

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

February 10, 2021

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

Dear Administrator Brooks-LaSure,

The Robert J. Margolis, MD Center for Health Policy at Duke University (“Duke-Margolis Center” or “Duke-Margolis”) appreciates the opportunity to comment on the Centers for Medicare and Medicaid Services (CMS) National Coverage Analysis (NCA) Proposed Decision Memo for Monoclonal Antibodies (mAb) Directed Against Amyloid for the Treatment of Alzheimer’s Disease. Duke-Margolis analyzes evidence across the spectrum of health policy and supports the triple aim of better care, better health, and lower costs. A core mission is to increase the value of biomedical innovation. Our experts are engaged in policy research and development efforts to improve the processes, resources, and infrastructure needed at CMS to ensure efficient and appropriate access to new and innovative technologies.

Alzheimer’s Disease (AD) is a neurodegenerative condition that affects an estimated 6 million Americans,¹ and this number is expected to triple by 2060.² Previous pharmacologic treatments for AD have only targeted symptoms. Further, AD treatment models are largely fragmented, reactive, and provide only limited help in avoiding and managing the heavy costs on families and Medicaid for supportive care. Some promising patient-focused “memory clinics” and whole-person care models have demonstrated improvements in patient experience and reduced complications, but they are not widely accessible or well supported by existing payment policies. There is an urgent need for disease modifying treatments that can slow, halt, or even reverse the neurodegeneration associated with AD. Accordingly, there is a need for such comprehensive care models that improve the standard of care and health outcomes that matter for Medicare beneficiaries living with AD, building in appropriate use of new pharmacologic treatments and other effective interventions in person-centered care models.

The last decade has seen growing activity in the scientific community in developing treatment approaches for AD. Aducanumab is the first disease-modifying treatment FDA approved for patients with mild cognitive impairment (MCI) and early-stage AD.³ There are other disease-modifying treatments similar to aducanumab currently being evaluated in pivotal trials with promising early results. These treatments potentially represent the first of additional types of therapies that—while not yet fully developed or proven—could significantly impact the treatment course of millions of Americans with early-stage AD. Thus, while this NCA understandably focuses on aducanumab and past clinical research for all mAb treatments, CMS has noted that the analysis potentially applies to all products in this class. The approaches that CMS establishes here will have implications for the development of other AD treatments as well.

Our comments are informed by Duke-Margolis’s independent analyses of the proposed decision memo and recent convenings with a broad set of stakeholders that include patient advocacy groups,

researchers, payers, and developers of mAb treatments. Our recommendations describe opportunities for CMS to refine their proposed decision in light of the growing and evolving body of evidence for mAb treatments, which CMS policies will undoubtedly influence.

Our recommendations are summarized below:

CMS Should Clarify the Pathway for Expanding Coverage Beyond RCTs – Building on RCTs Already Underway

- The final NCD should conduct a careful review of comments to determine whether current evidence on mAbs is not sufficient for a broader NCA at this time, and if not, provide clearer guidance on what evidence is needed for broader coverage for a particular mAb treatment and the class.
- CMS should leverage FDA’s regulatory guidance for ongoing trials to provide more clarity on requirements for broader coverage of individual mAbs and the class of mAbs.
- CMS should clarify whether it will rely on FDA’s future determinations about the validity of plaque reduction as a surrogate endpoint for the class of mAbs.

CMS Should Clarify How Broader Coverage with Evidence Development Can Resolve Further Key Questions About Safety and Effectiveness in Diverse Beneficiary Populations

- CMS should describe and support a pathway for addressing important safety and effectiveness questions not addressed in “traditional” RCTs – and for advancing better care for AD patients.
- For AD mAb treatments that have produced substantial evidence of effectiveness and safety, CMS should describe more specific evidence expectations for subgroups of patients (based on race, ethnicity, risk of complications, or other important characteristics) and how this evidence can be developed through feasible real-world evidence (RWE) strategies that do not unduly restrict access.

CMS Should Implement CMS-FDA Collaboration, with Sharing of Evidence from Manufacturers and Inclusion of Other Stakeholders and Federal Expertise to Inform Coverage Decisions

- CMS and FDA, with other public health agencies, should implement a coordinated, ongoing process to assess the growing evidence related to classes of AD products and individual products—promoting comprehensive and timely evidence evaluation, and predictability in agency action. Product developers and other stakeholders should have transparent mechanisms for input into this process.

Our detailed comments on our recommendations follow, framed in terms of the relevant context and history of Medicare’s coverage processes for new technologies.

The National Coverage Analysis Context for the Proposed mAb Coverage Decision

Reasonable and Necessary Medicare Coverage Standard

Medicare coverage is based on whether items and services fall in benefit categories contained under 1861(S)(2)(A) or 1861(S)(2)(B) of the Social Security Act and a determination of if they are reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of Medicare beneficiaries. CMS considers an item or a service reasonable and necessary⁴ if it is: (1) safe and effective, (2) not experimental or investigational, and (3) appropriate for use in Medicare beneficiaries.^a

While it is not codified in statute, the definition of reasonable and necessary has been a longstanding basis for coverage. The reasonable and necessary standard fosters predictability in the evidence development needed by developers to secure Medicare coverage, which in turn, ensures the best outcomes for Medicare beneficiaries. Coverage is critical in whether Medicare beneficiaries have access to novel, often high-cost technologies.

Importantly, coverage determinations are not based on cost or cost-effectiveness considerations. The proposed NCA included no analysis of cost issues and was instead based entirely on analysis of the implications of the use of mAb treatments that would be most appropriate for the well-being of Medicare beneficiaries given currently available evidence.

While the vast majority of new medical products are covered routinely or through local coverage decisions (LCDs), certain new types of medical products have raised issues about whether and how the reasonable and necessary standard applies. In these cases, a formal national coverage determination (NCD) is generally made at the level of a product class or procedures specific to a product class. In cases where there are only single products that fall under an NCD, CMS aims to ensure that the final coverage determination also provides appropriate access to future approved products. The resulting coverage generally depends on the strength of the evidence at the time of the determination, which in turn depends on the types of clinical studies used to evaluate the new item or service. CMS places greater confidence in data that comes from well-designed randomized controlled trials (RCTs) compared to other studies, as RCTs are the most rigorous approach to establish causality between an intervention and outcomes, with minimum bias. This approach generally aligns with FDA approvals for new products or technologies that are based on the results from pivotal trials, usually RCTs.

In its assessment for Medicare coverage, CMS evaluates how the available clinical evidence can be applied and generalized to Medicare beneficiaries. When there is insufficient evidence to make an assessment on reasonable and necessary for Medicare beneficiaries, CMS has used Coverage with Evidence Development (CED) to provide patient access while requiring evidence development that can substantiate and further expand the reasonable and necessary determination if supported by the evidence.⁵ CED has not been codified in regulations; however, it has been CMS's policy for over 15 years.

^a Reasonable and Necessary: The third criterion includes the duration and frequency that is considered appropriate for the item or service in terms of whether it is: 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; Furnished in a setting appropriate to the patient's medical needs and condition; Ordered and furnished by qualified personnel; One that meets, but does not exceed, the patient's medical need; and At least as beneficial as an existing and available medically appropriate alternative.

CED has been a crucial tool in ensuring earlier and wider diffusion with greater confidence for important, innovative technologies to the Medicare population, particularly technologies that are approved through expedited pathways and are FDA approved with preliminary evidence.⁶ As CED requires evidence development, it has been used to assess how well an intervention works in real-world practice settings, for subpopulations of the diverse Medicare population which are typically not well represented in pivotal trials for approval, and (particularly for diagnostics) the technology's impact on medical decision-making. In many cases, CED has resulted in evidence development on treatment effects for diverse patient subgroups and practices that lead to clinical insights and better decisions for current and future Medicare beneficiaries related to expectations and management of complications of treatment, long-term effects, and treatment durability—data that are generally not available through RCT pivotal trials.

Evidence Needed on mAb Treatment for Reasonable and Necessary Coverage

For this NCA for the mAb product class, CMS's evidence review included an analysis of current published and peer-reviewed literature on mAb treatment and available data from the aducanumab pivotal trials, EMERGE and ENGAGE. This is a reflection of the published and peer-reviewed literature available. As aducanumab is the only FDA approved product, CMS's review mostly focused on the strength and quality of aducanumab's body of evidence along with evidence from older mAb treatments no longer in the late-stage pipeline.

