt. Sinai Hospital in New York City. Taking night classes, she received her Master's in Public Health (MPH) from Columbia with a concentration in Biostatistics. She joined a research team at Weill-Cornell and co-authored in the New England Journal of Medicine the first article on the importance of medical second opinions, a novel idea at that time. She later became the COO of Beth Abraham, the largest long term care facility in New York City. In her final position at the Jewish Guild for the Blind, she developed a Medicare/Medicaid program to provide services to nursing home-eligible clients, enabling them to remain in their own homes. This program now serves over 80,000 individuals in NYC. In her last position, cognitive concerns began to occur, and she decided to retire sooner than planned. She was diagnosed with Alzheimer's shortly after retirement. Since her diagnosis our stories have been tightly interwoven; we have spoken to well over ten thousand people across the country and in Europe. We speak to address the stigma of Alzheimer's, to emphasize living full and purposeful lives, and to strongly encourage participation in clinical trials. After her diagnosis, [spouse] knew immediately that she wanted to participate in a clinical trial. We were very fortunate that she found the Phase 1 aducanumab trial at Yale even though it meant driving two hours both ways eighteen times a year for infusions and tests. But the Phase 1 results were very successful and widely publicized. I thought the phase 3 trial would fill in six to twelve months. It took three years, potentially delaying a disease modifying therapy from the hands of those who desperately need it by two years. I was saddened and angered, and I've dedicated myself to increasing Alzheimer's clinical trial participation. We have no question that [spouse] benefitted from having participated in the aducanumab clinical trial. Her pace of cognitive decline in the early years was extremely slow; we traveled frequently for speaking engagements and she managed an extremely active life. Then the trial was halted for twelve months, and the rate of [spouse]'s decline was noticeably faster during that period. Her*

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<sup>47</sup> Dennis Selkoe, M.D., Comment, *CMS Plans to Limit Coverage to Clinical Trials*, ALZFORUM (Jan. 20, 2022), <https://www.alzforum.org/news/research-news/cms-plans-limit-aduhelm-coverage-clinical-trials>.

<sup>48</sup> *Id.*

<sup>49</sup> *Id.*

*communication skills began to degrade during this period. I'm currently the FDA appointed (non-voting) patient advocate for Alzheimer's, but I was not allowed to participate in the Aducanumab Advisory Committee in November 2020 because [spouse] is in the trial. My substitute was completely silent throughout the discussion and unanimous negative vote. No one spoke up for the AD community. We are dying; we are in a race against time and yet you propose to classify future FDA approved drugs, perhaps unanimously endorsed by its Advisory Committee, as CED medication when that drug could give us better quality and longer years to enjoy our families, when we alone among the top ten deadly disease are the only community that does not have a medication that will prevent, slow or cure our disease. The FDA has reformed many of its policies since the AIDS crisis because it understands the urgency of getting drugs as quickly as possible into the hands of a suffering & dying community. I fear that CMS has not heard the cries of anguish of the six million Americans dying of Alzheimer's disease. Thank you for letting us raise our voices and we hope that you will take our words and passion to heart! (patient and family caregiver story, Jan. 2022).*

#### A. The CMS Proposal is in Direct Conflict with FDA's Conclusions

CMS is blunt in its study objectives: It seeks to determine through the proposed clinical trial(s) whether mABs “demonstrate a clinically meaningful benefit in cognition and function.”<sup>50</sup> Yet, CMS' sister agency, FDA, has already determined that aducanumab is safe and effective for use. CMS should not undermine FDA's mission and statutory authority to protect the public health by requiring additional clinical trials and denying hundreds of thousands of patients with AD access to aducanumab (or other soon-to-be approved mABs). Even if the legal standards are different, CMS should not second-guess FDA's expert judgment on issues of safety and effectiveness. By issuing a proposed NCD that does nothing more than flatly contradict FDA' settled conclusions, CMS misapplies the applicable statutory standards in violation of both the Medicare Act and CMS' own policies—which require deference to FDA on all determinations of safety and effectiveness.<sup>51</sup>

In June 2021, FDA approved aducanumab, an mAB indicated for the treatment of MCI and mild AD.<sup>52</sup> FDA granted approval upon the rigorous review of results from two identical Phase 3, multicenter, double-blind, RCTs.<sup>53</sup> FDA agreed that one of the studies satisfied the criteria for statistical significance for the primary endpoint.<sup>54</sup> After balancing the benefits and risks, FDA concluded that aducanumab provides a meaningful therapeutic advantage over existing treatments on the basis that it may reduce amyloid beta plaque in the brain—a hallmark of AD—

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<sup>50</sup> Proposed NCD Memo, *supra* note 7, at Sec. I.C.

<sup>51</sup> See 42 U.S.C. § 1395y(a)(1)(A); *see, e.g.*, 54 Fed. Reg. 4384, 4306 (Jan. 30, 1989); Ctrs. for Medicare & Medicaid Servs., MEDICARE PROGRAM INTEGRITY MANUAL Ch. 3 § 3.6.2.2 (eff. Aug. 27, 2020); Ctrs. for Medicare & Medicaid Servs., MEDICARE BENEFIT POLICY MANUAL Ch. 15 §§ 50.4.1 and 50.4.2 (rev. Oct. 1, 2003).

<sup>52</sup> ADUHELM™ Full Prescribing Information (revised July 2021), available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/761178s003lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s003lbl.pdf).

<sup>53</sup> Proposed NCD Memo, *supra* note 7, at Sec. IX.

<sup>54</sup> Patrizia Cavazzoni, Director, CDER, *FDA's Decision to Approve New Treatment for Alzheimer's Disease*, U.S. FOOD & DRUG ADMIN. (June 7, 2021), <https://www.fda.gov/drugs/news-events-human-drugs/fdas-decision-approve-new-treatment-alzheimers-disease>.

and is reasonably likely to predict a clinical benefit.<sup>55</sup> Dr. Patrizia Cavazzoni, Director of FDA’s Center for Drug Evaluation and Research (“CDER”), stated, “[a]t the end of the day, we followed our usual course of action when making regulatory decisions in situations where the data are not straightforward. We examined the clinical trial findings with a fine-tooth comb, we solicited input from the Peripheral and Central Nervous System Drugs Advisory Committee, we listened to the perspectives of the patient community, and we reviewed all relevant data. We ultimately decided to use the Accelerated Approval pathway—a pathway intended to provide earlier access to potentially valuable therapies for patients with serious diseases where there is an unmet need, and where there is an expectation of clinical benefit despite some residual uncertainty regarding that benefit. In determining that the application met the requirements for Accelerated Approval, the Agency concluded that the benefits of Aduhelm for patients with Alzheimer’s disease outweighed the risks of the therapy.”<sup>56</sup> FDA is further committed to ensuring that aducanumab is safe and effective by requiring Biogen, the drug sponsor, to conduct and complete a post-marketing confirmatory trial.<sup>57</sup> In addition to FDA requiring a phase 4 confirmatory trial to verify clinical benefit, Biogen also has an ongoing long-term extension study and a real world observational study. Given the work that FDA has done and post-marketing requirements, as well as the two clinical trials and patient registry being conducted by Biogen, it is inappropriate for CMS to require additional or parallel clinical studies as a way to block Medicare coverage. Yet, that is precisely what the proposed CED trial(s) would do.

