February 10, 2022

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Center for Clinical Standards and Quality
Centers for Medicare & Medicaid Services

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

Dear Ms. Syrek Jensen:

Thank you for the opportunity to offer public comment on this issue of existential importance to millions of Americans currently living with Alzheimer's disease and millions more facing its prospect in years to come. Thank you also for the ongoing open and vigorous dialogue with the stakeholder community in which you and your colleagues have participated throughout this process.

Of the 21 National Coverage Determinations (NCDs) requiring Coverage with Evidence Development (CED) ever issued by CMS, a grand total of zero have been issued for on-label use of an FDA-approved medication. Only one CED has been applied to a medication, but – importantly – that was for off-label use.[i] More revealing still, among the more than 275 medications receiving FDA Accelerated Approval, the sole medication to be subjected to the inherently duplicative CED requirement is the first-ever disease modifying therapy to treat Alzheimer's disease. In its January 11 draft NCD,[ii] CMS proposed to break with the entire history of its CED process and neither acknowledged this shocking deviation nor attempted to explain its abrogation of precedent. When this sort of radically dissimilar treatment occurs in the absence of a reasonable explanation (see public comment from the Alzheimer's Association), and negatively affects an often marginalized population, it raises the possibility of discrimination. Any such discrimination, regardless of intent, must not stand. Additionally, the proposed NCD would undermine the Food and Drug Administration's (FDA's) statutory authority while failing to meet the draft NCD's own stated goals. **In its final decision, due by April 11, CMS should follow its own precedent and the plain meaning of the law by removing CED requirements of the NCD and allowing coverage for FDA-approved uses[iii] of these Alzheimer's disease medications for Medicare beneficiaries nationwide. The magnitude of unmet need is enormous, there are no FDA-approved alternatives to this class of therapies, and coverage to label is reasonable and necessary.**

In lieu of repeating evidence and explanations provided by other stakeholders, I humbly associate myself (but take no credit for their independent work) with public comments submitted by individuals and organizations I hold in the highest esteem including the National Minority Quality Forum, Voices of Alzheimer's, Dr. Jeffrey Cummings, Dr. Dennis Selkoe, Dr. Marwan Sabbagh, the Global CEO Initiative on Alzheimer's Disease, the Alzheimer's Association and the Early Stage Advisory Group of the Alzheimer's Association, the LuMind IDSC Foundation, the Alzheimer's Disease Policy Task Force, UsAgainstAlzheimer's, BrightFocus Foundation, and others who believe the draft NCD is entirely unacceptable and inherently antithetical to the very principles stated by CMS as guiding its draft decision. Their public comments powerfully

and persuasively address issues such as fundamental misunderstanding reflected in the draft NCD about the science at hand and the broader scientific process (see public comments from Dr. Cummings and Dr. Selkoe), the arbitrary and capricious nature of the draft NCD, the lack of legal authority for the CED mechanism, the destructive over-reach of the proposed CED requirements, the counter-productive implications of the CED on our shared commitment to genuine health equity and the development of real world evidence, the dangerous weaponization of the coverage determination process as a cudgel in political battles over health system costs, and the staggering number of people with early stage Alzheimer's disease who would be condemned to an inexorable descent into dementia by the proposed CED.

More important, I stand with the courageous women and men living with Alzheimer's disease who are calling upon CMS to reverse course and allow them their only present or near future opportunity to slow progression of their fatal disease. FDA, rightly, has placed the decision about utilizing a promising medication into the hands of individuals living with Alzheimer's disease and their treating physicians. CMS should not, must not, rob Medicare beneficiaries of this meaningful and deeply personal choice.

No human being should be defined by, or marginalized because of, their health condition

People living with Alzheimer's disease should not be defined by their health condition. They are not "Alzheimer's patients," "Alzheimer's victims," or "Alzheimer's" anything else. They are – unconditionally and uncompromisingly – full human beings entitled to equal treatment under the law and by both private and public insurers. Good intentions cannot and will not excuse any marginalization, whether in the form of paternalism toward or discrimination against people living with Alzheimer's disease.

Not "normal" and not just memory loss

While Alzheimer's disease is common, it is neither a normal part of aging nor just *"a little memory loss."* For many people, Alzheimer's disease becomes a form of torture. Alzheimer's disease causes aphasia leaving people unable to communicate their wants, needs, fears, and pain. Alzheimer's disease causes agnosia, leaving people unable to recognize basic dangers in and beyond their homes (such as wandering with the risk of serious injury or succumbing to the elements). Alzheimer's disease causes apraxia and can result in choking, weight loss, deconditioning, falls, and pressure sores. Alzheimer's disease causes disorientation of day and night. Alzheimer's disease causes hallucinations, delusions, and paranoia that can result in self-harm and violence against loved ones. Alzheimer's disease causes not just loss of bladder and bowel control that can be contained to an incontinence brief, but also loss of impulse control to the point where many families report their loved ones frequently urinating and smearing feces on the walls. Alzheimer's disease is fatal, always fatal. But it is not a peaceful or gentle death. An Alzheimer's disease death is as brutal as it is certain. In the last years of Alzheimer's disease, people waste away physically, emotionally, and intellectually. I have witnessed it with numerous family and friends. It is as searing as AIDS, cancer, or any other disease. For all but a lucky few whose symptoms are abnormally mild compared to what the vast majority experience,