As described earlier, aducanumab is the first treatment of its kind to be approved by the FDA. Aducanumab received approval through an accelerated approval pathway based on a surrogate endpoint—the drug's effect on amyloid plaque removal—that the FDA concluded was reasonably likely to predict clinical benefit. Importantly, while the clinical trial evidence from the aducanumab pivotal trials demonstrated a significant difference in amyloid plaque removal, neither trial met their primary effectiveness endpoint.^{7,8} The FDA reported that a post-hoc secondary analysis for the EMERGE trial did demonstrate statistical significance for its primary endpoint and for secondary effectiveness endpoints on cognition and function.⁹

CMS's overall assessment was that mAb treatment for AD was not reasonable and necessary for Medicare beneficiaries. They concluded that the evidence supporting effectiveness of mAb treatment, which it defined as a clinically meaningful difference in decline in cognition and function, was inconclusive. Their assessment emphasized the following main points:

- While CMS agreed with FDA that aducanumab effectively clears amyloid plaque, it also noted evidence that suggests that amyloid plaque reduction is a heterogeneous marker with a less proximate connection to clinical outcomes. CMS stated that the role of amyloid plaque in AD remains controversial and cited a study¹⁰ that concluded that there is no published peer-reviewed evidence that confirms that a change in any biomarker (like amyloid-plaque removal) predicts a clinical benefit.
- CMS highlighted the findings of the FDA's Peripheral and Central Nervous System Drugs Advisory Committee that voted against the approval of aducanumab, stipulating that there was not sufficient evidence to show that the drug was effective in slowing cognitive decline based on its two phase 3 studies. It further noted that while the post-hoc analysis of the EMERGE trial demonstrated *statistical* significance of outcomes assessing cognition and function, there are open questions regarding the reliability of those results and thus conclusive evidence can only be substantiated by further RCT evidence.¹¹

- In discussing safety issues, including headaches, dizziness, falls, and amyloid-related imaging abnormalities (ARIA), CMS highlighted the breadth of the proposed patient population for coverage, including diverse subgroups of patients common in Medicare with conditions that could exacerbate risks from the treatment. The safety issues highlighted a need to better predict and manage adverse events when they occur both short- and long-term especially for beneficiaries at higher risk.

Based on these points, CMS concluded that due to a lack of clear clinical benefit and potential frequency of adverse events for many Medicare beneficiaries, the evidence did not support that the benefits outweighed the harms of mAb treatment for Medicare beneficiaries.

In lieu of non-coverage, given the very high burden of disease and urgent need for effective treatments, CMS proposed to issue limited coverage of mAb treatment through CED in approved RCTs in hospital outpatient settings only, to ensure appropriate safety measures and improve the evidence regarding effectiveness.

The available published and trial data on safety showing significant risks, coupled with the limited evidence on effectiveness, was the basis for the CMS proposed decision. Reflecting the NCA's focus on existing evidence, CMS's analysis of the evidence of mAb treatment, while comprehensive, did not include emerging evidence from leading mAb candidates currently in phase 3 studies with expected primary completion dates in 2022 and 2023.

In the proposed decision, CMS provides general guidance on desired evidence, in the context of new RCTs, with several notable features. The patient inclusion criteria in this CED are similar to those in other AD mAb trials, with the added specificity that peer-reviewed, validated tests to measure cognition and function must be used to diagnose MCI or early-onset AD. Exclusion criteria are also consistent with ongoing trials and are another means to ensure that patients are protected against adverse events. In addition, also for safety, the site of service is limited to the hospital-based outpatient setting to minimize any potential harms from the treatment. Finally, and importantly, CMS proposed that the diversity of patients in each trial must be representative of the national population with AD, likely to capture accurate data on any potential subgroup effects and to promote clinical trial diversity. But the opportunities for many ongoing trials, registries, and other existing longitudinal data collection to advance these goals are not described, even though they represent a substantial foundation of evidence development capacity on these topics.

This underscores one of the main tenets in Duke-Margolis's recommendations. Important RCT data on safety and effectiveness is forthcoming on multiple mAb products, with primary endpoint readouts likely to come out within months of the expected final decision memo in April – as soon as June and September 2022 (see Table 1 in the Appendix). CMS NCAs must be based on evidence, and CMS will need to respond to extensive comments on its analysis of the implications for coverage of the evidence to date. In addition, as different mAb treatments may have different safety and effectiveness profiles and as more class-level evidence on the validity of plaque reduction as a surrogate marker may emerge, CMS should provide guidance on how additional evidence on safety and effectiveness from this near-term evolving body of studies would impact its reasonable and necessary assessment for coverage to newer mAb treatments.

Precedents and Differences from other NCAs with RCT Requirements for CED

Aducanumab is not the first accelerated approval product for which CMS has had questions regarding effectiveness. CMS has historically covered accelerated approval drugs for on-label uses, many of which have been in the oncology and immunology space.¹² With very few exceptions, there are no NCDs that impose criteria on their adoption and use. Moreover, for these exceptional NCDs, requirements generally did not extend beyond FDA approved phase 4 confirmatory studies. In one NCD for colorectal cancer drugs including Oxaliplatin (Eloxatin™), irinotecan (Camptosar®), cetuximab (Erbix™), and bevacizumab (Avastin™), which had specific labeled indications for patients without alternative treatments, CMS provided coverage for off-label uses for “clinical trials identified by CMS and sponsored by the National Cancer Institute (NCI).” Notably, no new clinical trials resulted from these CED frameworks.¹³ While all of these accelerated approvals based on surrogate endpoints resulted in coverage, the Medicare populations covered were relatively narrow, generally with advanced disease and a much more proximate risk of severe complications and death, compared to the AD mAB proposed population. Some accelerated approvals have come under FDA review due to the failure of completion of confirmatory trials showing improved health outcomes.¹⁴

CMS’s assessment of mAb evidence to date (mainly aducanumab) noted not only the absence of clear evidence of effectiveness but also other major distinctions from these prior covered accelerated approval drugs. CMS noted that while AD clearly represents an unmet medical need, the labeled population of early-stage patients was very broad and may have years of minimally-impaired quality of life ahead. Many of these beneficiaries have conditions that could exacerbate risks from treatment side effects or may not respond to treatment.

For other categories of products, particularly devices and diagnostics, CMS has proposed CEDs through RCTs only. CMS has proposed such RCT requirements for coverage when:

- Published peer-reviewed literature did not provide evidence on long-term health impacts or product durability.
- CMS had safety concerns due to the nature of the procedure or the rates of adverse events in Medicare populations.
- Completed studies were not methodologically rigorous by CMS’s standards (for example, retrospective studies, studies with small sample sizes, samples without or with few representatives of Medicare populations, lack of comparators) and thus could not demonstrate sufficient benefit for Medicare populations.
- Disease history, pathway, and management were not well understood.
- In the case of diagnostics, an effect on clinical management of the patient’s condition was not shown, even if there was strong evidence that the diagnostic worked.

After reviewing comments, CMS *retained* the RCT or concurrent control arm requirement in the final coverage determination in cases where:

- The peer-reviewed literature available had too many limitations to draw conclusions about product benefit^{b, c} and,

^b Vagus Nerve Stimulation (CAG-00313R2): CMS analysis found that traditional treatments can still successfully ameliorate the symptoms of Treatment Resistant Depression, highlighting the need for double-blind studies to prevent potential bias between treatment and control group.

^c Transcutaneous Electrical Nerve Stimulation (TENS) for Chronic Lower Back Pain (CAG-00429N): A 2010 report from the American Academy of Neurology summarizing literature on the topic concluded that TENS was not effective in relieving chronic back pain, spurring CMS to reevaluate existing coverage for TENS. Upon their own

- The effect of the diagnostic on care management was not clear and did not result in clear benefits to health outcomes.^d

For most of the cases where CMS proposed RCT-only criteria, CMS ultimately expanded these CED criteria beyond RCTs in response to public comments. Indeed, in this proposed NCA, CMS invited public comments regarding additional clinical data and evidence on mAb treatment, particularly evidence relevant to aducanumab. To the extent that proposed CED criteria provide general guidance on evidence that *could* substantiate reasonable and necessary coverage, now and in the future, this public comment period allows stakeholders to address *how* CMS can best address their evidence questions through CED or other coverage criteria. Prior CMS decisions consistently emphasize that a key issue is whether the peer-reviewed literature has too many limitations to draw conclusions about product benefit, especially if significant safety risks appear to be present.

