UsAgainstAlzheimer's
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Comment on

CMS Draft National Coverage Determination
Monoclonal Antibodies Directed Against Amyloid for the
Treatment of Alzheimer's Disease

February 10, 2022

Mr. Secretary and Madame Administrator:

Thank you for the opportunity to comment on the Centers for Medicare and Medicaid Services' (CMS's) proposed National Coverage Determination (NCD). UsAgainstAlzheimer's (UsA2) is an organization founded by people whose families have been savaged by Alzheimer's disease (AD) and who have created a national movement to end this disease. We speak to you with the voice of the millions of AD patients and caregivers around the country and are deeply concerned about the devastating effects the proposed NCD will have on them.

The proposed NCD is anti-patient, anti-science, and anti-Food and Drug Administration (FDA). The proposed decision would effectively deny access for millions of Americans to the entire class of the first-ever disease-modifying therapies for AD. Every day, 1,000 Americans move from a diagnosis of mild AD to moderate AD,[1] a stage when no new therapies can stop progression to the horrific end-stage of this deadly disease. The math is simple, and the result is irrefutable. By the decision, the government would be consigning millions of Americans to inevitable decline and death, with no possibility of appeal. As one AD patient said in response to a recent survey of over 700 A-LIST® participants,[2] "Without a cure or a way to stop progression, we will die! Plain and simple!"

We are at a key inflection point in the fight against AD. For the first time in 20 years, a new drug has been approved and several more are in late-stage development. We recognize the value of post-approval evidence development to understand what works, for whom, and how. This shared goal is not going to be accomplished by the proposed NCD. People with AD cannot afford to wait while CMS effectively reverses FDA's approval of one drug and pre-judges the results of other FDA-required trials that have yet to be completed.

We urge CMS in the strongest of terms to revise this draft determination to provide coverage to label for FDA-approved monoclonal antibodies (mAbs) in this class. CMS must weigh the benefits of new drugs against AD's inexorable progression toward a loss of a sense of self, of ability to function, and, ultimately, life. It is inhumane to deny patients who meet the label criteria the choice of whether to use this or other future, FDA-approved drugs in the class. The proposed NCD leaves such access only to those privileged few who might be able to pay for the drug out-of-pocket. We should call this decision what it is: it is a "non-coverage" decision with the requirement for unneeded, duplicative, limited evidence development.

Our concerns about the proposed NCD and our recommendations are detailed below.

The proposed NCD will delay access to much-needed treatments for people with Alzheimer's, resulting in millions of them progressing beyond the reach of these drugs

The requirements of the proposed CED will prevent nearly every American who might benefit from a mAb from accessing one of these treatments for a decade or more. The projected timeline developed by the Global Alzheimer's Platform Foundation charts a course of more than ten years from start-up to read-out and review by CMS for each of the randomized controlled trials (RCT) proposed under its CED strategy.[3]

By making RCTs the only way that Medicare beneficiaries can access these treatments, CMS elects to cover a few thousand while leaving nearly two million Americans without access. We estimate that only about 50 hospital locations in the entire country are capable of running the types of trials CMS proposed,[4] so only people fortunate enough to live near one of those sites could feasibly secure one of the estimated 1,500 slots available in those trials.[5] Of that small number, half would be on a placebo and not on a drug. This structure could be fairly characterized as a sophisticated mechanism for rationing care.

For those unable to participate in a trial, they will have to wait as long as a decade for the completion of the trials and the possible removal of the CED restrictions.[6] During this time, as discussed above, an estimated 1,000 people per day will progress from mild to moderate AD,[7] meaning over 3.6 million people will move beyond the reaches of these treatments while we wait for the system proposed by CMS to play out. In a field where a new treatment has not been approved for nearly two decades, where there has never been a disease-modifying treatment, and where the number of people with the disease is projected to triple in the next four decades,[8] another decade is unconscionable. As one A-LIST® survey respondent put it, "the decision is shortsighted and hurts families like mine who are in a race against time to control this disease."

CMS has said that it might reconsider this NCD at some point in the future, after new mAbs report data from their pivotal trials. The draft NCD offers no assurances, however, as to the timeline that CMS may require for such reconsiderations, either of a mAb that receives accelerated approval or one that is given traditional FDA approval. The CMS-reported two-year average timeline to implement past reconsiderations[9] is concerningly slow, and given CMS's lack of AD experience, unquestionably optimistic (and unenforceable). Again, for every day CMS takes to unwind a mistake it made in pre-judging science, 1,000 patients will lose their shot at hope and will progress inexorably toward cognitive and functional decline and death.

