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Alzheimer's Disease Monoclonal Antibodies with Traditional Approval:
Clarifying the Pathway for Medicare Postmarket Evidence Development and Use

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EXECUTIVE SUMMARY

Evidence on the safety and efficacy of Alzheimer's disease (AD) amyloid-targeting monoclonal antibodies (mAbs) has continued to emerge through pivotal randomized control trials (RCTs). However, with at least two mAb treatments potentially reaching traditional approval by the Food and Drug Administration (FDA) based on clinical endpoints, questions remain about additional evidence from postmarket settings that could help ensure these treatments' safe and appropriate real-world use for Medicare beneficiaries and the best ways to advance such evidence in the context of Medicare coverage.

According to the Centers for Medicare & Medicaid (CMS) final National Coverage Determination (NCD) issued in 2022, Medicare will cover mAbs that have received traditional FDA approval based on clinical endpoints under coverage with evidence development (CED) through prospective comparative studies. But the extent of the postmarket evidence requirements for coverage and the infrastructure available to support evidence development is unclear, adding urgency to questions about what steps can be taken now to enable evidence development while supporting appropriate access to these products under Medicare's coverage standards. Most stakeholders support the goals of better data collection and evidence generation on AD mAbs without imposing excessive costs or other burdens that could inappropriately limit access to treatment. There is less consensus on how best to achieve these goals.

Reflecting recent analysis and stakeholder convenings, this paper explores options to conduct evidence generation for AD mAbs in the most efficient and least burdensome way to answer key questions that may plausibly remain after their traditional FDA approval. In contrast to "pivotal" RCTs conducted prior to approval to clearly answer questions about a medical product's effectiveness and safety in a cohort of enrolled patients who are randomized under carefully controlled conditions, real-world evidence (RWE) methods focus on community-based contexts of care delivery. The methods are complementary in that the former is designed for determining causal relationships using rigorous data collection and randomization, while the latter can provide evidence on generalizability to patient groups and circumstances that are less feasible to study using traditional RCT methods–e.g., to understand experiences of different types of patients in their usual settings of care over the duration of their disease.

For example, data on rates of serious safety events associated with AD mAb use in different types of patients in community practices are relatively less burdensome to collect on a broad scale, and often can be captured through claims data. With additional progress in the coming months and years, CMS-supported updates to electronic health records (EHRs) could facilitate reporting of key clinical data elements that providers would be expected to track according to the AD mAbs' label.

However, it is typically more difficult to develop matched comparison groups, especially without randomization, potentially raising questions about whether associations of outcomes with treatment use actually represent causal relationships. In addition, real-world data may be missing or unreliable in ways

that introduce "noise" or bias. Current challenges in AD RWE generation include the lack of routine, consistent administration of cognitive function testing and lack of documentation of results in actual practice outside of clinical trials, as well as the limited collection in clinical practice of validated outcome measures used in clinical trials. These factors create concerns not only about the availability of data but also about the comprehensiveness of community-based care for patients with AD who will consider using newly approved mAbs.

Recognizing the limitations in the existing evidence-generation infrastructure for AD mAbs, this paper describes two potential registry approaches for AD mAb CED. The first is a large-scale registry that includes all Medicare beneficiaries eligible for mAbs but specifies relatively few data elements, for example not requiring extensive reporting on cognitive and functional status due to the insufficient infrastructure to do so in broad clinical practice. The second registry option would provide for more extensive data collection with richer data elements, such as important cognitive and functional outcome measures, for both treated patients and similar non-treated patients. But such data collection would realistically be more limited in terms of participating sites since many practices are not currently equipped to provide such reliable, longitudinal clinical data. With a focused effort, enough sites might be able to participate in developing additional needed evidence for Medicare subpopulations in a reasonable time period. Relevant initiatives are underway now to develop such evidence and could potentially be supported and expanded outside of CED.

As the existing infrastructure is mostly limited to claims-based collection and analysis, CMS could prioritize additional steps through a stakeholder process (e.g., notice and comment of a proposed path to expanding data collection) in the coming months to broaden this infrastructure while further clarifying the three CED questions and identifying ways to support their resolution. Such steps are described throughout this report and include engagement to address the important evidence questions that may have already been answered by the full evidence package leading to traditional approval; important further questions that can reliably be answered by a broad registry; support for existing and planned RWE systems for addressing questions that require more clinical data; identifying and promoting ways to increase the feasibility of and reduce the burden for comprehensive data collection; and in the meantime, placing appropriate coverage requirements and restrictions given the available evidence.

In particular, payers consider the strength of available evidence to make coverage decisions regarding the appropriate populations (patient selection), providers, and sites of service, and may initially restrict coverage based on available evidence relevant to these concerns. Indeed, the "reasonable and necessary" coverage standard for Medicare requires consideration of whether the treatment is as safe and effective as alternative approaches for beneficiaries that might be covered, which potentially includes diverse beneficiaries receiving care in a wide range of settings.

In the case of AD mAbs, CMS and other payers, such as the Veterans Administration (VA), have raised concerns about current gaps in the available evidence. For example, initial mAb coverage at the VA includes significant restrictions reflecting major patient subgroups and care settings where the available evidence on the risk-benefit profile is currently less favorable or less clear. Further evidence and patient experience developed through other, non-CED means would lead to updates on these restrictions over time and would encourage the development of more evidence. Even in the absence of a broad CED requirement, CMS could pay for mAb treatment in additional registries or trials involving Medicare beneficiaries and settings where evidence gaps exist. We describe opportunities to support an effective RWE infrastructure to accelerate that process.