CMS *expanded* their proposed CED (RCT or concurrent control arm) criteria in cases where:

- Product was a treatment of last resort with evidence of effectiveness in a targeted patient population and there was certainty of confirmatory phase 4 post-approval studies.^e
- Evidence could be developed outside the confines of an RCT, with enough reliability in patient populations and care pathways that further needed evidence could be addressed through pre/post-test designs, prospective cohort studies, or other comparative studies that obviated the need for a randomized control arm.^{f, g}

investigation, CMS decided that the studies examining the effects of TENS were either methodologically limited or reported little to no clinical benefit.

^d Pharmacogenomic Testing for Warfarin Response (CAG-00400N): CMS analysis found that although pharmacogenomic testing of different alleles did predict warfarin responsiveness, there was not enough evidence to show how test results influenced patient care management and treatment plans. As a result, the effect of testing for warfarin response on health outcomes was unclear.

^e CAR-T Cells (CAG-0051N): CMS proposed CED for CAR-T therapies for cancer treatment for CMS-approved clinical studies or prospective registries that follow patients for at least two years. However, after reviewing public comments, CMS acknowledged that “CAR T-cell therapy is indicated for very ill patients [...] patients who have failed multiple lines of therapy may have limited remaining treatment options. CAR T-cell therapy has been shown to induce remission in carefully identified relapsed or refractory cancer patients in appropriate settings of care.” Combined with the promise of upcoming FDA-approved postmarket studies, CMS offered national coverage for qualifying patients.

^f Extracorporeal Photopheresis (ECP) for Bronchiolitis Obliterans Syndrome following Lung Transplant (CAG-00324R2) CMS found that there was no clear standard of care for treatment. The intensity, frequency, and duration of treatment were different across all studies, making it difficult to determine overall effectiveness for Medicare populations. In this case, CMS recommended clinical studies designs that would qualify for CED, such as pre/post-test designs or prospective clinical trials, that would develop methodologically rigorous evidence that could help CMS determine a standard of care and examine the appropriateness of the treatment for Medicare beneficiaries.

^g Autologous Platelet-rich Plasma (PRP) (CAG-00190N, R, and R2); after a reconsideration of a non-coverage decision, CMS proposed a CED with RCT framework to determine if Medicare beneficiaries with chronic wounds have clinically significant outcomes compares to those who do not receive PRP treatment because of a lack of standardization among trials. CMS eventually offered coverage for prospective studies with a comparison arm to help standardize care around the product, eliminating the formal RCT requirement.

- A registry or prospective longitudinal studies could address CMS’s evidence concerns regarding potential diversity of treatment effects across the diverse Medicare population.^h Notably, in these cases, CMS acknowledged that longitudinal studies in real-world settings would better reflect the burden of disease and the actual treatment experience across all populations.

In revising final decisions, CMS has demonstrated a willingness to consider comments from providers and other key stakeholders that describe the challenges associated with meeting control arm requirements. Importantly, it considered alternative data collection approaches when such approaches can address evidence questions potentially more effectively and efficiently compared to an RCT design.

In cases where CMS had fundamental real-world safety concerns as part of these evidence concerns, CMS has specified operator (provider) and site of service criteria to ensure appropriate safety measures were in place, and, when available, deferred to professional society consensus guidelines. For instance, in prior NCDs for novel devices and procedures, CMS has implemented operator requirements aimed at ensuring clinicians providing the treatment and managing the patient had the experience and expertise to assure appropriate use of the new treatment and monitor its effect. Such requirements included specialty expertise, multidisciplinary team assessment, and shared decision making.ⁱ Similarly, CMS has specified facility or site of service requirements to assure that the facilities where patients were treated were appropriately equipped to manage safety issues. These have been relaxed as real-world evidence accumulated. For example, site of service for bariatric surgery¹⁵ and transcatheter aortic valve replacement procedures¹⁶ were initially limited to specialized, experienced centers with special capabilities. Over time, CED expanded the evidence base, leading to broader criteria for use that enabled broader access to these treatments. Collectively, these past NCDs establish a precedent for the use of registries to address issues related to safety and course of treatment in a diverse group of patients when basic evidence of effectiveness and safety was already established through pivotal trials. Table 2 in the Appendix reviews these NCDs.

In the AD mAb context, there are similarly formal safety assessments that CMS can further consider in its final decision regarding CED criteria, provided it concludes there is sufficient evidence for effectiveness. For instance, an expert panel that formulated Appropriate Use Recommendations for aducanumab in 2021 stipulated that treating providers must have access to MRI facilities and to radiologists familiar with detection and reporting of ARIA, cautioning against potential failures in detecting this side effect by inexperienced clinicians (also requiring robust access to MRI as CT is an insufficient tool for ARIA detection).¹⁷ Furthermore, the panel stipulated that patients should have access to a timely clinical assessment and a neurological examination if they present symptoms that could be related to ARIA. This might require specialized capabilities, at least until more evidence is generated on effective management for avoiding complications from this common but usually mild or asymptomatic side effect. On this topic, FDA concluded that a risk evaluation and mitigation strategy (REMS) to restrict and control prescribing was not needed for aducanumab while also noting that the drug will likely be prescribed by memory disorder specialists who are familiar with AD.¹⁸

^h In the case of both the Leadless Pacemakers (CAG-00448N) and the Percutaneous Left Atrial Appendage Closure (CAG-00445N) final decision memos CMS remarked that national prospective registries and longitudinal trials should help alleviate some of the data collection disparities by race and gender. For Transcatheter Aortic Valve Replacement (CAG00430R), CMS acknowledged gender disparities in health outcomes, and hoped that the new, “innovative all-women WIN-TAVI registry should begin to address gender disparities.”

ⁱ Percutaneous Left Atrial Appendage (LAA) Closure Therapy (CAG-00445N); Transcatheter Aortic Valve Replacement (CAG-00430R); Transcatheter Edge-to-Edge Repair (CAG-00438R).

Proposed CED Criteria for AD mAbs Compared to Prior NCA Decisions' CED Criteria

CMS has a wide spectrum of CED approaches to provide earlier access to novel therapies given the available evidence base. Prior NCA decisions sometimes required RCTs, even after comments urging broader coverage, when CMS did not find clear evidence of effectiveness and there were prevailing concerns regarding the heterogeneity of the indicated treatment population. In contrast, CMS moved away from RCT requirements when there was meaningful evidence of effectiveness that could be augmented by prospective longitudinal observational studies, instead requiring observational evidence generation on subpopulations, including safety profiles and differences in course of illness with treatment.

In this proposed coverage determination, CMS found an absence of clear evidence on the core question of the effectiveness of aducanumab to date. The core questions around effectiveness of a treatment intended to have an incremental impact on decline in cognitive function that CMS identified in the NCA is very difficult to address through any mechanism less rigorous than well-designed and well-controlled RCTs. This is reflected in a lack of community consensus based on the available evidence around standard of care. In particular, two evidence gaps seem feasible to address only through RCTs:

- Validating a surrogate endpoint for the class of mAbs: CMS noted that outcome has not yet been established, as we describe above;
- effectiveness of mAb products on primary endpoints related to cognitive decline, which require RCT assessments, since trends in measures of cognition experienced by this large and heterogeneous patient population with MCI and early-stage AD may be influenced by many factors other than mAb use.

In the absence of well-controlled randomized trials, estimates of these could be biased by differences in unmeasured characteristics of patients (for example, the patients that would opt to receive treatment are likely those that already experience faster cognitive decline). Further, even in “simple” or pragmatic randomized trials without detailed data collection and rigorous treatment protocols as part of randomization, noise may be introduced, and outcomes may be biased toward zero by unmeasured differences in how subgroups of patients are treated.