Alzheimer's disease is torture. Those who trivialize it either haven't seen it up close, have lost touch with their humanity, or are engaging in discriminatory disease-ism (see public comment from Dr. Marwan Sabbagh).

That many people living with Alzheimer's disease seek to and, in fact, do live well with their disease does not mean they are in denial about what all-too-typically accompanies disease progression. Perhaps their determination to live well and to have others recognize their ability to live well for as long as possible is testament to their full humanity. They are not giving up on themselves and they rightly demand that no one else give up on them either.

Alzheimer's disease is not immutable

It does not have to be this way. Alzheimer's is not an immutable disease. Science can and will defeat Alzheimer's disease, not all at once with a first medication, but through progress that will be catalyzed by a first step (see public comment from Dr. Marwan Sabbagh). NIH knows this. FDA knows this. President Biden, Secretary Becerra and all their predecessors over the past forty years have known this. On a completely bipartisan (non-partisan) basis, Congress knows this. Thousands of brilliant scientists and generations of courageous women and men who have volunteered for clinical research know this. Sadly, shockingly, the draft NCD calls into serious question whether CMS knows this.

People living with Alzheimer's disease deserve to make their own decisions

For 25 years, people living with Alzheimer's disease have told me with absolutely consistency and unanimity what they want, even as they rightly apply individually what these things look like in their unique lived experiences. They say they want a timely, accurate, compassionate, and actionable diagnosis. They say they want to have the highest quality of life possible. They say they want to be treated with dignity, respect, and fairness. They say that when – not "if" – there are medications that can change the trajectory of their disease, they want to reach their own decisions in consultation with their loved ones and their doctors and without the interference of insurers. Some individuals will choose not to utilize an available medication, and, for them, that will be the right decision. But others will weigh their own circumstances, their own level of confidence, their own preferences, the counsel of their own loved ones and doctors, and decide they do choose to utilize an available medication. For them, that will be the right decision. It is unconscionable that CMS would consider denying people living with Alzheimer's disease the ability to make the right choice for themselves.

People living with other serious and life-threatening conditions make these decisions, these choices, every day. CMS does not stand in their way. In fact, CMS does not stand in their way when the risk of side effects is greater (i.e. medications carrying a so-called black-box warning) or when the proposed use of off-label. We are left to wonder why CMS appears to be singling out and subjecting people with Alzheimer's disease for such interference. People living with Alzheimer's disease reasonably fear that CMS – however unintentionally – is acting paternalistically. People living with Alzheimer's disease recognize that the draft NCD only

deepens the prejudice that even in the earliest stages of disease they are not competent to make their own decisions with the support of their loved ones and doctors about appropriate treatment options.

It is precisely at these earliest stages of Alzheimer's when individuals have the most to gain from medications that change disease trajectory and when they have the most to lose if CMS stands in their way of gaining access. Heartbreakingly, the draft NCD suggests that CMS has this completely backwards in thinking that people in the earliest stages of Alzheimer's disease have the least to gain and the most to lose. That, perhaps, is the source of the perceived paternalism.

The proposed CED undermines clinical trial volunteerism

People living with Alzheimer's disease do not undertake lightly the decision to volunteer as clinical trial participants. They do so not because the path is easy, but in spite of it being arduous. They volunteer despite few doctors mentioning the option of trials, the complexity of finding trials, the likelihood of being rejected from trials (often for reasons that seem opaque, illogical, or worse), and the frequently oppressive physical, emotional, and financial toll on themselves and their study partners. People with Alzheimer's disease volunteer for clinical trials in hopes that they may benefit from early access to promising medications and that a much wider population facing the disease will benefit from these medications once approved by FDA.