This analysis leads to three policy options, detailed below, for CMS coverage and ongoing evidence development while providing appropriate evidence-based access to AD mAbs after traditional FDA approval. The options include: 1) eliminate CED for a fully-approved drug that meets "reasonable and necessary" standards for some Medicare populations, but impose coverage requirements and restrictions where the standard is not yet met, while evidence develops outside of CED; 2) implement

CED but through a limited registry that includes a few critical data elements that are feasible to collect reliably; or 3) implement CED through a differential data collection structure, with limited requirements beyond claims at many sites that meet "reasonable and necessary" requirements, and support more sophisticated evidence development at a subset of sites with greater capabilities. We describe steps that CMS and other stakeholders can take in advance of a potential FDA approval to make it easier to implement these options, mitigate uncertainty, and create a more robust foundation for developing AD evidence and improving AD care.

Coverage and Evidence Development for AD mAbs Receiving Traditional FDA Approval: Three Recommended Approaches

1. Eliminate CED but impose "reasonable and necessary" coverage requirements and restrictions while evidence outside CED improves—

CMS would not implement any mandatory data collection requirements in conjunction with coverage, however, certain subgroups and care settings with limited existing evidence may be excluded from coverage. That is, CMS could impose requirements and restrictions on providers and sites of care to assure the "reasonable and necessary" use of the mAbs for beneficiaries and settings where the preapproval evidence demonstrates a favorable risk-benefit profile. CMS would encourage the development of additional evidence and experience through non-CED means to revise the coverage decision at a later point after the relevant evidence improves for additional prescribing conditions and clinical subgroups.

2. Implement CED but through a limited registry that includes few data elements—

Implementing CED through broad scale but limited data collection will help address evidence gaps related to safety events and use across demographic groups, but not effectiveness related to cognitive and functional status, or differences across important clinical subgroups. The success of this approach would benefit from further steps to support routine, reliable data collection with limited administrative burden, and support for timely analysis of such data. Along with a set of reasonable provider and site requirements, evidence on other questions will need to be developed through other means.

3. Implement CED with differential data collection requirements—

CMS would seek to support additional data collection and analysis for providers with greater capabilities to produce and analyze more robust data, such as those typically included in prospective clinical registries. This approach would potentially imply broader coverage of additional groups of beneficiaries at such sites.

INTRODUCTION

The Centers for Medicare and Medicaid Services (CMS) plans to provide "same-day" coverage through registry-based studies under Coverage with Evidence Development (CED) to AD mAbs receiving traditional FDA approval. However, the pathway to feasible evidence generation for these products alongside appropriate access for eligible beneficiaries is not yet clear. Significant evidence based on the pivotal trial data and other sources will be available on the CMS CED questions if a mAb receives traditional approval. While the complete evidence package will not be available until and unless a new treatment is fully approved, it would presumably include clear evidence on slowing the decline in cognitive function across patients and sites included in the pivotal trials. However, as CMS and others have noted, additional evidence on these questions beyond that available at the time of approval would be helpful to further inform clinical decisions for diverse Medicare beneficiaries and care settings, and may be relevant to CMS decisions about CED, or could potentially be addressed through alternative mechanisms.

Registries or alternative adequately powered postmarket evidence platforms with reliable, feasible data collection can be costly and take time to implement at scale. To assure that postmarket data collection addresses important remaining questions about these treatments, and that patient access reflects the state of the available evidence, additional clarity is needed as soon as possible regarding the evidentiary gaps that will likely persist at the time of traditional FDA approval and the best way to facilitate sufficient data collection to address these gaps without excessive burden and with appropriate beneficiary access. This report aims to anticipate the most important evidence gaps and challenges to addressing them that are likely to remain at full approval, and the steps that CMS and other groups can take now to minimize delays and other complications for appropriate access, either through CED or other mechanisms. The report is intended to encourage further advance planning and collaboration to address these issues.

Background—FDA Approvals and CMS's Coverage Decision for AD mAbs

In June 2021, the Food and Drug Administration (FDA) approved Aduhelm (aducanumab) for the treatment of AD using the accelerated approval pathway based on a surrogate endpoint (in this case, reducing beta-amyloid plaques in the brain),[1] signaling the first of an emerging class of AD mAb treatments that target beta-amyloid plaques.

In April 2022, CMS issued its final coverage decision for mAbs for patients with a clinical diagnosis of mild cognitive impairment (MCI) due to AD or mild AD dementia. Based on the available evidence at the time, CMS determined that the clinical benefits of the mAbs are not yet shown to outweigh the potential harms for Medicare beneficiaries, and that evidence supporting mAb treatment does not meet the "reasonable and necessary" threshold for broad Medicare coverage. Rather than denying coverage for this class of drugs, CMS stated that it would provide coverage under a CED framework. Under the decision, individual AD mAbs will have variable coverage and data collection requirements based on the type and level of evidence available at the time of approval, as follows:

- CMS requires a CED framework **limited to RCTs for AD mAbs that are approved by FDA based upon evidence of efficacy from a change in a surrogate endpoint** (e.g., amyloid reduction) considered as reasonably likely to predict clinical benefit. Thus, all mAb products that receive FDA approval through the accelerated approval pathway based on beta-amyloid reduction as a surrogate endpoint (including the current status of aducanumab and lecanemab) will only be covered through RCTs. This could potentially change if additional evidence accumulates to more fully validate beta-amyloid reduction as a surrogate endpoint. Coverage for accelerated approval products is not the focus of this paper, which discusses mAbs that may receive traditional FDA approval and thus have an alternative CMS coverage option.
- CMS will provide coverage **through CMS-approved prospective comparative studies for AD mAbs that demonstrated evidence of efficacy from a direct—not surrogate—measure of clinical benefit.** This is a revision of CMS's stance in the proposed coverage decision, which did not differentiate between accelerated and traditional approvals, and thus required coverage limited to RCTs for all AD mAbs. In response to comments, CMS acknowledged that phase 3 trials for AD mAbs may support developing clear evidence on the effectiveness of the individual mAb treatment and that different mAbs in the pipeline may have distinct

mechanisms of action and different safety and effectiveness profiles. The distinctions between the various mAb products and the differences in the strength of the evidence in the initial, successful trial(s) leading to FDA's approval will inform the required rigor and detail of the CED study design:

1. High level of evidence with few or no deficiencies and findings generalizable to the broad Medicare population could warrant a reconsideration for full coverage;
2. Moderate level of evidence would require prospective comparative studies (such as a registry with a comparator) to answer the CED questions (below);
3. Low level of evidence would require a pragmatic trial (randomized with a comparator) to answer the CED questions (below).

The "reasonable and necessary" threshold will be met for broad coverage outside of CED if sufficient evidence is developed to answer the following three questions:

- Does the anti-amyloid mAb meaningfully improve health outcomes (i.e., slow the decline of cognition and function) for patients in broad community practice?
- Do benefits and harms (such as brain hemorrhage and edema) associated with use of the anti-amyloid mAb, depend on characteristics of patients, treating clinicians, and settings?
- How do the benefits and harms change over time?

In January 2023, the FDA approved Leqembi (lecanemab) using the accelerated approval pathway, based on the drug's phase 2 results. Leqembi's manufacturer has submitted the drug's pivotal phase 3 results to the FDA to confirm the drug's benefit and secure traditional approval, and an FDA decision is expected on or before July 6, 2023. Another AD mAb, donanemab, is expected to publish its phase 3 study readout later this year and apply for traditional FDA approval after its application for accelerated approval was denied by FDA in January 2023 because of the insufficient number of patients who received the drug for a minimum of 12 months.[2] **Table 1** provides information on emerging mAb treatments that have either concluded their phase 3 trials or will soon publish readouts. There are additional AD mAbs directed against amyloid in earlier stages of product development, and many other AD therapies in development, making any Medicare coverage action potentially applicable to a broader range of therapies.[3]

TABLE 1 Summary of Emerging AD mAbs and Timing

Product	Pivotal Trial Readouts	Accelerated Approval	Potential Traditional Approval	Safety and Efficacy Data to Date
Lecanemab	November 2022	January 2023	As early as Q2 2023	• The phase 3 trial, CLARITY-AD, showed a 27% slowing of decline--a 0·45-point difference on the CDR-SB compared to placebo; All key secondary endpoints were met, each evaluated by change from baseline at 18 months; • ARIA occurred in 21% of the lecanemab group and most cases were asymptomatic or temporary. ARIA was more common in ApoE4 carriers; • Some questions remain regarding the use of anticoagulants while taking the drug and different rates of ARIA in subgroups.
Donanemab	May 2023	Denied in January 2023	As early as Q4 2023	• The phase 3 trial, TRAILBLAZER-ALZ 2 topline results showed 35% slowing of decline in the iADRS score (primary endpoint) and 36% slowing of decline in the CDR-SB scale (secondary endpoint) over 18 months; • In addition to amyloid plaque, patients were also included in the trial based on the presence of medium to high levels of tau (those with medium level did better on the various AD scales); • ARIA-E occurred in 24% of treated participants, with 6.1% experiencing symptomatic ARIA-E. ARIA-H occurred in 31.4% of the donanemab group (with two related deaths) and 13.6% in the placebo group.

While the level of evidence on these questions for a specific AD mAb will not be known until FDA's final approval decision and the supporting data are published, it is clear that important aspects of these questions will not be fully resolved with the evidence available at the time of approval. Indeed, many aspects are not feasible to fully address within the scope of FDA-approved pivotal trials or other premarket evidence. These include questions relevant to the Medicare population about long-term outcomes and treatment-related differences across population subgroups. Addressing such questions would require larger-scale and longitudinal data collection, with broader participation of important subgroups of Medicare beneficiaries, enhancing the evidence on diverse patient subpopulations and practice settings compared to what has been feasible using RCTs.[4]

We note that stakeholders have differed on whether the evidence at traditional approval is sufficiently high for coverage without CED requirements. This primarily involves a disagreement over whether a fully approved AD mAb confers a clinical benefit that, while sufficient for FDA approval, is meaningful enough to meet Medicare coverage standards. The goal of this report is not to fully resolve this particular question, but to determine what kinds of questions are likely to remain after traditional evidence supporting traditional approval is released, where further evidence development is feasible to improve clinician and beneficiary care decisions and thus outcomes, and how alternatives to CED, as well as CED, would address these issues. Importantly, this assessment could help CMS and stakeholders anticipate and take steps in advance to avoid potential delays associated with the CMS determination of whether the evidence at traditional approval meets a particular level established in the coverage decision (low, moderate, high), and to assure that the size, scope, and duration of any postmarket data collection is as efficient and non-burdensome as possible.