However, there are other important evidentiary questions raised by CMS—including treatment effects across patient subgroups—that extensive real-world evidence experience at FDA and CMS has shown can be addressed through larger, observational studies, without randomized controls, including through prospective longitudinal studies. As noted earlier, CMS’s safety analysis highlighted that the proposed patient population was very large. While evidence on different groups of beneficiaries in the broad AD population is a highly important public health goal, we could find no CMS precedent for providing coverage only through clinical trials to reflect Medicare population diversity, including racial and ethnic diversity, once evidence of general effectiveness and safety had been established for a broad population through well-designed RCTs. In addition, we were unable to identify any previous RCTs funded by NIH or designed to meet FDA approval requirements for AD that met this proposed requirement, suggesting doing so may be difficult in the near future. This dilemma in AD evidence is well-known for subpopulations, like racial and ethnic minority populations, that face both limited evidence developed from their specific group and a higher prevalence of the disease and its burden. In the past, as we have summarized, CMS has generally addressed this dilemma by providing broader coverage with CED through registries once basic evidence on safety and effectiveness was established.

Below we describe how forthcoming evidence from ongoing phase 3 and phase 4 RCTs could help address some of these CMS evidentiary questions, building on prior approaches used in prior NCDs. To avoid this circumstance from recurring, CMS must take further steps in collaboration with NIH and FDA to advance the availability of longitudinal chronic-care models and link these to an improved capacity to conduct both randomized trials and postmarket evidence development to improve quality and increase ease of participation in evidence development for Medicare’s diverse patient population.

Evidence in Process from AD mAb Treatments Currently in Advanced Clinical Development

Table 1 (see Appendix) lists all the new mAb treatments in late-stage development, including the recently-announced Phase 4 study of aducanumab. As noted above, the CMS evidence review did not include these ongoing phase 3 RCTs on different mAb treatments because evidence from these studies has not been published in peer-reviewed literature. In general, mAb products differ in terms of molecular structure and formulation (and may have somewhat different indications), which could plausibly lead to different safety and efficacy profiles. Further, preliminary findings from most of these trials are also suggestive of evidence on effectiveness, though studies are limited. This evidence includes impact on plaque reduction¹⁹ and an incremental impact on cognitive impairment measures.²⁰ Positive results on primary endpoints from ongoing phase 3 trials could address CMS’s foundational questions on effectiveness, thereby potentially meeting the described threshold for broader reasonable and necessary coverage. The release of the final NCA is an opportunity for CMS to provide needed further guidance to maximize the value of this and future evidence development for current and potential forthcoming products in this class for mAb treatment—in particular, whether and how these studies need augmentation beyond FDA-approved primary endpoints to provide sufficient evidence on effectiveness and safety for broad coverage.

Key Recommendations

Below we address how the evolving evidence base from ongoing and planned RCTs can impact CMS’s final NCA and provide further clarity around standards and guidance for evidence for reasonable and necessary coverage, particularly as it relates to three themes from our contextual analysis.

Clarify the Pathway for Expanding Coverage Beyond RCTs – Building on RCTs Already Underway

1. The final NCD should conduct a careful review of comments to determine whether current evidence on mAbs is sufficient for a broader NCA at this time, and if not, provide clearer guidance on what evidence is needed for broader coverage for a particular mAb treatment and the class.

In sum, the proposed NCD stated that despite FDA approval, insufficient evidence was available to demonstrate the basic effectiveness and safety of mAb treatments, particularly aducanumab. CMS reached this distinct conclusion for the reasons we have noted above. We agree that only well-designed RCTs are likely to provide conclusive evidence on:

- The basic effectiveness of mAb treatments, which are intended to have incremental effects on slowing cognitive decline without disproportionate safety consequences, since these outcomes may be influenced by many patient and environmental factors.
- The validity of amyloid plaque reduction as a surrogate endpoint that predicts clinical benefit.

We expect that commenters with expert knowledge of the current state of such clinical evidence from trials will comment extensively on the evidence standards underlying the proposed decision, and we urge and expect CMS to consider all such relevant evidence thoroughly in making their final decision. Based on these comments, if CMS determines that current evidence is insufficient, we also urge CMS to provide more specific guidance on remaining gaps in the evidence on these key questions for clarity about how they can be most efficiently addressed.

The proposed NCA stated that any threshold for what constitutes a “clinically meaningful” improvement for a primary effectiveness outcome must be supported by peer-reviewed published medical literature. We note that the definition of what is considered “clinically meaningful improvement” may have different interpretations. CMS provided an example of the measures and effect sizes that could be the basis of a proposed broader coverage decision, but this is not the only plausible approach to define “clinically meaningful improvements.” For example, there are studies that use other measures such as the Alzheimer’s Disease Assessment Scale–Cognitive Subscale, 13-item version (ADAS-Cog13), Alzheimer’s Disease Cooperative Study-Integrated Activities of Daily Living (ADCS-iADL), and their composite, the Integrated Alzheimer’s Disease Rating Scale (iADRS). These outcome measures have been validated and published in peer-reviewed literature.²¹ Moreover, there are several trials that use the outcome measures that CMS provided as examples in the proposed decision, but it is not clear that the minimal clinically important difference (MCID) suggested in the study referenced by CMS is meant to inform on trial endpoints or whether it is correlated with the effect size that these trials are powered to detect.

Similarly, if the final NCA determines that existing evidence on safety is insufficient, it should provide guidance on what additional safety evidence is needed. Table 1 includes the safety endpoints of mAb treatments in development. Most of these RCTs are tracking safety through adverse events (AE) monitoring. For example, in lecanemab’s phase 3 trial extension phase, outcomes focused on safety include measures such as the number of participants with AEs, clinically significant change from baseline in vital signs values, abnormal MRI and ECG values, clinically significant findings in laboratory values, positive anti-drug antibodies (ADAs), and any suicidality.²² Gantenerumab’s phase 3 safety and efficacy trial similarly tracks percentage of participants with AEs, change in Columbia-Suicide Severity Rating Scale score, percentage of participants with Amyloid-Related Imaging Abnormalities-Edema and -Haemosiderin (ARIA-E and ARIA-H) confirmed by MRI, and percentage of participants with injection-site reactions.²³ While the three ongoing phase 3 trials for donanemab do not list any safety measures, the TRAILBLAZER-ALZ-2 study features an addendum safety cohort.²⁴

Further, as noted above, CMS raised the important issue of gaps in more detailed evidence on safety and effectiveness in important subgroups of Medicare beneficiaries. We return to our recommendations on this important issue below, since none of the RCTs currently underway meet this proposed CMS criterion for coverage.

As part of its final decision, CMS should use the submitted comments and its own review to clarify the conditions for broader coverage of the entire mAb product class, if there is a clear and feasible path to class-level coverage. Like previous NCAs, the proposed NCA focuses on a coverage decision for the entire treatment class of mAbs for AD. However, most of the evidence currently available relates to aducanumab and older mAbs. As noted above, given the evolving body of evidence, it is plausible that stronger evidence may emerge for particular mAbs than for the entire class. CMS’s final decision should provide guidance for when the individual product or the mAb class as a whole would be granted broader coverage based on such evidence.

2. CMS should leverage FDA’s regulatory guidance for ongoing trials to provide more clarity on requirements for broader coverage of individual mAbs and the class of mAbs.

CMS should clarify that meeting the primary safety and effectiveness endpoints from trials underway—including the FDA-approved pivotal RCTs and phase 4 trials, and other relevant NIH-funded studies—would support broader coverage with less restrictive CED, at least for that particular mAb. If not, once again, CMS should provide greater clarity on what supplemental RCT evidence would be required. It will be invaluable for researchers and patients to understand whether the effectiveness endpoints of these ongoing FDA-approved clinical trials for other mAbs meet CMS’s expectation for a clinically meaningful benefit. If they do not, these ongoing trials may need to be modified and supplemental evidence development activities initiated as soon as possible to meet the CMS standard and prevent the loss of their value, including the value of patients’ willingness to participate in clinical research.