The proposed NCD pre-judges an entire class of drugs, rather than recognizing the scientific distinctions among each drug in this class of mAb therapies

At present, there is only one mAb, Aduhelm, approved by the FDA for the treatment of AD. As CMS notes in the draft decision memo, there are multiple other mAbs currently in late-stage trials.[10] These therapies vary in specific mechanism of action, targets, safety profile, and method of administration.[11] The evidence underlying their approval will be unique to each drug, complex, and worthy of unprejudiced, individualized, and timely evaluation.

The class of mAb therapies hold the promise that people with AD may soon have multiple FDA-approved disease-modifying therapies from which to choose. The proposed CED, however, applies a one-size-fits all approach to these treatments. It requires that each and every mAb become subjected to yet another round of CMS-directed clinical trials designed to demonstrate clinical benefit. Per the proposed NDC, these trials would be required even for those drugs that demonstrate clinical benefit in an FDA-approved pivotal trial – a situation that should mean CED would not be needed for that particular therapy at all.

The proposed NCD also shows a callous disregard for the contributions of time, energy, data, and personal risk made by thousands of AD patients in current and past FDA-required trials for any one of the mAbs in the pipeline. CMS owes it to these patients not to discount *a priori* their contribution to science, and yet this is the effect of the duplicative and ethically questionable CED requirement.

The proposed NCD ignores FDA's expert review and presentation of the latest science around the amyloid cascade

For years, the AD research and treatment field has acknowledged the connection between the buildup of beta amyloid plaques in the brain and a decline in cognition. This is evidenced by the considerable investment in private-sector drug development targeting beta amyloid plaques as well as the many hundreds of millions of dollars in National Institutes of Health- (NIH) funded research related to this topic over the past decade.[12]

Early mAb trials did not prove effective due to limitations such as inadequate dosing and a lack of confirmation of beta amyloid plaques in the brain. For example, many participants in a trial of bapineuzemab were not good candidates for the therapy because position emission tomography (PET) scans were not used to confirm the presence of beta amyloid.[13] Fortunately, this area of research has made great strides in recent years. The latest generation of mAbs that would fall under the NCD have different mechanisms of action and targets, use PET scans to confirm amyloid, and have improved dosing protocols. Ongoing trials show that these therapies can markedly reduce the level of beta amyloid in the brain and show evidence of predictable clinical benefit.

Although beta amyloid is not the only factor in AD, it is widely recognized as a key piece in the causal chain. Furthermore, recent data on the newest mAbs from trial results reported since Aduhelm approval demonstrate that these therapies lower certain species of phosphorylated tau, the protein that causes the "tangles" that develop in the brains of people with symptomatic Alzheimer's after beta amyloid plaques appear.[14] This early evidence showing the lowering of not only beta amyloid but also tau presents further support for the probable clinical value of these new agents.

Over half of trials cited in the proposed NCD were completed five or more years ago. These trials studied therapies with notably different targets and/or dosages and some were later determined to include a significant percentage of trial participants without amyloid. CMS, which has little or no scientific expertise regarding AD, is suggesting it should make this decision using a relatively narrow and obsolete slice of the body of research on these therapies, ignoring the

latest evidence, and pre-judging evidence that is yet to come. This manifest disregard for science will result in millions of people being summarily denied access to these innovative therapies, rather than being able to consider with their physician whether a new mAb therapy is right for them.

The proposed NCD will limit treatment access for people of color, perpetuate the lack of inclusion that CMS seeks to address, and fail to generate the level of evidence needed to understand drug effect and safely across diverse and under-represented populations.

UsA2 has worked for many years to reduce the disparate impacts of AD on Blacks, Latinos, and women, and we agree that we need adequate representation of diverse populations, achieving representativeness in Alzheimer's clinical trials. As CMS recognizes in the proposed decision memo, African Americans and Latinos are disproportionately affected by AD: they are more likely than Whites to have AD and make up a miniscule percentage of participants in clinical trials, including those funded by the NIH.[15,16] And yet, despite CMS's stated commitment to representativeness, the proposed CED is likely to continue to cement these disparities into the CMS-directed trial design.

First, the proposal to exclude people with "medical conditions, other than AD, likely to increase significant adverse events" from the CMS-proposed trials will disproportionately restrict minority participation in the trials. African Americans and Latinos are more likely to have comorbidities such as heart disease, hypertension, and diabetes, conditions that are likely to be disqualifying factors for the CMS-directed RCTs.[17] Likewise, individuals with Down syndrome would be excluded. As discussed below, a real-world evidence registry and study would allow people with comorbidities and intellectual disabilities to access mAbs while we gain more clinical evidence and experience about the use of these new therapies in these and other subpopulations.