Below we highlight key areas where CMS and other groups could help advance evidence development and evidence-based patient access, to inform the most effective and efficient coverage approach for any fully-approved AD mAb. We first describe considerations related to CMS' key evidence questions for coverage, and then turn to prescriber and site-of-care capabilities. Based on these considerations, we describe options for accelerating the development of additional evidence while providing coverage that meets "reasonable and necessary" standards.

Matching CMS Key Evidence Questions to Necessary Evidence Generation Capabilities

CMS created a pathway to full coverage for a particular AD mAb if the CMS-approved study addresses its three CED questions with sufficient evidence or if the evidence supporting traditional FDA approval is "high," requiring that the findings are stable and the conclusions are generalizable to broad community treatment of Medicare beneficiaries. But without any AD mAbs with traditional FDA approval to provide a basis for implementing the National Coverage Determination (NCD), the evidence needed to answer the three CED questions adequately to potentially eliminate the need for CED is not yet clear–and neither is there a clear path to developing that evidence.

CMS has typically framed CED in terms of enabling broader access than might be possible in the absence of such evidence generation. We consequently consider what might happen if there is sufficient evidence that a particular mAb is "reasonable and necessary" for some or many groups of beneficiaries, prescribers, and settings but not all—for example, patients who appeared to experience significant AD slowing benefits treated in clinical settings that are able to monitor closely for safety issues, or for whom safety risks are lower or better understood.

To plan for the necessary evidence development to answer CMS's three CED questions, we break down these questions into sub-questions with additional detail on the evidence needed to answer them:

1. **Does the anti-amyloid mAb meaningfully improve health outcomes (i.e., slow the decline of cognition and function) for patients in broad community practice?** This basic question accompanies most drug approvals involving Medicare beneficiaries: was the benefit shown in the pivotal trial(s) demonstrated in the general Medicare population, and is there insufficient evidence for any major types of Medicare beneficiaries? The question can be further broken down into the following areas:

- *Is FDA's **determination of clinical benefit** as part of its determination of safety and effectiveness (supporting traditional approval) **sufficient for coverage,** based on the populations and care settings studied in the pivotal trials?* Some stakeholders have concerns that CMS may not deem studies meeting the FDA-supported primary endpoints as demonstrating a meaningful clinical benefit.[5] To avoid this uncertainty, CMS could clarify what additional endpoints or magnitude of treatment effect would be required to show a meaningfully improved health outcome. There are certainly outstanding questions on an AD mAb benefit that will not be fully resolved in premarket studies–for example, the extent to which the cognitive benefits lead to improved outcomes related to independence and activities of daily living, and for how long. However, these questions may also not be easily addressable through postmarket observational studies as envisioned in the NCD. Observational comparisons between treated and untreated patients have methodologic limitations in terms of what additional conclusions can be reached about effectiveness, since the treatment effects may be small relative to the potentially unmeasured patient, care, and environmental factors that also influence the course of dementia. Without sophisticated study design and data collection methods, registries could easily be biased by patient- or treatment-related factors that are difficult to measure and not balanced between treated and untreated groups.
- *Are there likely to be important remaining questions about improvements in health outcomes (slowed decline of cognition and function) in **subgroups of beneficiaries and different types of clinical practice settings** (different settings within "broad community practice" where beneficiaries might receive treatment) that **were not represented adequately in pre-approval trials,** and where benefit-risk profiles could plausibly differ?* A clinical trial is not representative of distinct patient groups excluded from the trial (e.g., patients with recent hemorrhagic events or on other immunologic therapies). Such patient groups would benefit from additional evidence development, as would patient subgroups that we describe in the next category. Larger scale, longitudinal data collection on such patient groups is possible with an adequate postmarket clinical evidence infrastructure and could answer important questions about differences in outcomes across such excluded or insufficiently represented patient groups and sites of care, and has been an objective of prior CED activities mainly involving medical devices. Further CMS guidance on such subgroups, and further steps by stakeholders to develop such evidence, would help clarify needs and then speed the development of postmarket evidence.

2. **Do benefits, and harms such as brain hemorrhage and edema, associated with use of the anti-amyloid mAb, depend on characteristics of patients, treating clinicians, and settings?** As RCTs are often difficult and costly to perform in diverse settings with adequate samples of particular patient subgroups to be powered to detect potential differences, large "real world" data science efforts have been increasingly used to refine evidence on particular groups of patients after product approvals. This question addresses:
   - *Is there evidence of significant differences in outcomes (slowed cognitive decline, serious adverse events caused by treatment), or clear reasons to suspect such differences, across **significant subgroups of Medicare beneficiaries,** based on clinical characteristics (e.g., coagulation disorders, complex circulatory conditions, certain gene carriers such as ApoE4 and multiple comorbidities), or **demographic characteristics** (e.g., race, ethnicity, age, socioeconomic and urban vs. rural status)?* There may be subgroups of Medicare beneficiaries for whom the benefit-risk profile for an AD mAb may plausibly not be as favorable as for other groups. For example, it is possible that higher adverse event rates may indicate a less favorable risk-benefit profile in certain subgroups, if it is not correlated with plaque reduction. Because premarket clinical trials are generally not large enough to detect important differences in risk profiles across subgroups, postmarket evidence is commonly used to address these issues. Critical to the success of such efforts is the infrastructure available to collect adequate data without substantial provider and patient burden. For this reason, such questions are often addressed through clinical registries or fit-for-purpose RWE evidence systems that typically include only some treated patients and sites. Furthermore, postmarket studies could also assess issues like the impact of alternative dosing and duration of therapy, and approaches to manage or avoid adverse events (randomization for some of these questions may also be feasible).