Additionally, CMS should clarify whether a mAb that receives FDA approval based on evidence on meeting its primary pivotal study endpoints would still require CED (potentially involving prospective longitudinal observational studies) or would meet the reasonable and necessary standard for full coverage. We provide further comments related to CED recommendations below.

3. CMS should clarify whether it will rely on FDA’s future determinations about the validity of plaque reduction as a surrogate endpoint for the class of mAbs.

The FDA has worked with stakeholders and the scientific community to develop a process to validate surrogate endpoints for clinical trials. Validated surrogate endpoints are supported by a clear mechanistic rationale and clinical data providing strong evidence for a specific clinical benefit:²⁵

“Before a surrogate endpoint can be accepted in place of a clinical outcome, extensive evidence must accumulate, including evidence from epidemiological studies and clinical trials. Usually, clinical trials are needed to show that the surrogate endpoint can be relied upon to predict, or correlate with, clinical benefit in a context of use. Surrogate endpoints that have undergone this extensive testing are called validated surrogate endpoints and these are accepted by the FDA as evidence of benefit.” *CDER 2021*²⁶

As CMS (and FDA) noted, the surrogate marker of amyloid plaque reduction has not yet met these validation standards, in contrast to stronger evidence on surrogate markers such as those used in cancer studies e.g., progression-free survival and metastasis-free survival,²⁷ for instance, for which the FDA has more extensive experience and precedent.²⁸ The ongoing studies evaluating this biomarker are designed to provide more insight into the validity of this endpoint.

All three mAb treatments currently in development listed in Table 1 are undergoing trials that evaluate plaque reduction or elimination as surrogate endpoints. These studies have shown preliminary evidence that mAb treatments can decrease amyloid plaques (and tau plaques in the case of donanemab and gantenerumab) with suggestive preliminary evidence of a small directional impact on cognitive and functional decline. Preliminary results from the gantenerumab and lecanemab clinical trials demonstrate a reduction in plaque buildup and cognitive decline, and the donanemab trial demonstrated reduction in plaque buildup and slower declines in cognitive testing.²⁹ Once completed, these studies may provide substantive evidence on whether amyloid plaque reduction is a valid surrogate endpoint for cognitive or functional benefit.

In addition to the ongoing phase 3 pivotal trials, the endpoints for the phase 4 confirmatory study for aducanumab were recently announced. The proposed primary endpoint is change in Clinical Dementia Rating scale Sum of Boxes (CDR-SB) from baseline at 18 months, and the secondary endpoints are change from baseline in ADAS-Cog13, Alzheimer’s Disease Cooperative Study-Activities of Daily Living in patients with Mild Cognitive Impairment (ADCS-ADL-MCI), iADRS, Mini-Mental State Examination (MMSE), and Neuropsychiatric Inventory-10 items (NPI-10). The detailed study design, with methods to support validating plaque reduction as a surrogate endpoint, has not yet been disclosed. However, as part of the accelerated approval process, the FDA requires the confirmatory phase 4 to show that the surrogate endpoint, amyloid plaque reduction, can be relied upon to predict, or correlate with, clinical benefit.³⁰

While CMS noted that evidence was not yet sufficient for validation, it did not state whether it would accept a subsequent determination by FDA based on their validation standards that the evidence is sufficient. If additional evidence is required to meet the reasonable and necessary standard, clarity on these issues would help assure that current and future trials will maximize the value of ongoing evidence development.

Mechanisms to Clarify How Broader Coverage with Evidence Development Can Resolve Further Key Questions About Safety and Effectiveness in Diverse Beneficiary Populations

As we have noted, it seems difficult to develop clear evidence on effectiveness of treatment and clear evidence validating a surrogate endpoint for effectiveness, except through well-designed RCTs. Once sufficient evidence of the basic effectiveness and safety of a mAb treatment is established, however, it will be difficult (and different from CED precedents) to limit coverage to RCTs alone to expand the evidence relevant to Medicare beneficiaries. First, there are practical and ethical obstacles to conducting RCTs after a treatment is already approved. Patients who are willing to undergo mAb treatment may not agree to be randomized to a control group given the presumptive evidence. Many may be willing to accept the safety risks associated with the treatment. Second, RCTs particularly in the AD context to date have been limited in scope of sites and populations, suggesting feasible trials in the near term may yield limited insights into the broader early AD population that receives care in a wide range of geographies. Third, RCTs are generally conducted at certain types of facilities, raising questions about how well they can support equitable access to this therapy. For all these reasons, our traditional clinical trial system has often fallen short in including diverse populations. For many drugs, meeting the primary endpoints for FDA-approved pivotal trials has been sufficient for broad coverage despite this important gap. Nonetheless, as CMS has noted, many questions related to safety and effectiveness particularly for diverse groups of Medicare beneficiaries remain.

CMS’s history of assessments of novel technologies shows multiple examples of cases when pivotal RCTs showed evidence of safety and effectiveness in some Medicare beneficiaries, and registries enabled the data collection necessary to gain a deeper understanding of adverse events, course of the disease, and disease management on treatment in real-world practice, for a much broader and more diverse range of Medicare beneficiaries. As in many of these previous cases, it is plausible that newer mAb treatments with expedited FDA approval will have evidence skewed toward patients with a more favorable benefit-risk profile. Anticipating that, the finalization of this NCA should establish what *additional* evidence development will be required, alongside broader reasonable and necessary coverage, once basic safety and effectiveness have been established – and preferably through feasible longitudinal observational data collection as in prior NCDs.

4. CMS Should Describe and Support a Pathway for Addressing Safe Use Concerns for mAbs Not Addressed in “Traditional” RCTs – and for Advancing Better Care for AD Patients

CMS explained in the proposed coverage decision that, even if individual mAb products demonstrate substantial evidence of effectiveness such as by meeting pivotal clinical trial endpoints, evidence on outcomes and risks with mAb treatment in diverse populations of beneficiaries will have important gaps, including those with different racial and ethnic backgrounds who face higher risks from AD and patients with comorbid conditions that may influence ARIA-related adverse events. CMS stated a general desire to support “representative” RCTs to address these questions. However, understanding adverse events in particular subgroups of beneficiaries would likely require very large sample sizes (and potentially long follow-ups), resulting in substantial delays and reduced access to a treatment that has demonstrated overall safety and effectiveness – if such trials are feasible at all.

Our review of prior NCDs showed many cases where CMS has supported CED using prospective longitudinal data, such as through registries, as a means of generating evidence on the remaining questions that bear on expanding its reasonable and necessary determination. We describe such approaches in the next section.

As noted above, in some NCDs, CMS has implemented broader coverage including evidence development alongside requirements on providers who are delivering the covered services or products. That is, steps for additional evidence development could be coupled with appropriate restrictions on conditions of use to assure safety and appropriate prescribing of the mAb treatments that would evolve with the evidence. Such initial restrictions must be clinically based, for example, limiting coverage not based on site of service (e.g., outpatient hospital only) but on reasonable expectations about the capabilities of prescribers to implement clinically appropriate monitoring and adverse event management steps (e.g., care models such as described in Cummings et al., or other up-to-date clinical guidance from specialty providers).

It is possible that a limited set of clinical data collection requirements might both help assure appropriate care using mAb treatments that have demonstrated evidence of safety and effectiveness and help improve care for AD patients. For example, patient monitoring for the occurrence, management, and resolution of ARIA symptoms, particularly in patients who might be at high risk of adverse events from ARIA, is an important element of existing practice guidelines. Thus, reporting data related to ARIA and adverse events on treatment could help both assure safety and inform subsequent coverage. However, such data collection should be part of an overall strategy of real-world data collection and evidence development, with clear ending conditions as we describe in the next section.

Expert commenters will likely provide further insights, in addition to existing evidence such as practice guidelines and FDA’s review of issues related to safe prescribing, as to whether any additional provider requirements and potential data reporting are appropriate, on top of pivotal RCT evidence.