Second, minorities are less likely to be served by the hospital outpatient sites to which these trials will be limited. African Americans and Latinos typically have lesser access to hospitals than their White counterparts, and, even if they theoretically have access based on proximity, they are less likely to receive care at these locations. A recent study of more than 1,400 hospitals found that "only 29%... treated a proportion of Black patients that was comparable to or higher than the proportion of Black residents in the community. And only 18% and 5% of hospitals met that bar for Hispanic and Asian/Pacific Islander patients, respectively."[18] CMS will be hard-pressed to achieve diversity if such hospitals are the only locations where Medicare beneficiaries are able to access mAbs.

The proposed NCD is a significant overreach of CMS's statutory authorities and usurps the authority of the FDA, the only agency with the congressionally-mandated authority and scientific expertise to review and approve drugs

FDA approval of a drug means that the agency has determined, based on substantial evidence, that the drug is effective for its intended use and that the benefits of the drug outweigh its risks when used according to the product's approved labeling. For CMS's part, the agency's current guidance for the use of CEDs provides: "CED will not duplicate or replace the FDA's authority

in assuring the safety, efficacy, and security of drugs, biological products, and devices."[19] This proposed NCD is in direct conflict with the clear intent and language of this guidance and with the authority Congress vested in the FDA when it established the accelerated approval pathway.

FDA has statutory authority to use accelerated approval to approve drugs that treat "serious or life-threatening disease[s] or condition[s]" based on the drugs' demonstrated "effect on a surrogate endpoint that is reasonably likely to predict clinical benefit".[20] The program began in 1992,[21] a time when HIV/AIDS was destroying lives and communities. In seeking to curb the epidemic, the FDA recognized that basing its reviews solely on whether medicines prevented death could take years during which many more people would die. Instead, the FDA looked to surrogate endpoints and evaluated potential treatments on their ability to reduce viral load. The concept worked. Treatments for HIV/AIDS were approved faster, deaths plummeted, and HIV/AIDS became a manageable illness. Similar examples followed as this mechanism was used in oncology to accelerate the approval of new therapies, saving an estimated 3.5 years on average in moving new cancer therapies into the clinic. In 2012, Congress authorized expanded use of accelerated approval for rare or life-threatening diseases or conditions.

When using accelerated approval, the FDA applies the same statutory standards of safety and efficacy as in traditional approvals.[22] Therapy development using biomarkers is not a compromise; a surrogate endpoint such as the reduction of beta amyloid is a measure of clinical effect that is backed by substantial evidence. Biomarkers are tools to detect the presence of disease pathology or genetic abnormality, to predict outcomes before they occur, and to measure progression. The use of a biomarker allows for faster diagnosis and earlier intervention at a time when prevention, slowing of cognitive decline, or preservation of function may be possible.

The use of biomarker data in AD as a predictor of clinical benefit is key to the future of drug development in this field – just as it has been in cancer and HIV-AIDS. Existing AD scales, developed for use in later phases of disease progression, are often not sufficiently sensitive to capture changes that occur in early disease stages when mAb therapies hold their greatest promise. Seeing changes in biomarkers, however, provides the opportunity for intervention before progression of disease makes it too late to maintain the patient at the earlier, more functional stage of the disease. The FDA understands the science supporting this advancement in AD drug development. CMS's questioning of these findings is naïve, harmful to patients, and a setback to the future of drug development in AD.

CMS is proposing an unduly restrictive CED to collect data showing "clinically meaningful benefit" and yet that type of data is explicitly not required for accelerated approval by the FDA, although it is required in post-approval, confirmatory trials. Further, the two agencies differ in their definition of what constitutes clinical benefit: CMS proposes to require evidence of a change in cognition *and* function, whereas FDA guidance requires change in cognition *or* function.[23] CMS is undercutting FDA's statutory authority to use accelerated approval and confusing evidentiary standards and shifting regulatory expectations for drug developers who must comply with the more restrictive standard.

Finally, the FDA is directed by statute to require confirmatory trials to demonstrate the association between the surrogate biomarker and the predicted clinical benefit in products receiving accelerated approval. The CMS-proposed trials would duplicate this requirement and

waste precious resources and time for patients experiencing this deadly progressive disease. This is all being done because CMS—breaking with any past precedent—has elected to find that an FDA-approved therapy, here Aduhelm, is not "reasonable and necessary," a standard which is not defined in statute, regulations, guidances, or manuals.