- *Could **certain provider types and sites of care** result in Medicare beneficiaries having different treatment outcomes?* This is another topic where RWE generation from larger populations of patients receiving care from diverse providers and settings can be helpful, and which has been addressed through prior applications of CED mainly involving medical devices.

3. **How do the benefits and harms change over time?** Evidence related to long-term health outcomes and harms cannot be fully ascertained from RCTs (in the case of AD mAb trials, duration is typically about ~18-24 months). Such long-term benefits may include delays in the ability to maintain independence and autonomy; sustained ability to perform activities of daily living; delayed institutionalization or use of in-home care; behavioral change; quality of life; caregiver impact; and long-term risks and complications. But this question also presents some challenges for postmarket evidence. For example, as noted, there are likely to be confounding factors related to the patient and their care and living environment that may impact disease progression and limit the usefulness of registries in answering questions on long-term benefits or risks. On the other hand, the association of long-term benefits and harms with patient characteristics can be assessed with RWE over time, but there must be an evidence-generation infrastructure available that is fit for purpose for addressing these particular questions about benefits and harms over time.

Potential Evidence or Coverage Issues Related to Prescriber and Site of Care Capabilities and High-Risk Groups

As reflected in the above questions, CMS has particular concerns about treatment use in practice settings with capabilities that differ from and may be more limited than those of practices that participated in the premarket RCTs. (We note that many AD mAb clinical trials aimed to enroll a broad range of treatment sites in their research protocols.) The CMS NCD did not discuss direct restrictions on prescriber and site capabilities. However, previous CMS coverage decisions, including for drugs, have included such restrictions,[6] and the NCD described safety-related considerations for the treating care centers in the final coverage decision. The NCD describes the need for a multidisciplinary dementia team and adequate clinical infrastructure to support longitudinal care; and a care team that includes clinicians with appropriate training in the assessment and staging of patients with AD and interpretation of AD biomarker results, the ability to perform lumbar punctures to assess cerebrospinal fluid (CSF)-based measures of amyloid (particularly where PET imaging is less available, such as in rural areas), assessment of treatment response and evaluation of potential adverse events, and access to radiologists and neurologists trained to diagnose ARIA. Together, these considerations imply that AD mAb administration would require substantial expertise and monitoring capabilities to assure the safety and appropriate use of the mAbs, particularly in the initial post-approval period when real-world experience is limited.

Some of the evidentiary concerns related to provider and site capabilities about AD mAb use that CMS has identified above may be addressable outside of CED, by setting clear provider and site requirements. In addition, CMS could also consider restricting coverage for certain major subgroups for which the risk-benefit profile does not appear as favorable based on existing data while evidence is generated through other, non-CED means.

FDA-approved product labels are likely to include a set of recommendations to prescribers related to appropriate screening, ongoing monitoring, and timely treatment for benefits and risks (e.g., the accelerated approval label for lecanemab includes a substantial list of warnings and safety considerations). CED data collection requires certain provider capabilities related to these label recommendations (e.g., reporting on MRI results and ARIA complications, clinical characteristics of patients, and associated treatments). But with provider and site capability requirements and restricting coverage in high-risk subgroups while the evidence develops through other means, CED may not be needed as a mechanism to assure safety through the reporting of critical data that reflects the drug's label. For example, CMS could implement appropriate use recommendations that have been developed by clinical experts[7] as a basis for prescriber

requirements, to assure a "reasonable and necessary" use of the mAbs. Initial Veterans Administration (VA) coverage of lecanemab described by the VA Pharmacy Benefits Management Services included prescriber requirements and coverage eligibility limits based on the VA's interpretation of the evidence generated in the preapproval studies.[8] Moreover, the VA's interoperable electronic record capabilities provide the foundation for forming a clinical registry akin to a CED approach to assess some of the questions identified by CMS (see **Table 2**), which reduces the costs and burdens for evidence generation relative to a Medicare CED, since Medicare providers generally have not implemented interoperable longitudinal electronic data sharing and validation for beneficiaries with AD.

Limiting Medicare coverage to prescribers who possess these capabilities would have some impact on access, just as CED requirements could. But as the NCD seemed to envision in describing potential CED questions and data requirements, those requirements could be more beneficial for patients who may face higher risks of complications. For example, vascular disease severity and intracerebral hemorrhage rates are higher in historically marginalized populations, which may lead to a higher risk of ARIA,[10] and providers in underserved communities may be less likely to have these additional capabilities to assure safe treatment. As RWE and experience with treatment accumulate, CMS would need to have a clear plan for the evidence required (within or outside of CED) to update and potentially ease such prescriber requirements and beneficiary exclusions.