For the longer term, CMS could address concerns about safe prescribing and quality of care by taking further actions to improve access to effective chronic care models for Medicare beneficiaries with AD. As has been noted by patients, their families, patient advocates, health care providers, and the agency itself, AD care today is often fragmented, with substantial burdens on patients and their caregivers to anticipate needs and organize and integrate services. CMS has announced an overarching strategic aim³¹ of providing access for all Medicare beneficiaries to comprehensive, accountable systems of care

designed around their needs within the next decade. Few groups of Medicare beneficiaries face both greater needs and less current access to such care models than beneficiaries with debilitating and ultimately fatal neurodegenerative diseases like AD. Developing an AD-focused component in this Medicare strategy would help advance the data systems and infrastructure for improving outcomes like functional status and independence that matter for AD patients and would enable a broader range of providers to deliver more effective, longitudinal AD care in the longer term. Broader access to more advanced, patient-centered care models for AD – with accountability for slowing decline in functional status and independence – would encourage appropriate use of new drugs, better use of diagnostics, and non-pharmaceutical interventions that lead to better patient function and independence over time. This would also facilitate better models of payment for AD drugs, which would be easier to reimburse on a population rather than a fee-for-service basis and could be linked to evidence of impact on key outcomes. All of these are substantial reforms that will take time, but initial steps can happen now and would demonstrate CMS’s commitment to the goals of better evidence and better care models stated in the proposed decision.

5. For AD mAb treatments that have produced substantial evidence of effectiveness and safety, CMS should describe *more specific* evidence expectations for subgroups of patients (based on race, ethnicity, risk of complications, or other important characteristics) and how this evidence can be developed through feasible real-world evidence (RWE) strategies that do not unduly restrict access.

For mAb treatments that have evidence of safety and effectiveness (i.e., the primary endpoints of FDA-approved pivotal clinical trials or phase 4 trials), CMS has extensive CED precedents to specify a path to broader coverage that evolves with the evidence, if CMS confirms the need for such evidence beyond RCT results. For example, for both the TAVR and TEER final coverage decisions, CED criteria specified operator and site of service requirements that were applied to RWE generation efforts through a national registry that also served to satisfy FDA post-approval surveillance requirements.³² Data collection as part of these CED criteria resulted in greater evidence that informed clinical practice guidelines, expanded indications, and an overall broader scope of coverage. For TEER, specifically, the expanding evidence base, as a result from CED, produced enough evidence to support expanded CED criteria regarding patient evaluation, facility requirements and operator requirements.³² Given the broad interest in additional RWE to improve care and outcomes for AD patients, registry initiatives and other real-world data collection efforts are already underway that could address these questions. For instance, the Alzheimer’s Association and collaborating organizations have announced an expansion of their existing registry systems to develop further evidence on disease-modifying AD treatments,³³ in conjunction with the development of standard data collection methods that could be integrated into other registries or data collection initiatives.

Building on previous CED experience with postmarket data collection, CMS could design data collection requirements to strike a balance between the depth of the data collected and assuring appropriate availability for diverse beneficiaries across geographic, urban/rural, and practice setting environments. Data collection should be limited to factors that are important clinical considerations given the current state of evidence, e.g., beneficiary characteristics that could influence the impact of treatment, data reflecting regular monitoring for side effects of treatment, data on steps taken to manage serious side effects, and (over time) practical assessment of patient independence and functional status. Such data are already collected by many memory clinics and AD treatment facilities and have been an important part of patient monitoring and management in existing RCTs and AD registries.

Further, such postmarket data collection should focus on the size and scope of the data needed to answer clear and specific questions about safety and effectiveness in beneficiary subgroups. Not all prescribers need to participate so long as safety issues can be managed. CMS could consider quality improvement payments for providers that submit additional data.

The evidence required to stop data collection on the key postmarket questions should also be described. Such a clearly specified, feasible pathway for better evidence and broader evidence-based coverage will help advance clinical care for AD, and increase confidence of prescribers, patients, and payers, while avoiding unnecessary restrictions on access to treatment in this area of great unmet medical need.

Such a clear, evidence-based pathway for broad coverage is challenging for CMS to develop except in collaboration with other key stakeholders. Notable uses of CED in the past for broad areas of unmet need have generally featured early and ongoing collaborations among CMS, product developers, FDA, the relevant clinical and patient community, and other stakeholders. One such example is Medicare's NCD for TAVR¹⁶, which featured a collaboration across all of these groups well in advance of expected product approvals in this space, enabling the formulation of an evidence development plan pertaining to outcomes and adverse events in diverse Medicare beneficiaries, leading to both broader initial coverage than would have occurred otherwise and subsequent evidence of effectiveness and safety that broadened uptake still further. It is relatively late to initiate a collaboration on efficient ways to address key postmarket evidence questions for AD, but there is strong stakeholder interest in doing so. We describe a process for doing so in the next section.

Together with steps to increase access to better chronic care models for AD patients, clarity from CMS about CED expectations will support needed investments in a better evidence infrastructure for AD patients. In turn, these better data systems will facilitate broader access to more advanced, patient-centered care models for AD including diagnostics, drugs, and non-pharmaceutical interventions that lead to better patient function and independence over time.

CMS Should Implement CMS-FDA Collaboration, with Sharing of Evidence from Manufacturers and Inclusion of Other Stakeholders and Federal Expertise to Inform Coverage Decisions

6. **Implement CMS-FDA collaboration, with sharing of evidence from manufacturers and inclusion of other stakeholders and Federal expertise, to facilitate clear standards for AD product coverage and to accelerate evidence development and care improvement.**

As we have noted, early and ongoing interactions among CMS and FDA staff, with input and support from product developers, has often helped to address coverage issues in a predictable way, including to support the development of additional postmarket evidence in ways that enabled more timely and potentially broader coverage for new types of products, including innovative new types of medical devices like transcatheter aortic valve replacements,³⁴ transcatheter edge-to-edge repair, and accelerated approval cancer drugs.³⁵ With clear awareness not only of completed studies, but also studies in process and under consideration in dynamic fields like this one, CMS NCDs can help with advance planning and preparedness to accelerate key evidence needed to meet the reasonable and necessary standard for coverage.

In some cases, CMS could also be supported by Technology Assessments from AHRQ or by convening a Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) panel with relevant expert

input. Previous MEDCACs have provided important insight for coverage decisions by offering expert opinions on specific evidentiary questions. Within the context of CED, MEDCAC panels have provided recommendations on broad evidentiary questions (such as how diagnostic testing can relate to health outcomes^j or confidence levels in sites of service for different procedures).^k A MEDCAC panel for AD mAb treatments could potentially help answer questions around clinically meaningful endpoints, standards of care, or other currently outstanding questions.

The complicated circumstances and controversy around the aducanumab approval were unfortunate. However, it has identified opportunities to increase interagency collaboration between CMS, FDA, product developers, other public health agencies, and stakeholders to inform key evidence issues like those raised in this proposed decision memo. Early and predictable collaboration can also create a more predictable process for sponsors to get independent feedback from CMS related to issues of clinical study design and strategies to improve evidence on diverse populations as CMS outlined.

Consequently, CMS and FDA, with other public health agencies, should implement a coordinated, ongoing process to assess the growing evidence related to classes of AD products and individual products—promoting comprehensive and timely evidence evaluation, and predictability in agency action. Product developers and other stakeholders should have transparent mechanisms for input into this process.

While such collaborations involving CMS and FDA have been implemented successfully in many instances, the current situation is another reminder that CMS needs updated resources and authorities to help anticipate and manage the coverage and postmarket evidence needs that arise as a result of the successes of accelerated approvals. The increasing pace of development of technologies that influence serious diseases “upstream” that may have important long-term effects, presents opportunities for learning more and creating more value from such products after approval.

Conclusion

The burden of disease of AD on the Medicare population is substantial and continuing to grow. There is an urgent need to address the unmet need of AD patients with safe and appropriate treatments. Aducanumab is the first approved treatment that aims to slow the rate of cognitive decline that is characteristic of AD, with pivotal RCTs underway that could lead to the approval of other similar treatments in this class soon. CMS has raised important questions about the available evidence on mAbs for AD, and in particular about the effectiveness of aducanumab, in its proposed determination that there is not sufficient evidence to support a reasonable and necessary coverage determination for Medicare beneficiaries with MCI and early-stage AD. We agree that there are important evidentiary questions about this evidence, and we appreciate CMS’s commitment to a thorough review of comments about this evidence and how to act on it and help augment it.