CMS and others have referenced the Peripheral and Central Nervous System Drugs Advisory Committee (“Advisory Committee”) recommendations in November 2020 as suggesting that there is controversy about the science behind FDA’s approval of aducanumab. In the intervening time between the Advisory Committee meeting and the FDA decision, however, was the release of several additional scientific articles, including a significant study published in the *New England Journal of Medicine* addressing donanemab.<sup>58</sup> The addition of this study not available to the Advisory Committee, in combination with published data related to aducanumab and lecanemab, led FDA reviewers to approve aducanumab. The Advisory Committee’s conclusions are not a reflection of any scientific controversy or question as to whether aducanumab or other mABs are reasonable and necessary—they are simply judgments at different points in time using different sets of available data. While much has been made in the media of this specific disagreement between FDA and the Advisory Committee on the approval decision—including a public (and published) declaration of resignation by three of its members—it is not unique.

#### B. CMS’ Proposal Improperly Challenges Accelerated Approval

Although implicitly called into question by the proposed NCD with CED, FDA’s approval under its congressionally authorized Accelerated Approval (“AA”) Program is also sufficient to establish that aducanumab is reasonable and necessary, and both the approval process and the historic literature have no bearing on whether other mABs should be covered. The use of AA has

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<sup>55</sup> *FDA Grants Accelerated Approval for Alzheimer’s Drug*, *supra* note 11. Even though FDA approved aducanumab through the accelerated approval pathway, accelerated approval does not affect FDA’s gold standard of approval on the basis of substantial safety and effectiveness. It simply allows FDA to accept a different type of data. *See* 57 Fed. Reg. 58942, 58944 (Dec. 11, 1992).

<sup>56</sup> Cavazzoni, *supra* note 54.

<sup>57</sup> *See* U.S. Food & Drug Admin., *BLA Accelerated Approval Letter: BLA 761178* at 3 (June 7, 2021), available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/appletter/2021/761178Orig1s000ltr.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/761178Orig1s000ltr.pdf).

<sup>58</sup> *See generally* Mintun, *supra* note 46.



been an important regulatory mechanism for FDA to allow for earlier approval of drugs that treat serious and life-threatening illnesses than would occur through the traditional approval program. Created in 1992, the AA Pathway was conceived as a direct response to patient therapy during the HIV/AIDS epidemic and in recognition of the urgency of access to new therapy needs faced by patients with life-threatening illnesses. As opposed to traditional approval, which is based upon a direct measure of clinical benefit or a validated surrogate, AA is intended to allow for the initial approval of a drug based on a demonstration of effect on a surrogate endpoint—or an intermediate clinical endpoint—that is reasonably likely to predict a clinical benefit.<sup>59</sup>

This regulatory pathway is used frequently in oncology and has been used for other life-threatening conditions such as multiple sclerosis and rare diseases, where patients and physicians have run out of, or lack entirely, options to treat a fatal illness. Under FDA regulations, sponsors conduct post-marketing studies that verify and describe the expected clinical benefit of the drug with a clinical trial design as agreed upon with FDA at the time of accelerated approval.<sup>60</sup> The statute also establishes provisions for withdrawal of an AA drug where confirmatory trials fail to verify clinical benefit or safety concerns arise.<sup>61</sup>

Since the inception of accelerated approval, FDA has approved hundreds of new drugs and biologics to treat serious or life-threatening illnesses through AA.<sup>62</sup> CMS already covers many of those drugs and biologics<sup>63</sup> because they meet the same FDA “safe and effective” statutory requirements and are approved through the same statutory provisions as non-accelerated approvals.<sup>64</sup> Any consideration of the specific pathway granted by FDA for aducanumab or other medications by CMS is improper and would run counter to Congressional intent of AA. As directly stated by a recent journal article, “[t]he decision of CMS to limit aducanumab to clinical trials is at variance with the purpose of this approach and inconsistent with the intent of the FDA to provide a mechanism for accelerated access to aducanumab for appropriate patients.”<sup>65</sup>

Moreover, at least one mAB manufacturer with a product in development has already announced that it will not be seeking accelerated approval status, yet the proposed CED would condemn that product to the same RCT requirement when it is approved by FDA. This only further compounds the arbitrariness of CMS’ categorical restrictions on mAB drugs targeted to the treatment of AD.

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<sup>59</sup> 21 U.S.C. § 356(c).

<sup>60</sup> U.S. Food & Drug Admin., GUIDANCE FOR INDUSTRY: EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS – DRUGS AND BIOLOGICS 22 (May 2014), <https://www.fda.gov/media/86377/download>.

<sup>61</sup> 21 U.S.C. § 356(c)(3).

<sup>62</sup> U.S. Food & Drug Admin., *CDER Drug and Biologic Accelerated Approvals Based on a Surrogate Endpoint as of December 31, 2021* (Jan. 27, 2022), <https://www.fda.gov/media/151146/download>.

<sup>63</sup> Compare *id.*, with Ctrs. for Medicare & Medicaid Servs., *CY 2022 September Formulary Reference File*, [https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/RxContracting\\_FormularyGuidance](https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/RxContracting_FormularyGuidance).

<sup>64</sup> 57 Fed. Reg. at 58944.

<sup>65</sup> J. Cummings, *Public Policy Should Foster Alzheimer’s Treatment Availability: Comment on the Draft US Medicare Decision to Limit Payment for Aducanumab (Aduhelm™) to Patients Participating in Clinical Trials*, J. PREVENTION OF ALZHEIMER’S DISEASE 1, 3 (Feb. 2022), available at <http://dx.doi.org/10.14283/jpad.2022.25>.

CMS appears to be joining the Institute for Clinical and Economic Review’s (“ICER”) assault on FDA’s AA program.<sup>66</sup> While ICER is recommending to Congress and the Medicaid program’s advisory committee that they restructure payment for the AA program (despite claims analysis demonstrating AA drugs’ *de minimis* cost impact), CMS has taken the ICER argument one step further and is proposing there not even be coverage for AA products at all until further clinical trials are concluded.<sup>67</sup> The proposed NCD demands “evidence sufficient to conclude that the use of monoclonal antibodies directed against amyloid for the treatment of Alzheimer’s disease improves health outcomes for Medicare beneficiaries,”<sup>68</sup> when the statute authorizing accelerated approval explicitly does not require evidence of improved outcomes. Accelerated approval and explicit outcomes in the AA process should not be a factor in CMS’ coverage decision-making, as it would have a significant negative impact on the development of future Alzheimer’s drugs, as well as cancer, HIV, and other novel therapies for life threatening diseases. In a 2018 commentary, then-CDER Director (now FDA Acting Commissioner) Janet Woodcock states, “Individuals with serious, life-threatening diseases (and their families, and the physicians who care for them) have repeatedly stated their desire and willingness to tolerate more uncertainty, including about effectiveness, in a trade-off for faster access. They point out that their lives may be the cost of waiting for definitive clinical outcome trials to be completed.”<sup>69</sup> CMS is not only directly challenging the FDA’s statutory authority, it is missing the point of AA for people living with deadly diseases that have no other options.