This approach usurps the authority of the FDA, confuses evidentiary standards, sets an unsupportable precedent in determining what is reasonable and necessary for a Medicare beneficiary, and puts patients awaiting access to Aduhelm or other promising mAbs on notice that, for them, the door is shut.

We strongly urge CMS to provide coverage to label for this class of therapies while supporting and monitoring the development of additional evidence through mechanisms being developed by the field.

We urge CMS in no uncertain terms to provide coverage to the label for any FDA-approved anti-amyloid mAbs. As stated by a respondent to the A-LIST® survey, treatment decisions "should be [patients'] personal choice and a decision that is made between doctor and patient not dictated by an insurance company."

In parallel, we urge CMS to support and monitor the collection of additional data on mAbs to learn more about these treatments. Those alternative evidence development mechanisms are already being developed by sponsors and patient advocacy organizations anticipating the real-world populations which will emerge in a coverage to label environment. By supporting those mechanisms outside a CED, CMS will be able to monitor the generation of evidence developed in traditional clinical settings and gain a thorough understanding of clinical benefits and safety issues. This approach would align with CMS's mission to provide better healthcare and access and generate rich, diverse data and clinical evidence to advance the care of Medicare beneficiaries stricken with AD.

As we have described, the stringent requirements of the CED approach, as proposed, would effectively deny meaningful access for ten years to any drugs in a class of mAb therapies as these become approved by the FDA. It will make it very difficult to rapidly collect valuable information on the use of these therapies in a large and diverse real-world population.

As an alternative, we recommend an approach that allows for broad access to mAbs—without a CED—in conjunction with a carefully designed system of evidence development, collection, and analysis from a patient registry coupled with an optional longitudinal study or set of studies. This will generate data from hundreds of thousands of patients across the country who will have access to these drugs —not just the approximately 1,500 that might enroll in a CMS-proposed RCT, many of whom would be on placebo. Such an approach will yield greater participation by underrepresented communities than CMS's current requirement for RCTs with the true prospect for a cohort that is representative of the population with AD.

Many efforts to create registries of varying natures are emerging in the Alzheimer's community. With each accelerated approval of a new mAb, the FDA will require a Phase 4 trial. Sponsors of mAbs that receive traditional approval to market will have compelling interests to understand the

performance of their drugs in real world populations, over time, and in comparison, to other drugs in class. Ideally, these efforts would not continue to evolve in their various silos. UsA2 is ready to work across the public and private sectors, in collaboration with CMS, to unite these efforts, respecting their autonomy and distinct purposes, while assuring a networked architecture that facilitates data sharing, data standardization, and accelerated leveraged results to inform CMS and the rest of the field on what is working, for whom, and in real time.

To accomplish this, UsA2 is in the early stages of developing the Alzheimer's Disease Evidence Accelerator (ADEA). The ADEA will be modeled on a similar COVID-19 Evidence Accelerator, an FDA public-private partnership convened and managed by the Reagan-Udall Foundation and designed to forge collaboration and data sharing around the development of vaccines, diagnostics, and treatments for COVID-19.[24] The ADEA will focus, initially, on evidence related to new AD therapies, specifically anti-amyloid mAbs. The ultimate goal of the ADEA would be to facilitate rapid learning to support decision making on all aspects of the diagnosis and care of patients with suspected or confirmed AD.

The ADEA would design, build, and launch a patient-centered, centralized real-world data resource: the AD Real-World Evidence Learning System (ADRLS). We envision the ADRLS as a resource for the evaluation of real-world impacts of new therapies across a wide array of patient populations. This system would be able to compare and analyze data from existing sources of RWD such as EHRs, insurance claims, Phase IV trials, and registries. In addition, it would support collection of data provided by and with the consent of individual AD patients, regardless of whether they are on a mAb therapy or otherwise enrolled in a post-market study or registry. We envision the ADRLS supporting data analytics delivering an improved understanding of the clinically-meaningful benefit and comparative impact of mAbs and other therapies on a broad range of populations in a way that the narrow, CMS-proposed trials cannot.

This is the future: one where patients have broad access to novel therapies and can serve as partners in collecting more information on these therapies. This system would work only in an environment where large numbers of patients with widely varying characteristics can access AD therapies in a range of clinical settings. The future state is a health learning system, supported by the patient, providers, payers, sponsors, government, and scientific communities. We are ready and eager to help you chart this course and achieve these aims in the context of a coverage-to-label environment where large numbers of patients, in collaboration with their clinicians, contribute towards a cure of this devastating disease.