The draft NCD's CED would decimate these core motivations for people with Alzheimer's disease to volunteer for current and future clinical trials. Arguably, the wildly unrealistic expectations for CED trial designs (e.g. full RCT with a placebo arm, laudable representativeness *outcome* requirements that take no *implementation* consideration of 400 years of systemic racism – the CED equity requirements are "flatly unattainable, because our national health systems aren't structured to give equitable care to begin with."[iv]) mean the trials are destined to fail before they start, not on scientific grounds but on recruitment grounds. But even if CMS addressed the most unrealistic and discriminatory elements of its CED proposal, leaving CED in place would send two unambiguous messages to current and potential future Alzheimer's disease clinical trial volunteers. First, CMS will be telling these courageous women and men living with Alzheimer's disease that once their Phase III trial participation is done and even if FDA approves the medication that has worked for them already, they will lose access to the medication because Medicare will not provide coverage. Second, CMS will be telling them that the wider population of people living with Alzheimer's disease also will have no Medicare coverage to gain access to these FDA-approved on-label use medications. The only people who will have access will be a privileged few who win entry into the CED trials or who are wealthy enough to pay 100% out-of-pocket. (To be clear, FDA confirmatory trials do not create these barriers because CMS historically always has allowed coverage for people outside the FDA confirmatory trials while those trials are being planned and executed.)

This may be, in part, why CMS has never before imposed any CED requirement for on-label use of any FDA-approved medication or for any medication receiving FDA Accelerated Approval. It begs the question of why CMS now proposes such a fundamentally radical departure from both its own precedent and congressional intent, and why CMS has chosen to target people living with

Alzheimer's disease with this arguably unlawful, certainly counter-productive, and deeply hurtful plan.

The law is the law

Some public comments appear to urge CMS violate the law in its final NCD by considering cost. Other public comments appear to urge CMS to exceed its legal authority – and eviscerate FDA's legal authority – by engaging in regulatory determinations of safety and efficacy. Still other public comments appear to fundamentally misunderstand or disregard congressional intent in mandating the FDA Accelerated Approvals program (and then to double-down my mischaracterizing the Accelerated Approvals program's process, function, and substantive history of saving the lives of countless Americans over its three decades of existence). On day one of law school every student learns that ignorance of the law is no defense. Similarly, wishing the law were different does not make it so. CMS rightly points out that the law is clear that CMS is not permitted to consider cost in its coverage decisions. CMS rightly points out that FDA, not CMS, is the regulatory agency and sole decision-maker about safety and efficacy. CMS knows – as amply demonstrated by its perfect record to date of providing coverage to all medications granted FDA Accelerated Approval – that the Accelerated Approvals program is congressionally mandated (and an overwhelming success as measured by lives improved and lives saved). Advocates who wish the law were different should not press CMS to ignore the law and CMS must not consider such misguided pleas to ignore the law.

CMS delay is not benign

The draft NCD proposes to place the entire class of mAbs under the devastatingly misguided and harmful CED rubric. The draft NCD would bury the entire class of drugs in an inescapable decade or longer morass of ill-defined, unachievable, and ever-shifting CMS requirements (see public comment from the Alzheimer's Disease Policy Task Force). It matters not at all if CMS has good motives, so long as its decision does harm to people living with Alzheimer's disease. CMS delays of months, years or decades will results in vast numbers of people being denied their only opportunity for an FDA-approved medication before their disease progresses past the point of on-label use (see public comment from UsAgainstAlzheimer's).

CMS narrowing the harm is not curative

CMS has said that it *could* (not that it "*would*") engage in expedited reconsideration of CED requirements for meritorious medications. Of course, CMS has not laid out plainly what would merit reconsideration, how quickly such reconsideration would be completed, what metrics or other concrete criteria would ensure liberation of an FDA-approved medication from CED, or given any meaningful explanation of why people with Alzheimer's disease should take seriously such vague non-promises. In fact, CMS has a distinct history of stretching out CED by adding new demands just as the previous requirements were met.

But even discussing potential reconsideration processes assumes that CMS has any legitimate basis whatsoever for an all-of-class CED requirement. FDA *does not* issue pre-emptive all-of-class regulatory approvals for the same reason CMS *should not* engage in the anti-scientific hubris of pre-emptive all-of-class CED: within a class, each medication has fundamentally different characteristics, clinical trial characteristics, and evidentiary strengths or weaknesses. In this instance, as CMS knows full well, beyond the first-in-class medication, none have completed their Phase III trials or even been put before FDA for regulatory review. Intentional or not, CMS appears in its draft NCD intent to condemn an entire class of medications based on an obviously erroneous presumption akin to saying that because all apples are fruits then all fruits must be apples.

Good intentions that worsen health equity

Among the most painful ironies in a proposed NCD awash with "*Alice in Wonderland*" contradictions is that the CED purports to take a long-overdue stand on health equity. Beyond the mechanics of CED requirements that actually would make it harder and less likely for people of color and those in rural areas to participate, and beyond the nationwide non-coverage outside of the miniscule trial cohorts that would prevent many people among these populations from access altogether (see public comment from the National Minority Quality Forum), the CED ignores entirely the most obvious example of clinical trial under-representativeness in the entire Alzheimer's disease community: people living with Down Syndrome who have a 90% lifetime risk of Alzheimer's disease. The proposed CED literally would require trials to exclude people with Down Syndrome. As the LuMind IDSC Foundation public comment most ably explains, the proposed NCD essentially guarantees not only that people with Down Syndrome will have no access to this generation of mAbs but also that the field will learn nothing about how future medications might or might not work to address Alzheimer's disease among people living with Down Syndrome. The proposed CED effectively condemns another generation or more of these individuals to the near certainty of dying with dementia. The proposed CED is antithetical to the core principles of health equity.