### C. Coverage of Aducanumab and the Other mAB Products is “Reasonable and Necessary”

CMS proposes issuing an NCD with CED for the entire class of FDA-approved mABs directed against amyloid for the treatment of AD on unsteady grounds that there is insufficient evidence to demonstrate that aducanumab is “reasonable and necessary” under Section 1862(a)(1)(A) of the Social Security Act.<sup>70</sup> While there is no statutory definition for “reasonable and necessary”, CMS posits that, “[g]enerally, an intervention is not reasonable and necessary if its risks outweigh its benefits.”<sup>71</sup> CMS further focuses its proposed NCD on whether there is “evidence sufficient to conclude that the use of monoclonal antibodies directed against amyloid for the treatment of Alzheimer’s disease improves health outcomes for Medicare beneficiaries.”<sup>72</sup> Under this framework, however, CMS’ proposed NCD runs contrary to FDA’s determination that has answered all these questions (*see* Sec. VI.A, *supra*) and even contradicts CMS’ past practice with other similar therapies.

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<sup>66</sup> Michael McCaughan, *Revisiting Accelerated Approval: A Provocative Rebate Proposal*, PINK SHEET (Apr. 15, 2021), <https://pink.pharmaintelligence.informa.com/PS144164/Revisiting-Accelerated-Approval-A-Provocative-Rebate-Proposal>.

<sup>67</sup> Partnership to Fight Chronic Disease, *New Analysis of Medicaid Spending Reinforces Value and Patient Impact of FDA Accelerated Approval Pathway* (Mar. 30, 2021), <https://www.fightchronicdisease.org/latest-news/new-analysis-medicaid-spending-reinforces-value-and-patient-impact-fda-accelerated>.

<sup>68</sup> Proposed NCD Memo, *supra* note 7, at Sec. IX.

<sup>69</sup> Janet Woodcock, *Expediting drug development for serious illness: Trade-offs between patient access and certainty*, 15(3) *Clinical Trials* 230, 230–34 (2018).

<sup>70</sup> Proposed NCD Memo, *supra* note 7, at Sec. IX.

<sup>71</sup> *Id.*

<sup>72</sup> *Id.*

CMS recognizes that the scientific community accepts that the development of mABs that interrupt the production of amyloids or clear amyloids in the brain is the “therapeutic approach of choice.”<sup>73</sup> CMS also cites trials that have “demonstrated that some anti-amyloid mABs, such as the most recent FDA-market authorized anti-amyloid mAB, aducanumab, effectively clear amyloid plaques.”<sup>74</sup> CMS references the EMERGE trial—which the FDA also relied upon to grant aducanumab’s approval—because it demonstrates “statistical significance of a primary health outcome.”<sup>75</sup> CMS further references the NIA’s recent meta-analysis of anti-amyloid mAB Phase 3 trials, which “found evidence of statistical significance.”<sup>76</sup> Even if CMS believes that the evidence is not sufficiently conclusive and there have been adverse events (all of which were considered by FDA during the approval process), CMS cannot convincingly rule that the benefits of aducanumab outweigh the risks in light of FDA’s approval and the body of scientific evidence. Health care professionals will have different medical judgments about aducanumab and future mABs, and CMS has no authority to overrule or substitute those judgments with its own through coverage determinations. CMS should defer those decisions to the physicians treating the patients,<sup>77</sup> who will weigh the very evidence considered by FDA as to whether treatment is appropriate (*i.e.*, whether the “risks outweigh the benefits”).

Aducanumab is also reasonable and necessary within the meaning of the CMS Manual. The CMS Manual’s definition was finalized into regulation in January 2021 through formal notice-and-comment rulemaking, and even if the definition was later repealed for other reasons,<sup>78</sup> the existing Manual provision still remains a reflection of the Agency’s current thinking. The CMS Manual defines “reasonable and necessary” to mean: (1) safe and effective; (2) not experimental or investigational; (3) appropriate, including the duration and frequency that is considered appropriate for the item or service, in terms of whether it is: (i) furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient’s condition or to improve the function of a malformed body member; (ii) furnished in a setting appropriate to the patient’s medical needs and condition; (iii) ordered and furnished by qualified personnel; (iv) one that meets, but does not exceed, the patient’s medical need; and (v) at least as beneficial as an existing and available medically appropriate alternative.<sup>79</sup>

FDA’s approval of aducanumab (and its future approvals of other mABs) decisively satisfies these criteria.<sup>80</sup> That is, aducanumab is safe and effective, is not experimental or investigational,

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<sup>73</sup> *Id.*

<sup>74</sup> *Id.* at Sec. IX and Sec. VII.B tbl. 1.

<sup>75</sup> *Id.* at Sec. IX.

<sup>76</sup> *Id.* at Sec. IX and Sec. VII.B tbl. 2.

<sup>77</sup> Experts have already developed Clinical Use Guidelines to guide the use of aducanumab in treatment. See J. Cummings et al., *Aducanumab: Appropriate Use Recommendations*, 4(8) J. PREVENTION OF ALZHEIMER’S DISEASE 398, 404–06 (July 2021), available at <https://link.springer.com/content/pdf/10.14283/jpad.2021.41.pdf> (recommending use with patient population studied in clinical trials, including titration recommendations, and discontinuance for symptomatic ARIA and for moderate-severe ARIA, among others).

<sup>78</sup> See 86 Fed. Reg. 2987, 2993 (Jan. 14, 2021) (repealed by 86 Fed. Reg. 62944, 62953 (Nov. 15, 2021)).

<sup>79</sup> MEDICARE PROGRAM INTEGRITY MANUAL, *supra* note 51, at Ch. 3 § 3.6.2.2.

<sup>80</sup> As discussed in note 55, FDA’s approval pursuant to the accelerated approval pathway does not alter FDA’s standards of safety and effectiveness. Neither should accelerated approval affect CMS’ coverage decision. FDA has rigorously reviewed the evidence and concluded that the drug is safe and effective for patients with serious and life-

and is appropriate for use to improve beneficiaries' cognition by reducing decline. CMS would be misguided to rest its proposed NCD with CED solely on the prong "furnished in accordance with acceptable standards of medical practice" to conclude that aducanumab is not reasonable and necessary. "Accepted standards of medical practice" means, in the context of a drug, "furnished to label." It does not mean whether some healthcare practitioners like or dislike the drug—as noted above, that medical decision should be made between individual practitioners and their patients, and not arrogated to the Medicare program itself. Nor does it mean that there is scientific controversy about the side effects of the drug and the risk-benefit calculus—again a decision already made by FDA and to be made by individual practitioners and their patients. Yet, the proposed NCD with CED, if finalized, *will* be making medical decisions for the thousands of clinicians and patients who would in concert consider mABs for the treatment of AD—both the product approved now and the products to be approved in the near future.