Conclusion

For all of the reasons enumerated above, we urge CMS in the strongest of terms to revise the proposed approach to remove the CED and provide coverage to label while supporting community-led, field-wide efforts to develop additional evidence regarding the safety and efficacy of these promising new therapies. We believe this will allow for more rapid collection of evidence that will be of value to CMS, AD therapy developers, and AD patients and caregivers. If CMS finalizes the NCD as proposed, millions of Medicare beneficiaries will be unable to access any treatments appropriate for them and evidence development efforts will be stunted, including only small, narrow, and discriminatory segments of the population.

On behalf of these AD patients, we ask CMS to revise this decision and take part in a new era of AD therapeutic care where innovative treatments offer real hope in the fight against this insidious disease. Thank you for considering our comments.

About UsAgainstAlzheimer's[25]

UsAgainstAlzheimer's was founded in 2010 to disrupt and diversify the movement to cure Alzheimer's. Through urgent and inclusive mobilization, UsAgainstAlzheimer's has worked to dramatically increase funding for Alzheimer's and dementia research. Our advocacy focuses on a wide array of issues including prevention, treatment, research, access to care, and equity and inclusion. Everything we do is grounded in the needs of Alzheimer's patients and caregivers around the country. Our goal is to ensure that brain-span equals lifespan – for everyone.

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[2] Survey conducted by UsAgainstAlzheimer's of the A-LIST® from January 27-February 2, 2022.

[3] Global Alzheimer's Platform Foundation. Projected Timeline NCD/CED. February 2022.

[4] Based on the number of sites in national networks for clinical trials, including the National Institute on Aging-supported Alzheimer's Clinical Trials Consortium.

[5] Based on an enrollment of approximately 1,500 in most therapeutic and NIH-sponsored trials for AD and assuming some trial enrollees are on a placebo or in another non-mAb control arm.

[6] Global Alzheimer's Platform Foundation. Projected Timeline NCD/CED. February 2022.

[7] Davis M, et al doi: 10.2174/1567205015666180119092427. PMID: 29357799; PMCID: PMC6156780.

[8] Centers for Disease Control and Prevention. Alzheimer's Disease and Related Dementias.

[9] Centers for Medicare and Medicaid Services. Report to Congress: Medicare National Coverage Determinations for Fiscal Year 2020.

[10] Eisai: lecanemab (Phase III trial readout estimated Q3 2022), Eli Lilly & Co.: donanemab (Phase III trial readout estimated late 2022); Roche/Genentech: gantenerumab (Phase III trial readout estimated late 2022/early 2023).

[11] https://link.springer.com/article/10.14283/jpad.2022.25

[12] NIH Project Reporter. February 2022.

[13] Clinicaltrials.gov. Bapineuzumab in Patients With Mild to Moderate Alzheimer's Disease (ApoE4 Non-Carrier).

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[15] UsAgainstAlzheimer's. Key Findings and Policy Recommendations: The Costs of Alzheimer's and Other Dementia for African Americans. 2018.

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[17] Centers for Disease Control and Prevention. Minorities and Women Are at Greater Risk for Alzheimer's Disease.

[18] U.S. News and World Reports. Analysis of Racial Gaps in Hospital Care. July 27, 2021.

[19] Centers for Medicare and Medicaid Services. Guidance for the Public, Industry, and CMS Staff: Coverage with Evidence Development. 2014.

[20] Food, Drug, & Cosmetic Act. U.S. Code Sec. 356.

[21] U.S. Food and Drug Administration. Accelerated Approval.

[22] U.S. Food and Drug Administration. Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics. May 2014.

[23] "This historical dichotomy of functional and cognitive assessments has led to common use of the terms cognition and function with respect to outcome assessment in AD clinical trials, with the implication that an effect on

cognition is non-meaningful unless accompanied by a benefit on an independent endpoint assessing function in a meaningful manner. FDA rejects this dichotomy and finds such usage inappropriate, because it implies that an effect on cognition itself, regardless of the nature of the observed effect and the manner in which it is assessed, cannot be clinically meaningful. This is certainly not the case." U.S. Food and Drug Administration. Early Alzheimer's Disease: Developing Drugs for Treatment - Draft Guidance for Industry. February 2018.

[24] COVID-19 Evidence Accelerator.

[25] Disclosure: UsAgainstAlzheimer's is governed by a Board of Directors with no representation from pharmaceutical companies. UsA2 is supported by thousands of individuals, companies, and foundations, including pharmaceutical companies developing mAbs.