^j CMS called a MEDCAC meeting within the context of the Pharmacogenetic Testing for Warfarin Response (CAG-00400N), although the MEDCAC meeting did not pertain specifically to the issue of the specific CED. Instead, CMS hosted a MEDCAC meeting to address the broader question of what might qualify as appropriate evidentiary standards for diagnostic genetic tests.

^k This was the case in the reconsideration of the TAVR CED (CAG-00430R) in which a MEDCAC was requested to consider hospital and operator requirements for performing a TAVR procedure.

CMS should recognize that evidence on this class of treatments will evolve in the coming year, with expected clinical trial reports involving multiple AD mAb therapies. In addition to considering this substantial emerging evidence on the safety and effectiveness of mAbs, we commend CMS for its interest in ensuring that diversity and equity are a core focus of further evidence development. However, we also recognize the practical and ethical challenges of RCTs once pivotal trials have concluded, including patient willingness to participate and difficulties enrolling diverse populations. CMS should consider past CED precedent and the tools at its disposal for implementing differential CED options as needed beyond evidence from the RCTs. Using a CED framework that focuses efforts on efficient ways to develop key postmarket evidence without excessive access restrictions, CMS can play an important role in promoting needed data collection and analysis related to AD, including consistent use of meaningful measures related to functional outcomes, quality of life, independence, use of supportive care, and complications.

This coverage decision is part of discussions and debates around accelerated approvals, breakthrough therapies, and coverage for truly novel technologies, highlighting the need for increased collaboration among stakeholders in the approval to coverage process. This situation serves as a further reminder that CMS needs updated resources and authorities to help anticipate and manage the coverage and postmarket evidence needs that arise as a result of the successes of accelerated and breakthrough approvals. The increasing pace of development of technologies with potential long-term benefits, including by working “upstream” to slow disease progression over time, presents opportunities for learning more and creating more value from such products after approval.

We hope that the final CMS coverage decision will be an important step toward advancing learning systems of healthcare and comprehensive care models, which promote greater care coordination, promote greater evidence development, better patient and disease management, and mitigate barriers to access to care. Ultimately, any coverage decision should help patients, clinicians, and caregivers get the information and care systems to make the best treatment decisions for their needs.

Opinions differ greatly about what CMS should include in its final decision. But all stakeholder groups show a deep commitment to use this opportunity to improve evidence and care for all Americans touched by AD. The Duke-Margolis Center and our colleagues appreciate CMS’s consideration of our comments.

Sincerely,

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³⁴ “NCA - Transcatheter Aortic Valve Replacement (TAVR) (CAG-00430R) - Decision Memo,” CMS Medicare Coverage Database, 2019, <https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=293&bc=ACAAAAAAQAAA>.

³⁵ “NCA - Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers (CAG-00451N) - Decision Memo,” CMS Medicare Coverage Database, 2019, <https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&ncaid=291>.

Appendix

Table 1: Ongoing Clinical Trials of mAb Treatments for AD

Product	FDA Clinical Trial	Safety and Efficacy Endpoints	Surrogate Endpoint	Expected Timeline(s)	Relevant Sources
Aducanumab	“221AD301 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer’s Disease (ENGAGE),” Phase 3, NCT02477800; “221AD302 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer’s Disease (EMERGE),” Phase 3, NCT02484547	Primary: CDR-SB Secondary: MMSE, ADAS-Cog13, ADCS-ADL-MCI	Amyloid plaque reduction	FDA Approval: June 7, 2021	https://clinicaltrials.gov/ct2/show/NCT02477800 ; https://clinicaltrials.gov/ct2/show/NCT02484547
	“A Study to Evaluate Safety and Tolerability of Aducanumab in Participants With Alzheimer’s Disease Who Had Previously Participated in the Aducanumab Studies 221AD103, 221AD301, 221AD302 and 221AD205,” Phase 3b, NCT04241068	Safety Endpoints: Number of participants with AEs and SAEs, AEs leading to treatment discontinuation, ARIA-E, ARIA-H, and presence of ADAs	N/a	Estimated study completion date: October 2023	https://clinicaltrials.gov/ct2/show/NCT04241068
	ENVISION Confirmatory Study, Phase 4, protocol submission to FDA anticipated in March 2022	Primary: CDR-SB Secondary: ADAS-Cog13, ADCS-ADL-MCI, iADRS, MMSE, NPI-10	N/a	Estimated primary completion date: around 2023 (18 months after initiation); Study completion date: around 2026 (4 years after initiation)	https://investor.s.biogen.com/news-releases/news-release-details/update-phase-4-envision-confirmatory-study-aduhelmr
Donanemab	“A Study of Donanemab (LY3002813) in Participants With Early Alzheimer’s Disease (TRAILBLAZER-ALZ 2),” Phase 3, NCT04437511	Primary: iADRS Secondary: MMSE, ADAS-Cog13, CDR-SB, ADCS-iADL, amyloid and tau plaque deposition, change in brain volume, serum concentration of donanemab, presence of ADAs (Safety cohort endpoints not published)	Amyloid and tau plaque reduction & complete clearance	Estimated primary completion date: February 2023; Study completion: December 2023	https://clinicaltrials.gov/ct2/show/NCT04437511

	<p>"A Donanemab (LY3002813) Prevention Study in Participants With Alzheimer's Disease (TRAILBLAZER-ALZ 3)," Phase 3, NCT05026866</p>	<p><u>Primary</u>: CDR-GS <u>Secondary</u>: ISTL, CPAL, iDSSTm, Category Fluency, FNAME, BPS-O, CBB, CDR-SB, CFI, MoCA, serum concentration of donanemab, presence of ADAs</p>	N/a	<p>Estimated primary completion date: September 2027; Study completion: November 2027</p>	<p>https://clinicaltrials.gov/ct2/show/NCT05026866</p>
	<p>"A Study of Donanemab (LY3002813) Compared With Aducanumab in Participants With Early Symptomatic Alzheimer's Disease (TRAILBLAZER-ALZ 4)," Phase 3, NCT05108922</p>	<p><u>Primary</u>: Percentage of participants who reach complete amyloid plaque clearance <u>Secondary</u>: mean absolute change and percent change amyloid plaque, time to reach complete amyloid plaque clearance</p>	Amyloid plaque reduction & complete clearance	<p>Estimated primary completion date: June 2022; Study completion: June 2023</p>	<p>https://clinicaltrials.gov/ct2/show/NCT05108922</p>
Lecanemab	<p>"A Study to Confirm Safety and Efficacy of Lecanemab in Participants With Early Alzheimer's Disease (Clarity AD)," Phase 3, NCT03887455</p>	<p><u>Primary</u>: CDR-SB (core study and extension phase) <u>Extension Phase (safety)</u>: Number of participants with AEs, clinically significant change in vital signs values, abnormal MRI and ECG values, clinically significant findings in laboratory values, positive ADAs, and suicidality <u>Secondary</u>: Amyloid PET SUVR composite, ADCOMS; ADAS-cog14</p>	Amyloid plaque reduction	<p>Estimated primary completion date: September 2022; Study completion: 2024</p>	<p>https://clinicaltrials.gov/ct2/show/NCT03887455</p>
Gantenerumab	<p>"Efficacy and Safety Study of Gantenerumab in Participants With Early Alzheimer's Disease (AD)," Phase 3, NCT03444870</p>	<p><u>Primary</u>: CDR-SB; <u>Secondary</u>: MMSE, ADAS-Cog11, ADAS-Cog13, Verbal Fluency Task Score, FAQ, ADCS-ADL, percentage with AEs, change in Columbia-Suicide Severity Rating Scale score, percentage of participants with ARIA-E and ARIA-H, injection-site reactions, ADAs, amyloid and tau load, CSF marker of disease</p>	Amyloid and tau plaque reduction	<p>Estimated primary completion date: September 2022; Study completion: October 2026</p>	<p>https://clinicaltrials.gov/ct2/show/NCT03444870</p>
	<p>"A Study to Evaluate the Safety, Tolerability, and Efficacy of Long-term Gantenerumab Administration in Participants With Alzheimer's Disease (AD)," Phase 3, NCT04374253</p>	<p><u>Primary</u>: Percentage of participants with AEs, SAEs, change in Columbia-Suicide Severity Rating Scale score, percentage of participants with ARIA-E and ARIA-H, injection-site reactions <u>Secondary</u>: CDR, MMSE, ADAS-Cog11, ADAS-Cog13, Verbal Fluency Task Score, FAQ, ADCS-ADL, ADAs</p>	N/a	<p>Estimated primary completion date: October 2024; Study completion: December 2024</p>	<p>https://clinicaltrials.gov/ct2/show/NCT04374253</p>