CMS cannot justify its determination that there is insufficient evidence to demonstrate that aducanumab (and all other mABs targeting amyloid for the treatment of AD) improves health outcomes. CMS acts against the weight of the evidence around anti-amyloid mABs. The Agency is also running afoul of its own definition of "reasonable and necessary" in taking into its own hands the medical decision-making authority of doctors and patients across the country who would choose mAB therapy.

## **VII. The Proposed NCD Preempts FDA Approval for, and Medicare Access to, the Entire Class of mAB Drugs**

Not only does CMS' proposal to issue an NCD with CED fail to follow its own policies and standards, but this decision, if finalized, would go against existing precedent in that CMS (for good reason) has never before made a final determination to require a CED trial for a class of drug products previously approved by FDA. Of the 21 NCDs with CED that CMS has issued to-date, CMS has only issued one NCD with CED for a drug and only in the context of off-label use.<sup>81</sup> CMS has never: (1) refused to cover an FDA-approved drug based on its on-label use; or (2) denied coverage of an entire class of drugs based on the safety and efficacy profile of one FDA-approved drug.<sup>82</sup> That is for two good reasons. First, the expertise lies within FDA, and respectfully, not within CMS. Second, each FDA-approved drug has a unique molecular structure, different mechanism of action, and different side effect profile, making it wholly inappropriate for CMS to issue class-wide coverage determinations. Yet, CMS has created the host of problems outlined in this letter by departing from its past practice. We urge CMS to return to its historical approach and issue an NCD covering the FDA-approved mAB therapies.

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threatening conditions for which there are no meaningful alternatives. If anything, FDA's approval of aducanumab under the accelerated approval pathway underscores the urgent need to provide patients with faster access to new drugs and better health outcomes.

<sup>81</sup> See Ctrs. for Medicare & Medicaid Servs., *Anticancer Chemotherapy for Colorectal Cancer Decision Memo* (Jan. 28, 2005).

<sup>82</sup> Even though CMS has created a reconsideration process that allows CMS to reevaluate whether a particular drug should fall under an NCD, reconsideration is not an adequate solution because, under the best of circumstances, the process takes 9 months. During that time, tens of thousands of new patients will have been diagnosed with mild AD and existing patients will have experienced decline in cognitive abilities.

The proposed NCD with CED would inexplicably sweep under its purview all other mABs that have yet to receive FDA approval and present different safety and efficacy profiles. Putting aside any issue that CMS has with aducanumab, CMS inexplicably aspires to deny coverage for an entire class of anti-amyloid mABs, including products currently in late-stage development from Eisai Co., Eli Lilly & Co., and Roche.

CMS recognizes that the “spectrum of AD therapies currently in various stages of investigation extends from anti-amyloid, to anti-tau, neurotransmitter-modifying, cognitive-enhancing, anti-neuroinflammatory, and neuroprotective therapies.”<sup>83</sup> In 2019, there were over 100 trials dedicated to AD therapies. Of these, 9 phase III trials target amyloid and 4 phase III trials use anti-amyloid mABs. Most relevant here, “[t]here are promising data emerging from trials of plaque-lowering mAbs including donanemab, lecanemab, and gantenerumab (13, 14, 18). These agents have different delivery approaches, dosing strategies, titration schedules, and target epitopes. Preliminary observations suggest that they may have different rates of ARIA [amyloid related imaging abnormalities], and comparative efficacy is unknown. It is premature to suggest that a CED will be required for all plaque lowering mAbs.”<sup>84</sup>

Of course, the phase III clinical trial data is not yet available for these other medicines. They may offer a more favorable safety and effectiveness profile, but CMS denies coverage to beneficiaries (except for a small few in further clinical trials) before it sees the data. Moreover, CMS homogeneously groups together fundamentally different treatments, with different molecular entities, than those used to generate the clinical trial data involved in the aducanumab approval. It is thus wildly inappropriate for CMS to reach *any* conclusions as to whether these products will be reasonable and necessary for coverage under the Medicare program at this juncture.

The draft NCD with CED statement that “[t]his NCD addresses anti-amyloid mAbs as a class since the drugs have a similar function of reducing amyloid in the brain” is simply wrong. As noted by Dr. Eric Siemers, “solanezumab, which targets A $\beta$  monomers, does not lower amyloid plaque and is not associated with ARIA. Thus, the notion that all monoclonal antibodies used for the treatment of AD should be considered as a class is mistaken.”<sup>85</sup> This is but one of the many reasons that CMS has not historically subjected any FDA-approved drugs, much less an entire class of FDA-approved drugs, to a CED trial—the products within the class are different in molecular structure, in mechanism of action, in side effect profile, and in safety and efficacy. Moreover, FDA is the agency that Congress has entrusted with the approval of drugs, not CMS, and that determines whether the risks outweigh the benefits on a drug-by-drug basis—not by ruling on an entire class of drugs based upon one drug in the class.

CMS should also consider the damage to innovation that will follow if it finalizes its proposed decision. As noted by Dr. Jeffrey Cummings in his recent article: “[D]rug development for AD is a costly and lengthy enterprise requiring extensive financial and time investment. Pharmaceutical

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<sup>83</sup> Proposed NCD Memo, *supra* note 7, at Sec. IX (citations omitted).

<sup>84</sup> Cummings, *supra* note 65, at 5.

<sup>85</sup> Eric Siemers, M.D., Comment, *CMS Plans to Limit Coverage to Clinical Trials*, ALZFORUM (Jan. 20, 2022), <https://www.alzforum.org/news/research-news/cms-plans-limit-aduhelm-coverage-clinical-trials> (citation omitted).

and biotechnology companies must realize a return on investment to warrant committing resources to a therapeutic area. Delaying a return on mAb development costs while a CED is conducted will disincentivize drug development for AD.”<sup>86</sup> Dr. Cummings’ prediction is not speculative—already, just 20 days after CMS’ proposal, Eli Lilly announced a significant delay in the development of donanemab due to the proposed lack of coverage it now expects as a result of CMS’ announcement.<sup>87</sup> Similarly, other Alzheimer’s treatments in development are likely to be delayed if CMS does not reverse its proposal.