If CED requirements could be implemented without significant additional costs on providers, however, additional types of beneficiaries could potentially be covered as part of the CED, to help assure that these questions are resolved. While that may not be feasible in the near term, CMS in collaboration with stakeholders could take steps to improve provider capabilities to diagnose AD, monitor for disease progression, and use and interpret imaging for adverse event monitoring. For example, CMS could promote AD support "hubs" to augment capabilities for community providers–for example, by assisting with imaging interpretation; providing tools to track disease progression, monitoring for ARIA and other potential complications; and providing guidance in case of adverse events. CMS could also extend mAb coverage to additional types of beneficiaries in these sites. Such capabilities could also be supported by a comprehensive AD alternative payment model (to include the mAbs and other important care services) that would be tested by the Center for Medicare and Medicaid Innovation (CMMI), or a quality improvement initiative for AD care supported by Medicare payments for care coordination or AD care quality improvement, as we describe below.

TABLE 2 VA Provider Requirements for AD mAbs Use and Potential Associated Evidence Generation Capabilities, February 2023

Key Provider Requirements in VA Lecanemab Criteria for Use[9]	Potential Data for Evidence Development
Board-certified neurologist, geriatric psychiatrist, or geriatrician specialized in treating dementia is required to authorize each treatment	Provider capabilities and expertise to prescribe the mAb, administer applicable functional and cognitive tests, and assess the patient for risk
Amyloid PET and/or CSF analysis consistent with AD	Screening test results
MRI scan in last 12 months	Screening test results
Functional Assessment Staging Test (FAST) Stage score of 2-4, meeting criteria for MCI or mild AD dementia	Patient baseline cognitive status and symptoms
Mini-Mental State Examination (MMSE) score > 21, or Saint Louis University Mental Status (SLUMS) score or Montreal Cognitive Assessment (MoCA) score of > 16	Patient baseline cognitive status and symptoms
Neuroradiology is available to review serial MRI scans, either at site, or through National Teleradiology	Findings on ARIA and other potential adverse events

Developing Additional Evidence Efficiently—CED or Alternative Measures

Determining a strategy to address important evidence gaps requires weighing the costs and burdens of data collection against the value of the data being collected with the associated impact on access and outcomes. CED is an important mechanism that allows CMS to provide Medicare coverage while gathering further evidence on novel technologies' impact on health outcomes, potentially expanding access while promoting the appropriate use of new technology and facilitating more effective use for Medicare beneficiaries over time. CED has played an important role in other medical product areas, particularly for advanced medical devices. Successful CED programs require support outside of CMS for an evidence-collection infrastructure aligned with the CED questions, and clear guidance on how the required data collection will successfully address those questions, providing clarity about how the need for CED can be resolved over time. At the time of this writing, there are both substantial gaps in the broad postmarket evidence infrastructure related to the CMS questions, and (as we described above) a need for greater understanding among stakeholders about what aspects of the three AD mAb CED questions are both meaningful and answerable through feasible data collection and analysis approaches. Here, we describe steps that can be taken now to develop a feasible path for successful data collection and evidence development. As we note, there are likely to be significant limitations on what will be feasible to implement as part of a broad CED requirement over the next few years.

In the face of significant hurdles to implementing an effective CED infrastructure for AD mAbs, alternative mechanisms should be considered to develop critical evidence on the questions described above, in conjunction with (non-CED) coverage requirements to assure safe use while this additional evidence accumulates.

Product developers already collaborate with companies specializing in RWE development, registries, and clinical research networks, both to address important questions related to safe prescribing and to meet FDA postmarket (Phase IV) evidence requirements. These efforts by product developers may also support additional evidence on safety and effectiveness, including for particular groups of beneficiaries. For example, long-term follow-up studies of patients in pivotal randomized trials will provide some additional evidence on long-term benefits and risks, and product developer investments in safety surveillance systems (as well as FDA's Sentinel Initiative) will provide further evidence on safety and some effectiveness issues.

The Alzheimer's Association and collaborating organizations have launched a national registry effort, the Alzheimer's National Registry for Treatment and Diagnostics (ALZ-NET), which will collect longitudinal real-world data on approved AD mAbs, including cognitive and functional outcome measures and clinical imaging. ALZ-NET will also leverage existing infrastructures, such as the multi-site longitudinal IDEAS study, and create a biorepository for samples and genetic information such as APoE4 genotype (as FDA recommended testing in lecanemab's label). ALZ-NET will also provide educational resources to participating clinics and work to assure they are aware of appropriate use guidelines and that they safely deliver the mAb treatment to patients, thereby helping to mitigate safety concerns associated with using the mAbs. The National Institute on Aging (NIA) has announced its intent to support a very large real-world data network for AD, though this effort is likely to take some time to start up.

To reflect these opportunities, we consider both CED and ex-CED pathways to develop additional important evidence, alongside coverage requirements that are linked not to data collection but to "reasonable and necessary" beneficiary, prescriber, or clinical site capabilities based on the mAb's label and appropriate use guidelines.