Notes:

1. Acronyms in the “Safety and Efficacy Endpoints” column:

Instruments:

- ADAS-Cog11 and ADAS-Cog13: The Alzheimer’s Disease Assessment Scale–Cognitive Subscale (11- and 13-item versions)
- ADCOMS: Alzheimer’s disease composite score (see Note 2)
- ADCS-ADL-MCI: Alzheimer’s Disease Cooperative Study-Activities of Daily Living (ADL) in patients with Mild Cognitive Impairment (MCI)
- ADCS-iADL: Alzheimer’s Disease Cooperative Study-Integrated Activities of Daily Living
- BPS-O: Behavioral Pattern Separation-Object test
- CBB: Cogstate Brief Battery
- CDR-SB and GS: Clinical Dementia Rating scale Sum of Boxes and Global Score
- CFI: Cognitive Function Index
- CPAL: Continuous Paired Associate Learning
- FAQ: Functional Activities Questionnaire
- FNAME: Face Name Association Test
- iADRS: Integrated Alzheimer’s Disease Rating Scale (see Note 3)
- IDSSTm: International Daily Symbol Substitution Test-Medicines
- MMSE: Mini-Mental State Examination
- MoCA: Montreal Cognitive Assessment
- NPI-10: Neuropsychiatric Inventory-10 items/domains

Other:

- ADAs: Anti-drug antibodies
 - AEs, SAEs: Adverse events, severe adverse events
 - ARIA-E and H: Amyloid-Related Imaging Abnormalities-Edema and Haemosiderin
 - ECG: Electrocardiogram
 - CSF: Cerebrospinal Fluid
 - MRI: Magnetic resonance imaging
 - PET SUVR: Positron Emission Tomography (PET) Standardized Uptake Value Ratio
2. ADCOMS consists of 4 ADAS-Cog subscale items, 2 MMSE items, and all 6 CDR-SB items: Jinping Wang et al., “ADCOMS: A Composite Clinical Outcome for Prodromal Alzheimer’s Disease Trials,” *Journal of Neurology, Neurosurgery, and Psychiatry* 87, no. 9 (September 2016): 993–99, <https://doi.org/10.1136/jnnp-2015-312383>.
3. The iADRS score is a composite of ADAS-Cog13 and the ADCS-iADL: A.M. Wessels et al., “A Combined Measure of Cognition and Function for Clinical Trials: The Integrated Alzheimer’s Disease Rating Scale (IADRS),” *The Journal of Prevention of Alzheimer’s Disease* 2, no. 4 (December 1, 2015): 227–41, <https://doi.org/10.14283/jpad.2015.82>.

Table 2: Relevant Past CED Proposed and Final Decisions

Product or Treatment	Proposed Coverage Decision	Final Coverage Decision	Reasons for Changing or for Maintaining Proposed Decision
Percutaneous left atrial appendage closure (LAAC) for non-valvular atrial fibrillation (CAG-00445N)	RCTs, with any non-RCTs needing to compare non-interventional controls of OAC therapy to answer additional research questions.	Coverage in cases where patients fit certain criteria and when hospitals are participating in a registry to collect information four years following procedure.	<ul style="list-style-type: none"> Removed registry control arm after receiving comments from providers that it would be difficult. Registry would better reflect disease burden across populations.
CAR-T Cell Therapy for Cancers (CAG-00451N)	CMS-approved clinical studies or prospective registries for FDA-approved indications	Coverage when administered at healthcare facilities enrolled in the FDA risk evaluation and mitigation strategies	<ul style="list-style-type: none"> Promise of upcoming FDA postmarket studies to supplement evidence For patients for whom CAR-T might be a treatment of last resort, there was enough evidence to show promising impact on health outcomes.
Leadless Pacemakers (CAG-00448N)	Coverage for FDA-approved clinical research studies	Coverage for FDA-approved studies, in addition to prospective longitudinal studies for devices with an ongoing or completed post-approval study.	<ul style="list-style-type: none"> Expanded proposed decision to include prospective longitudinal studies to address concerns about equitable access to the new technology. Because CMS was mostly concerned with long-term longevity and device durability, longitudinal studies were a promising option.
Percutaneous Image-guided Lumbar Decompression for Lumbar Spinal Stenosis (CAG-00433R)	Clinical trials (conducted by previous study sponsors who had conducted RCTs) with prospective cohort studies.	Prospective, longitudinal studies	<ul style="list-style-type: none"> CMS decided to cover prospective longitudinal studies after one RCT completion during the previous CED period showed promise of health improvements. Endpoints were not strong enough to prove clinical benefit in the long-term, partially because the disease pathway and symptoms are not fully understood.
Vagus Nerve Stimulation (VNS) for Treatment Resistant Depression (CAG-00313R2)	CMS-approved, double-blind, randomized, placebo-controlled trials	CMS-approved, double-blind, randomized, placebo-controlled trials. Possibility of prospective, longitudinal studies for existing RCT completion with positive findings	<ul style="list-style-type: none"> Not enough evidence on effectiveness, with evidence that traditional treatments could still successfully ameliorate symptoms. Saw a need to minimize bias in studies. Offered potential reporting measures and explanation that “positive findings” meant depression remission based on depression scales used in APA Practice Guidelines.
Autologous Platelet-rich Plasma (CAG-00190R3)	RCT	Prospective studies with comparison arm	<ul style="list-style-type: none"> Previous trials and studies were based on different preparation, concentration, and quantity of product, so registry data

			<p>alone would not have helped to control for a standard of care.</p> <ul style="list-style-type: none"> • One-third of public comments were not in favor of RCT design.
Allogeneic Hematopoietic Stem Cell Transplant for Multiple Myeloma; Myelofibrosis; Sickle Cell Disease (CAG-00444R)	Prospective clinical studies with concurrent non-transplanted controls	Prospective clinical study, with the possibility that alternative designs could be proposed, including retrospective controls	<ul style="list-style-type: none"> • Safety implications led CMS to a CED framework. • Recognized trials with control arm might be too challenging, but still required a comparison arm to ensure data on the benefit of stem cell transplants.
Pharmacogenomic Testing for Warfarin Response (CAG-00400N)	RCT	RCT	<ul style="list-style-type: none"> • Although acknowledged that the tests work as intended, there was insufficient data to demonstrate how tests improved health outcomes for Medicare beneficiaries. • No clear impact on care management or treatment plan in a way that improved health outcomes.
Extracorporeal Photopheresis for Bronchiolitis Obliterans Syndrome following Lung Transplant (CAG-00324R2)	Prospective clinical research studies	Prospective clinical research studies	<ul style="list-style-type: none"> • Past studies were mostly retrospective, thus not providing the most rigorous evidence on effectiveness. • Lack of a strong, standardized approach to therapy. • Implemented a two-stage proposed CED expiration process for clinical trials to submit for coverage.
Transcatheter Aortic Valve Replacement (2019) (CAG-00430R)	Registry, expectations for providers, site of service, and patient criteria	Registry, expectations for providers, site of service, and patient criteria	<ul style="list-style-type: none"> • Conflicting evidence regarding disparities in patients of different genders. • Recommended use of a new all-women registry. • Evidence gaps remain about overall impact of TAVR in real-world settings.
Transcatheter Edge-to-Edge Repair (2021) (CAG-00438R)	Registry, expectations for providers, site of service, and patient criteria	Registry, expectations for providers, site of service, and patient criteria	<ul style="list-style-type: none"> • Sufficient evidence of improvements in carefully selected patients who meet certain criteria. • Still evidentiary gaps in appropriate site of service & provider experience, and in real-world settings. • NCD expires 10 years from effective date if not reconsidered.

Notes:

Sources and further information about these CED decisions can be found at:

<https://www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development>