CMS should reverse course as it did when considering coverage of the entire class of CAR-T therapies. As CMS is aware, CMS originally proposed a CED trial for coverage of CAR-T therapies, only to later delay a decision<sup>88</sup> and eventually replace the proposal with national coverage without CED.<sup>89, 90</sup> In the final decision memorandum, CMS explained that it abandoned the CED pathway because: (1) “FDA has required post-marketing studies” for CAR T-cell therapies already; (2) the patient population has “limited remaining treatment options”; and (3) “CAR T-cell therapy has shown to induce remission.”<sup>91</sup> CMS rationally agreed that it could “leverage information obtained from the FDA’s required post-approval safety studies” and would defer treatment decisions to the “[i]nformed decision making between a physician and patient.”<sup>92</sup> In other words, CMS found that CAR T-Cell therapies were reasonable and necessary.

CMS is now presented with *essentially the same* conditions. There are no other FDA-approved anti-amyloid mABs for the treatment of AD that are expected to lead to an improvement in a patient’s disease trajectory. Further, CMS has provided no reasons why it should doubt the reliability of Biogen’s post-confirmatory trial intended to study aducanumab’s continued safety and effectiveness, particularly because Biogen has now announced it will increase its FDA study size and is committed to enrolling 18% of the trial participants from communities of color.<sup>93</sup> If CMS proceeds with the proposed CED trials, it will repudiate its CAR T-cell therapy NCD and

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<sup>86</sup> Cummings, *supra* note 65, at 5.

<sup>87</sup> Leroy Leo, *Eli Lilly pushes back timeline for Alzheimer’s drug application* (Feb. 3, 2022), REUTERS <https://www.reuters.com/business/healthcare-pharmaceuticals/eli-lilly-profit-falls-18-higher-costs-2022-02-03/>.

<sup>88</sup> Ctrs. for Medicare & Medicaid Servs., Press Release, *CMS STATEMENT: Delay in Final Chimeric Antigen Receptor (CAR) T-cell therapy National Coverage Determination* (May 19, 2019), <https://www.cms.gov/newsroom/press-releases/cms-statement-delay-final-chimeric-antigen-receptor-car-t-cell-therapy-national-coverage>; see Ctrs. for Medicare & Medicaid Servs., *Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers Proposed Decision Memo* (Feb. 15, 2019), <https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=Y&ncaid=291&fromTracking=Y&>.

<sup>89</sup> See *CAR T-cell Therapy for Cancers Decision Memo*, *supra* note 4.

<sup>90</sup> CMS’ NCD covered CAR T-Cell therapies when administered at healthcare facilities enrolled in FDA’s risk evaluation and mitigation strategies (REMs) program. *Id.*

<sup>91</sup> Proposed NCD Memo, *supra* note 7.

<sup>92</sup> Ctrs. for Medicare & Medicaid Servs., Press Release, *Trump Administration Makes CAR T-Cell Cancer Therapy Available to Medicare Beneficiaries Nationwide* (Aug. 7, 2019), <https://www.cms.gov/newsroom/press-releases/trump-administration-makes-car-t-cell-cancer-therapy-available-medicare-beneficiaries-nationwide>. (quoting Seema Verma, then-CMS Administrator).

<sup>93</sup> Katherine Foley, *Biogen Study of Controversial Alzheimer’s Drug to Meet Diversity Requirements*, POLITICO (Jan. 27, 2022), <https://subscriber.politicopro.com/article/2022/01/biogen-study-of-controversial-alzheimers-drug-to-meet-diversity-requirements-00002583?source=email>.

hijack the physician-patient relationship.<sup>94</sup> (*See* Sec. VI.C, *supra*.) CMS must modify this proposed NCD with CED to an NCD extending full coverage to anti-amyloid mABs.

### **VIII. CMS' CED Study Requirements Directly Compete With and Will Duplicate FDA-Required Post-Market Studies and Will Ultimately Prolong Evidence Collection**

A CED trial is both duplicative and unnecessary for purposes of the NCD, regardless of the questionable use of randomization and placebos. CMS states that the CED trial must be designed for the possibility of a longitudinal study upon completion (*i.e.*, a study to demonstrate that the benefits of aducanumab outweigh the risks).<sup>95</sup> However, as noted above (*see* Sec. VI.A, *supra*), FDA's approval of aducanumab already settles that the drug's benefits outweigh its risks, and FDA has already imposed a post-marketing confirmatory trial incident to aducanumab's approval to further solidify the Agency's confidence that the drug is safe and effective. All a CED trial will do is replicate and duplicate other clinical trial results, and potentially cannibalize the available patient population for the existing trials.

CMS purports to justify the need for the CED study, in part, by citing potential side effects of aducanumab. The Agency's concern is misplaced, as "the risks of ARIA do not exceed those of cancer therapies that are routinely covered by CMS."<sup>96</sup> Further, FDA has already required additional pharmacovigilance related to the risks of ARIA. However, even if CMS' concerns were well-founded, it could address those issues by requiring as a condition of coverage (or working with FDA to require) that the manufacturer utilize a Risk Evaluation and Mitigation Strategies ("REMS") program for the use of aducanumab. Instituting a REMS would limit access to facilities that register in the REMS program but would widen access to coverage for all Medicare beneficiaries that otherwise meet the FDA requirements.<sup>97</sup> This is not a new idea—in its Final NCD decision to fully cover the CAR-T therapies, CMS cited the FDA REMS programs for the two approved products CAR-T therapies then approved. Nor is the idea new to aducanumab's sponsor—Biogen submitted a REMS plan to FDA, which then concluded was not necessary to ensure the benefits outweighed the risks.<sup>98</sup> Further, CMS should take comfort in the fact that FDA reviewed the side effect risks and noted to Biogen: "[G]iven the accelerated approval pathway requires confirmatory trials and the clinical reviewer is recommending additional pharmacovigilance for the risk of ARIA, there should be additional data on the safety of aducanumab in a real-world setting. If new safety information becomes available, DRM can re-evaluate the need for a REMS. DRM does not object to the proposed voluntary activities;

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<sup>94</sup> *See also Encino Motorcars, LLC v. Navarro*, 136 S. Ct. 2117, 2120, 2126 (2016) ("An '[u]nexplained inconsistency' in agency policy is 'a reason for holding an interpretation to be an arbitrary and capricious change from agency practice.'").

<sup>95</sup> Proposed NCD Memo, *supra* note 7.

<sup>96</sup> Cummings, *supra* note 65, at 4.

<sup>97</sup> *See* FDA Clinical Review(s), aducanumab at 171,

[https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2021/761178Orig1s000MedR\\_Redacted.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000MedR_Redacted.pdf) ("It should be noted that this data arose from the controlled setting of a clinical trial. If approved, a reassessment of risk in clinical practice, for example in the absence of concomitant medication exclusion criteria and other clinical trial infrastructure, could be warranted based on the data at that time").

<sup>98</sup> *See generally* Ctr. for Drug Evaluation & Res., *Risk Assessment and Risk Mitigation Review(s) BLA 761178* (June 7, 2021), [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2021/761178Orig1s000RiskR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000RiskR.pdf).

however, as these materials are not part of labeling or a REMS, they should be reviewed by the Office of Prescription Drug Promotion.”<sup>99</sup> However, even though side effects will already be carefully monitored and reported by Biogen, to the extent that CMS desires additional vigilance it can work with FDA and the sponsor to add a REMS program, rather than refusing coverage for all Medicare beneficiaries other than those few who qualify for a possible CED trial. (See Sec. III, *supra*.)