Least Burdensome Evidence Development to Address Important Evidence Questions After Traditional FDA Approval

It is likely that a portfolio of studies would be needed to answer the range of evidence questions associated with AD mAbs, including the three CED questions, with different study designs and data collection methodologies. To address potential biases, postmarket data collection generally needs to include reliable information on key patient characteristics that may be associated with benefit and risk for mAb treatment, as well as other important aspects of patient care and environmental factors that could confound efforts to draw conclusions from observational empirical studies. Summarized below, such data would include key patient demographic characteristics, socioeconomic characteristics or proxies (e.g., dual eligibility status, zip code), major clinical comorbidities, and measures of AD status (i.e., the extent of cognitive decline, and data supporting its attribution to AD). Data on safety-related outcomes and their course (e.g., ARIA and any associated major clinical symptoms, their severity, and resolution over time) are very important for both evidence development and patient management. Also important are data on relevant treatments and medical utilization (e.g., hospitalizations related to complications). Finally, CMS's CED framework highlights data collection related to important cognitive and functional outcomes. **Table 3** summarizes these elements.

Some RWE studies will require more comprehensive and costly data than others. For example, precise standardized data on cognition, quality of life, and functional status is currently resource-intensive to collect and has to come from patients and providers (and is likely to be confounded with other clinical and environmental factors). Most providers do not have the capabilities or resources to support such "registry grade" data collection. In the absence of validated measures that would be easier to collect reliably in routine practice, such questions may need to be addressed outside CED, or in only a subset of prescribing organizations within a CED framework, as discussed earlier.

In contrast, rates of major adverse events in community practice are less burdensome to collect on a broad scale. In particular, for many important questions related to safety and disease complications, CMS already partners with FDA and researchers to use claims data on significant adverse events and Social Security death records, and already collects some data related to provider and site capabilities. Some evidence questions may thus be addressable through claims data (e.g., rates of major adverse events across different demographic groups, duration of treatment). Claims data can also be used for some utilization-based measures of clinical care (including frequency of MRI monitoring, dosing, discontinuation of treatment, hospitalizations, and emergency department visits due to ARIA and other major adverse events) across clinic and hospital visits, thereby providing important insights into the patient journey across all care settings.

TABLE 3 Summary of Important Data Elements for Postmarket Evidence

Key Patient Characteristics	Safety-Related Outcomes	Effectiveness-Related Outcomes
Demographic information, socioeconomic characteristics or proxies, major comorbidities, measures of AD status, other relevant treatments in addition to mAb use	ARIA and any associated major clinical symptoms, their severity, and resolution over time; also, any hospitalizations related to complications or adverse events	Independently validated and previously used cognitive and functional measurement instruments, with the opportunity for CMS to promote consistent adoption in CMS-approved studies

But most of the CMS evidence topics, including those related to important clinical subgroups of patients, require at least some additional clinical data collection beyond that reliably reported in claims. One path to such evidence development would supplement claims-based data collection to include capturing electronic data that clinicians view as critical for appropriate patient care. These data could include key test results that clinicians will be expected to perform based on the drug's label, including PET and MRI scans, and potentially ApoE4 genotyping (which is not standard practice today, and not all patients may choose to take this test prior to being administered the mAb). The data might also include key diagnostic findings, clinically relevant comorbidities and risk factors, and cognitive function assessments that are feasible to gather or conduct in routine clinical practice. This evidence development path still likely requires advance planning, investment, and time for most providers to participate.

Laboratory data, electronic health records (EHR), and other national data sets can potentially be linked to augment claims-based registry data,[12] but EHRs today are not generally designed for reliable and consistent data capture that is adequate for clinical research. Sufficiently reliable data collection of some key clinical characteristics would consequently require modifying EHR systems to support data reporting and an infrastructure for managing and analyzing the data, as well as additional technical support. For example, fit-for-purpose tools could be developed to enable more straightforward and reliable capture of key clinical data elements, such as by using certain test results (e.g., imaging findings) included as United States Core Data for Interoperability (USCDI) data elements, which are embedded in EHR systems.

Other important data elements that will need to be collected for the AD mAb registry, such as key risk factors and complications from treatment, but are not included in the USCDI, could be added to USCDI+, an extension of USCDI[13] that will augment it by adding datasets for specific use cases. Specifically, CMS is one of the first two federal agencies for which USCDI+ has been launched, to help it establish and advance the use of interoperable datasets in order to meet its programmatic requirements (here, data collection for CED and assuring the quality of care of Medicare beneficiaries), thereby presenting an opportunity to include AD-specific core datasets in the USCDI+. But such reforms will take time, and USCDI implementation as part of the Promoting Interoperability[14] (formerly Meaningful Use) program has been slow. Alternatively, registries have often used websites or portals for participating clinicians in registries to enter and verify data, which requires additional clinician time and effort to assure completeness and accuracy,[15] limiting the extent of feasible data collection. CMS has also used special claims codes and modifiers for providers to report additional clinical data in specific circumstances, but this too requires time and system modifications for providers, and may not yield data that are consistent with electronic records.

While claims and routinely collected EHR data could be leveraged to answer some key evidence questions over time, such data are not currently suitable for answering questions on some functional outcomes or outcomes like caregiver burden that are not collected in routine clinical practice. Questions about effectiveness, as we have noted, will also typically have more confounding factors, many of which will be feasible to collect only in specialized research centers. Such studies are not feasible soon as part of a broad CED program that includes most providers with appropriate clinical capabilities to prescribe AD mAbs; given the incremental expected benefits for the initial mAbs, the need for more extensive data on confounders or other study methods to address potential bias is important to consider. These methods will augment and not replace the RCTs needed to generate sufficient evidence on the efficacy of AD mAbs.[16]

Table 4 describes these two types of data collection—the relatively simple registry, including augmentation of claims data with routinely collected clinical data through USCDI/USCDI+ or new codes to identify processes or outcomes that are not captured in the current codes, and a more extensive clinical research registry.