Respect

I have the utmost respect for those who sincerely hold profound concerns about one or more of these medications, expressed over the past months in other forums and in comments CMS is receiving now. Either personally or by reputation, I know many of those taking divergent views. All have impeccable integrity, credibility, and allegiance to making the world a better place for people living with cognitive impairment until our collective efforts to advance science eventually and entirely eliminate Alzheimer's disease and other causes of dementia.

I would hope that it is unnecessary to articulate that people living with Alzheimer's disease deserve our equal respect, particularly since theirs are the lives on the line with the final NCD. People with mild cognitive impairment or mild dementia due to Alzheimer's disease have considerable challenges, but they are not naïve, and they do not need anyone's or any institution's paternalism. They understand that this class of medications is new and cannot

possibly provide either a cure or a uniform outcome profile across a vast and heterogeneous population. They want, need, and deserve the opportunity to weigh the potential benefits and risks of these medications as individuals with the support of their loved ones and their health providers. They want time to experience how the therapy works for them as individuals. They want time to be part of building the real-world evidence and how these therapies can be improved for a more diverse array of people. They want time still to be eligible when improved therapies become clinically available. They want more time to be as fully engaged as possible as the primary decision-maker in addressing the practical necessities of legal, financial, medical, and spiritual planning. They want more time to come to terms with their diagnosis and their prognosis -- and to help their loved ones come to terms as well. They want more time to be more cognitively present for life's mundane moments as well as life's transcendent moments. They want more time to help their loved ones build more memories of a life together that will endure when the disease exacts is worst toll. On April 11, CMS either will offer that time or CMS will take it away.

CMS must do more

If CMS does the right thing on April 11, by issuing a final NCD that provides full national coverage for on-label use of FDA-approved mAbs, that alone will not be enough to meet the true needs of Medicare beneficiaries. CMS must not operate in a vacuum regarding this NCD, as if it were unaware of, or unable to dismantle, its own coverage and payment barriers. Because amyloid confirmation is necessary for FDA-approved use of mAbs, **CMS must fully cover FDA-approved diagnostics when used for purposes of supporting clinicians in determining whether to prescribe and continue prescribing these medications; such diagnostics must be reimbursed at a level that does not disincentivize provision of these medically appropriate services. Additionally, CMS should provide coverage for all necessary ancillary costs related to safety monitoring.** Offering coverage for a medication without coverage for the steps required for initial and continued eligibility would be an unimaginably cruel triumph of regulatory bureaucracy over both common sense and human decency. Worse yet, leaving in place such barriers would further entrench health disparities and fundamentally undermine efforts to build the very real-world evidence necessary to our shared vision of health equity. By providing modernized and equitable coverage for the diagnostics and safety monitoring associated with use of medications in this class, CMS would address some of the most important health system infrastructure, socio-economic and geographic barriers to equitable access to the medications themselves and would help incentivize broader and more equitable availability of both the relevant specialists and specialized medical products.

In conclusion

As was the case with public comment submitted last August, the views expressed in this comment reflect repeated personal family experiences with Alzheimer's disease and over 25 years of professional experience in dementia policy working with world-class researchers, stakeholder organizations, and thousands of affected individuals.

On behalf of my family, for whom these medications come too late, and millions of other families for whom these medications may come in time, I encourage CMS to **issue a final NCD removing CED requirements and allowing coverage for FDA-approved uses of these Alzheimer's disease medications for Medicare beneficiaries nationwide, along with the diagnostic and other medical services necessary for continued use of these medications.**

I am deeply grateful to you along with your Coverage and Analysis Group and other CMS colleagues for your tireless efforts to communicate with all stakeholders. Despite our profound concerns about the proposed NCD and (at times) strongly worded expressions of those concerns, you have always been accessible, patient, and welcoming of our input. Ultimately, I am entirely confident that CMS will provide full nationwide coverage of FDA-approved Alzheimer's disease medications and the collateral services needed for their use because it is the right thing to do for Medicare beneficiaries, for the advancement of science, and for the attainment of genuine health equity. I would welcome the opportunity to continue constructive dialogue with CMS as you work toward these essential national priorities.

Sincerely,

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[i] *See* Ctrs. for Medicare & Medicaid Servs., *Anticancer Chemotherapy for Colorectal Cancer Decision Memo* (Jan. 28, 2005).
[ii] *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).
[iii] 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).
[iv] 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.