## IX. CMS’s Should Terminate the Amyloid PET Scan CED And Cover These Scans

*Personal Patient Story: Five years ago, I was diagnosed with early onset Alzheimer’s. In the time since, I have been participating in a clinical trial for the FDA-approved drug, aducanumab (Aduhelm), which would fall into the above class of treatments. And I firmly believe this treatment has helped me. Three years ago, I was a cognitive mess. I badly failed cognitive tests, and felt like much of the world was in a fog. Today, while I’m still forgetful, I’m being productive in the world, proofreading transcripts for court reporters and serving on the Alzheimer’s Association Delaware Valley Chapter Board of Directors. None of this, I believe, would be possible without the treatments I have been receiving. Unfortunately, I am now faced with a challenging decision. Do I pay tens of thousands of dollars a year for a treatment that by all rights should be covered by Medicare? Or do I cease treatment beyond what I may receive as part of this clinical trial? Almost a decade ago, CMS had a major decision before it. Its sister agency, the FDA, had approved a drug that would help doctors diagnose Alzheimer’s disease. And CMS had to decide whether or not to cover it. The drug under consideration bound itself to plaques in the brain believed to be a partial cause of dementia. Using a PET scan, the drug would light up the plaques, giving doctors an easy way to highlight dangerous changes in the brain. At the time, CMS dashed the hopes of the Alzheimer’s community and declined to pay for the drug, saying they were unconvinced of its utility. Last week, In a decision eerily reminiscent of its actions a decade ago, CMS once again crushed the hopes of people living with Alzheimer’s and their families, by issuing a draft decision declining coverage of monoclonal antibodies targeting amyloid for the treatment of Alzheimer’s disease outside of a clinical trial. This limits access to an entire class of drugs, which include a recently FDA-approved treatment for early or mild cognitive decline. The reason: despite FDA approval, CMS was, again, unconvinced of its effectiveness and utility. – (Jan. 2022).*

In its draft NCD for mAB therapies targeting amyloid for the treatment of AD, CMS has appropriately proposed that patients be screened through amyloid positron emission tomography (“PET”) scan (or other screening technology), but has proposed to only cover one PET scan (or other amyloid screen) per patient enrolled in a clinical trial.<sup>100</sup> This means that CMS will preclude coverage for any follow-up scans or screens needed to compare to the enrollment screen, even if the second scan is necessary to measure changes in the clinical trial subjects’ conditions (*i.e.*, to measure changes in the accumulation and distribution of amyloid and tau tangles in the brain). Consequently, CMS puts the financial burden on patients to pay for follow-

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<sup>99</sup> *Id.* at 18–19.

<sup>100</sup> Proposed NCD Memo, *supra* note 7, at Sec. I.A.



up PET scans. Unlike the IDEAS study, which was an open-label longitudinal study measuring whether the results of an amyloid PET scan would influence provider diagnosis and treatment,<sup>101</sup> the proposed CED trial is a RCT with a placebo group (*see* Sec. III, *supra*) and would study treatment outcomes, which require a comparison of amyloid measurements.

For CMS to propose paying for one scan, but not the second, eviscerates sponsors' or the NIH's ability to confirm one of the endpoints the community wants to measure—the reduction of BA loads in patients. Further, it will limit clinicians' ability to determine whether a particular patient should be taken out of the clinical trial. Ultimately, the limit compromises the ability of the trial sponsor(s) to complete the RCTs and add significant cost to beneficiaries who require additional scans and implicate the diagnosis and treatment of AD. CMS must reconsider its CED for amyloid PET scans and issue a final NCD covering these scans, which will facilitate the collection of mAB clinical trial data in the future.

The ability to test the accumulation and distribution of amyloid and tau tangles in the brain through PET imaging will aid diagnosis and ultimately help physicians make more informed decisions about patient care, including whether to treat with mABs. PET imaging has significantly helped in the diagnosis and staging of AD as well as in identifying which patients may benefit from treatment. A negative PET result rules the disease out. The IDEAS data analysis, published in JAMA in April 2019, found approximately 36% of patients clinically diagnosed with AD and 61% of patients with mild cognitive impairment (“MCI”) were negative for amyloid plaque by amyloid PET scan.<sup>102</sup> These PET results profoundly impacted the primary study endpoint, which was the post-PET care management plan. More than 60% of study participants in both the MCI and dementia patient groups had changes in care plans post-PET, most notably in the starting, stopping, or modification of AD drug therapy, but also in the use of other drug therapy and/or counseling about safety and future planning. Additionally, physicians reported that PET results contributed substantially to the post-PET management plan in 85.2% of instances in which a change was made, further validating the usefulness of the diagnostic.<sup>103</sup> Therefore, PET scans had a direct impact on changing patient diagnosis and management.

CMS' authority to tie together both the CED trial for PET scans and the CED trial for mABs targeting amyloids also is unclear. CMS must clarify the statutory and regulatory basis for integrating these two CED trials. To resolve the issue, we call on CMS to reconsider its NCD for amyloid PET scans and issue a final NCD covering without limitation such scans. The original justification for the CED —the lack of available treatment—is no longer valid given FDA's approval of aducanumab.<sup>104</sup>

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<sup>101</sup> New IDEAS Study, ORIGINAL IDEAS STUDY PROTOCOL, *available at* [https://www.ideas-study.org/-/media/Ideas/Files/Original-IDEAS/Original-IDEAS-Study\\_Protocol.pdf](https://www.ideas-study.org/-/media/Ideas/Files/Original-IDEAS/Original-IDEAS-Study_Protocol.pdf).

<sup>102</sup> Gil Rabinovici et al., *Association of Amyloid Positron Emission Tomography With Subsequent Change in Clinical Management Among Medicare Beneficiaries With Mild Cognitive Impairment or Dementia*, 321(13) JAMA 1286, 1286–94 (Apr. 2019).

<sup>103</sup> *Id.*

<sup>104</sup> *See* Ctrs. for Medicare & Medicaid Servs., *Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease Decision Memo* Sec. I (Sept. 27, 2013), <https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=265>.

Eight years ago, when CMS finalized its amyloid PET NCD for dementia, there were no FDA-approved disease-modifying therapies (“DMTs”) for AD. In the absence of effective dementia therapies, it was postulated that amyloid PET would need to show significant changes in dementia diagnosis and management and demonstrate improved clinical outcomes compared to those beneficiaries with dementia who had not undergone amyloid PET. Now that a disease modifying mAB therapy has recently received FDA approval, CMS should transition its NCD for amyloid PET with CED to a NCD with coverage to the FDA-approved label.

We caution, however, that CMS must take further action beyond coverage, and also address payment, to allow any future clinical trials (or treatment) to proceed by “unpackaging” the diagnostic radiopharmaceuticals used in amyloid PET imaging from the respective procedure payment. As CMS is well aware, and has been referenced by the Office of Inspector General (“OIG”), the inability of the NEW IDEAS trial (the improvident extension of the amyloid PET CED) to enroll clinical trial sites has been directly related to hospital outpatient departments’ unwillingness to conduct amyloid PET scans and face financial shortfalls due to a lack of reimbursement for the PET scan agents. More specifically, while the original IDEAS trial enrolled over 125 sites, at the time of this comment the NEW IDEAS trial has enrolled less than 20 sites.

As reported by the Government Accountability Office “[t]he study organizers said that those hospitals, which had all participated in the original IDEAS Study, declined to participate because the packaged payment would cause them to incur a financial loss for each procedure performed.”<sup>105</sup> The reimbursement issue is significant, and could itself derail the entirety of the proposed CED clinical trials. We call upon CMS to address this issue and “unpackage” diagnostic radiopharmaceuticals from hospital outpatient procedure payments, so that hospitals and other viable non-hospital sites of care will be able to participate in the proposed clinical trials should CMS proceed with the CED pathway.

## **X. CMS’ Use of CED is Arbitrary, Capricious, and Contrary to Law**

The NCD with CED is also improper for legal reasons. First, Congress never authorized a “Coverage with Evidence” pathway for the National Coverage Determination process, and CMS lacked the statutory authority to issue its 2014 “Guidance Document.”<sup>106</sup> Not only is the Guidance beyond the statute, but it would also constitute an illegal rulemaking if it were appropriately authorized.<sup>107</sup> Even the statutory authority cited by CMS to support its proposed pathway is invalid. More specifically, in its 2014 “Guidance for the Public, Industry, and CMS Staff: Coverage with Evidence Development,” CMS claimed that its statutory authority for CED

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<sup>105</sup> U.S. GOV’T ACCOUNTABILITY OFF., GAO-21-252, MEDICARE PART B: PAYMENTS AND USE FOR SELECTED NEW, HIGH-COST DRUGS (Mar. 2021), available at <https://www.gao.gov/assets/gao-21-252.pdf>.

<sup>106</sup> See generally Ctrs. for Medicare & Medicaid Servs., GUIDANCE FOR THE PUBLIC, INDUSTRY, AND CMS STAFF: COVERAGE WITH EVIDENCE DEVELOPMENT (Nov. 20, 2014), available at <https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=27>.

<sup>107</sup> See 42 U.S.C. § 1395hh; *Azar v. Allina Health Servs.*, 139 S. Ct. 1804 (2019); see also *HHS Advisory Opinion 20-05 On Implementing Allina*, U.S. DEP’T OF HEALTH & HUMAN SERVS. (Dec. 3, 2020), available at [https://www.hhs.gov/guidance/sites/default/files/hhs-guidance-documents/2101111604-mh-advisory-opinion-20-05-on-implementing-allina\\_12.03.2020\\_signed.pdf](https://www.hhs.gov/guidance/sites/default/files/hhs-guidance-documents/2101111604-mh-advisory-opinion-20-05-on-implementing-allina_12.03.2020_signed.pdf).

derives from sections 1862(a)(1)(A) and 1862(a)(1)(E) of the Social Security Act (“SSA”). Section 1862(a)(1)(A), however, requires that an item be reasonable and necessary to diagnose or treat illness or injury—not to conduct a clinical trial (which is likely why CMS does not reference the provision in the proposed NCD with CED).

The statutory authority that CMS does reference, section 1862(a)(1)(E), also does not authorize a CED trial. That provision only addresses research by the HHS Agency for Healthcare Research and Quality (“AHRQ”): “in the case of research conducted pursuant to section 1320b–12 of this title.”<sup>108</sup> The proposed NCD, however, does not explain how the proposed clinical trials could ever qualify as “research conducted pursuant to section 1320b-12.” While CMS cites AHRQ’s “support” of the proposed CED, Robert Charrow, then-HHS General Counsel, previously issued an HHS Office of General Counsel Advisory Opinion explaining that CMS’ interpretation of its statutory authority to use CED as the basis for coverage of items and services is “*unlawful* under Section 1862 [of the Social Security Act]” because CMS’ “broad reading of the term [support] is fundamentally inconsistent with the regulatory definition of ‘support’ at 42 C.F.R. § 93.221.”<sup>109</sup> While this advisory opinion has since been rescinded, the legal interpretation remains valid. No statute allows CMS to utilize CED, and its 2014 Guidance document seeking to justify its actions on novel interpretations of section 1862 and AHRQ “support” falls flat. The proposed CED is thus an illegal and *ultra vires* action.

CMS also has violated the law in using inappropriate and discriminatory evaluations of mABs to shift the balance in favor of risks over benefits. More specifically, CMS appears to have violated the Patient Protection and Affordable Care Act (“ACA”) to the extent that it has relied on an analysis by ICER, an organization that issues clinical data reviews on Quality-Adjusted Life Year (“QALY”). The ACA disallows the HHS Secretary to use QALY as “a threshold to determine coverage, [or] reimbursement” (*i.e.*, CMS cannot use a cost-effectiveness assessment in its coverage decision-making for patients with AD).<sup>110</sup> Despite this clear parameter, CMS concedes that it reviewed ICER’s May 5, 2021 report in its evidence consideration.<sup>111</sup> CMS’ claim that it has not considered cost in developing the proposed CED is belied by its improper reference to the ICER report, which itself has tainted the entire CED development process.

## **XI. Alzheimer’s Disease is Being Exploited to Influence the Political Debate Over Drug Pricing**

The draft NCD with CED cannot be viewed outside the context of the fierce political debate over drug pricing reform, and the continued reference to aducanumab’s initial June 2021 list price and the subsequent price reduction in December 2021. Fueling the debate before the Congress, in October 2021, CMS previously announced the standard monthly premium for Medicare Part B enrollees would increase to \$170.10 for 2022, an increase of \$21.60 from \$148.50 in 2021, and

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<sup>108</sup> Robert Charrow, *Advisory Opinion 21-03 on Medicare Coverage with Evidence Development*, U.S. DEP’T OF HEALTH & HUMAN SERVS. at 2 (Jan. 14, 2021) (rescinded).

<sup>109</sup> *Id.* (emphasis added).

<sup>110</sup> 42 U.S.C. § 1320e-1(e).

<sup>111</sup> Proposed NCD Memo, *supra* note 7, at Sec. VII.B.3; see Inst. for Clinical & Econ. Review, ADUCANUMAB FOR ALZHEIMER’S DISEASE: EFFECTIVENESS AND VALUE 27–32 (Aug. 5, 2021), available at [https://icer.org/wp-content/uploads/2020/10/ICER\\_ALZ\\_Final\\_Report\\_080521.pdf](https://icer.org/wp-content/uploads/2020/10/ICER_ALZ_Final_Report_080521.pdf).

cited the new Alzheimer’s drug as the reason behind half the increase.<sup>112</sup> The Task Force supports HHS Secretary Becerra’s announcement ordering Medicare to reconsider its 2022 Part B premium increase after Biogen reduced the list price by 50% for aducanumab.<sup>113</sup>

Unfortunately, CMS was not transparent about how it calculated the large Part B premium increase attributed to the new Alzheimer’s therapy. Additionally, we have found no record of CMS previously calling out the cost of care for a specific disease or chronic condition as the rationale for raising premiums. This was an unprecedented move for the Agency, and highly inappropriate. While we have heard CMS state that aducanumab’s price did not impact the draft CED, the June pricing announcement, CMS’ July initiation of the NCD process, the December announcement of the pricing change, and the January release of the proposed CED were not coincidental, and each event has influenced the others. We urge CMS not to let the pricing debate influence its decision to restrict beneficiary access to treatment—Congress is taking action to address pricing concerns. The Agency, guided by the Secretary, should not use coverage as a blunt price control tool to ration access to treatments. Nor can it: Courts have made clear cost is not a valid consideration in evaluating coverage,<sup>114</sup> and CMS itself has acknowledged this fact.<sup>115</sup> We urge CMS to honor its word and leave the pricing debate to others. What is at stake is beneficiary access—and that should be granted in full.

## **XII. Conclusion**

*Personal Patient Story: At 57 years old, I was married with 3 children and 4 grandkids. I was having an amazing life with my family and career. I had 25+ years in local government with the last 6 years as the Assistant City Manager in Fayetteville. I noticed something was wrong when I started struggling in meetings/recall/having to defer to other staff. I contacted a friend at Duke, who was a neurologist. Over the next 12 months, I received Neuro-psychologicals, MRI and cognitive testing until my wife and I received the diagnosis that no one wants to hear -- Early stage Alzheimer’s disease. I needed to retire early, get a will in place and jump through the hoops for Social Security disability. Right now, Aduhelm is the only option I have available, and I would like to try to see if it works for me. To those opposed to the treatment—give me an alternative—but do so quickly, I can’t wait. I have spent the last several months planning and preparing to start treatment by participating in the LEADS Study and now I am being forced to jump*

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<sup>112</sup> Dorothy Mills-Gregg, CMS: Aduhelm Coverage Determination Doesn’t Take Into Account Cost, INSIDE HEALTH POLICY (Jan. 11, 2022), <https://insidehealthpolicy.com/daily-news/cms-aduhelm-coverage-determination-doesn%E2%80%99t-take-account-cost>; Zachary Brennan, Just the Idea of Aduhelm’s Long-term Financial Risks has CMS Jacking up Premiums, Deductibles for 2022, ENDPOINTS NEWS (Nov. 15, 2021), <https://endpts.com/just-the-idea-of-aduhelms-long-term-financial-risks-has-cms-jacking-up-premiums-deductibles-for-2022/>.

<sup>113</sup> U.S. Dep’t of Health & Human Servs., Press Release, *HHS Secretary Xavier Becerra Instructs CMS to Reassess Recommendation for 2022 Medicare Part B Premium* (Jan. 10, 2022), <https://www.hhs.gov/about/news/2022/01/10/hhs-secretary-xavier-becerra-instructs-cms-reassess-recommendation-2022-medicare-part-b-premium.html>; Biogen Inc., Press Release, *Biogen Announced Reduced Price for ADUHELM to Improve Access for Patients with Early Alzheimer’s Disease* (Dec. 20, 2021), [https://insidehealthpolicy.com/sites/insidehealthpolicy.com/files/documents/2021/dec/he2021\\_3485.pdf](https://insidehealthpolicy.com/sites/insidehealthpolicy.com/files/documents/2021/dec/he2021_3485.pdf).

<sup>114</sup> See *Hays v. Sebelius*, 589 F.3d 1279, 1281–83 (D.C. Cir. 2009).

<sup>115</sup> Ctrs. for Medicare & Medicaid Servs., *Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease Tracking Sheet* (accessed Feb. 6, 2022), <https://www.cms.gov/medicare-coverage-database/view/ncacal-tracking-sheet.aspx?NCAId=305>.

*through additional hoops receiving PET Amyloid and TAU scans in an effort to receive Aduhelm. I ask you to try walking a day or week in my shoes. We are desperate for a treatment, and we deserve an opportunity to receive this treatment. I am a vibrant person who wants to keep living my life and enjoying my family. People living with Alzheimer's disease deserve the same access to therapies given to those living with other conditions like cancer, heart disease and HIV/AIDS. Treating people living with Alzheimer's disease differently than those with other diseases is simply unacceptable. I have contributed to Medicare for the past 45 years. The money I have contributed has helped others get healthcare and treatment when they needed it. Now I need it. If CED is sustained, I will definitely attempt to enroll in a CMS approved clinical trial. Even if I do enroll in a clinical trial—and that could take months—there is no guarantee I would receive treatment—I could get the placebo. Requiring people with early Alzheimer's to locate, enroll and participate in a clinical trial can be a time-consuming process—that will delay access and coverage to treatment in a timely fashion. Clinical trial sites may not be easily accessible to all who seek treatment. CMS has taken an unprecedented step to require an additional clinical trial for a treatment already approved by the FDA. It's time people living with a progressive disease simply do not have. – (patient story, Jan. 2022).*

**Based upon the personal patient stories reflecting the overwhelming needs created by this fatal disease, and the reasons stated in the above comments, CMS should modify the proposed NCD with CED. CMS should cover all FDA-approved mAB therapies directed against amyloid for the treatment of AD and allow patients and their physicians the ability to make appropriate medical decisions in the best interests of those suffering from Alzheimer's.**

Listening to, and having deep compassion for, Medicare beneficiaries with Alzheimer's disease is critical to your assessment of what is "reasonable and necessary." Thank you for the work you do to improve the health and well-being of our nation's older adults and people with disabilities, and for considering our views.

Please contact Susan Peschin, President and CEO of Alliance for Aging Research, at [speschin@agingresearch.org](mailto:speschin@agingresearch.org) for additional information.

Sincerely,

AfricanAmericansAgainstAlzheimer's  
Alliance for Aging Research  
American Society for Consultant Pharmacists  
BrightFocus Foundation  
Black Women's Health Imperative  
Caregiver Action Network  
Global Alzheimer's Platform Foundation  
HealthyWomen  
Infusion Providers Alliance  
LatinosAgainstAlzheimer's  
Men's Health Network

National Minority Quality Forum  
Partnership to Fight Chronic Disease  
ResearchersAgainstAlzheimer's  
The Balm In Gilead, Inc.  
The Global CEO Initiative on Alzheimer's Disease  
UsAgainstAlzheimer's  
Voices Against Alzheimer's