The table highlights the inherent tradeoff between collecting data broadly, which is likely to require some investment in systems modification to include even a limited set of key clinical data elements beyond existing claims and demographic data, and collecting more extensive data, which is likely to be feasible only in specialized practices with substantial data collection and registry infrastructure.

TABLE 4 Two Registry Options for CED Data Collection

#1: Registry That includes Few Data Elements But Applies Broadly	
Description and mechanism	This registry will only include relatively few data elements that are available in claims data as reported by the treated provider, making it fairly easy and straightforward to implement. This claims-based registry could be augmented to also include certain evaluations that treating clinicians may be expected to perform based on the drug's label. This latter component can be facilitated through: • The establishment of new Medicare special claims codes to enable provider reporting of key results or events (e.g., incidence of ARIA and descriptors), or: • The use of USCDI and USCDI+ datasets embedded in EHRs through CMS's Promoting Interoperability requirements in conjunction with its quality reporting systems
Data captured	• Claims-available information, including demographics, hospitalizations, emergency department visits, and associated diagnoses, death, frequency of MRI testing, frequency and discontinuation of treatment, and use of outpatient/pharmacy medications (e.g., anticoagulants) • With additional data reporting mechanisms: key supplemental information that treating clinicians would obtain as part of ordinary care as reflected in the drug's label–e.g., PET and MRI scan results, drug dosing, severity and resolution of ARIA events and whether they are symptomatic, and simple, reliable cognitive test results
Evidence questions that could be answered	• Safety event rates in demographic subgroups (and possibly a few major clinical subgroups) • Long-term safety event rates in broad real-world populations • Estimates of real-world change/stabilization of cognitive function • Prevalence of less common safety events • Differential patterns of mAb use by demographic subgroups and provider type/setting of care • Dosage and frequency of administration in real-world settings
#2: Extensive Registry with Additional Data Elements But More Limited Reach	
Description and mechanism	This option will provide for a more robust clinical research registry, collecting data elements in addition to those included in the more limited registry described above, primarily important cognitive and functional outcome measures and additional patient, treatment, and environmental confounders that could otherwise bias results of observational effectiveness studies. This more extensive data collection for CED may involve building out registries currently underway such as ALZ-NET, to generate evidence that is better suited for answering the three CED questions
Data captured	• Everything included in the simpler registry described above • More precise and detailed clinical outcome measures (cognitive, functional, behavioral, quality of life) • Archived clinical imaging • Biomarker data and biospecimen information • Confirmed comorbidities
Evidence questions that could be answered	• Those specified for the simpler registry described above • Impact of mAbs on long-term effectiveness outcomes—though observational studies have important limitations with respect to estimating treatment effects • Benefits across patient subgroups (including, racial and ethnic groups; ApoE4 gene carriers, especially homozygotes) and in various settings of care and treated by various types of clinicians • Harms across different subgroups of patients such as those with different genomic profiles, common comorbidities and taking concomitant medications, including those excluded from trials—not available as granularly through the simpler registry • Ways to avoid, detect, and manage adverse events and complications in various care settings • Consequences of discontinuation of therapy

Further work is also urgently needed to resolve challenges around outcome measurement. The NCD requires the use of independently validated and previously used cognitive and functional measurement instruments in protocols for CMS-approved CED studies. Adding such standardized cognitive and functional assessments is already feasible in some practices, and periodic assessment seems very relevant for appropriate AD patient management. But given current practice capabilities, this would create significant reporting burdens for most clinicians. The standard cognitive assessments used in some of the AD mAbs' preapproval clinical trials (e.g., CDR-SB, ADAS-Cog) are complex (and consequently require training and expertise) and time-intensive to administer and, therefore, are predominantly used in research settings rather than clinical practice. Thus, other validated instruments used as part of clinical care that capture clinically meaningful outcomes for patients and caregivers in early-stage disease and correlate with the outcome measures used in clinical trials should be considered for postmarket evidence generation in settings outside of RCTs. Importantly, there is a need for standardization of those scales so that data collection can be implemented effectively. CMS has stated their intention to work closely with investigators during the study design process to address this topic, but notable work remains to develop outcome measures appropriate for early-stage patients that both meet CMS's evidence goals and can also be applied reliably in broad and diverse care settings.

By supporting the development and consistent use of standard measures of patient cognitive and functional outcomes for use in both CED and routine clinical care as part of its quality measurement strategy, CMS can help advance evidence development and quality improvement. CMS could work with the National Quality Forum (NQF), the Agency for Healthcare Research and Quality (AHRQ), and potentially the National Institutes of Health (NIH) to reach a consensus around the most suitable standardized, usable and meaningful patient outcomes to be reported by providers who participate in the AD evidence development studies. To that end, product developers, professional societies, and other key stakeholders should propose and pilot approaches to advance such measures as soon as possible.

CMS's coverage decision also requires that when using a registry as a CMS-approved CED study, study sponsors use a comparator to enable well-matched comparisons between treated and untreated patient groups. A registry would need to collect or link demographic, clinical, and other data elements for both mAb-treated and untreated patient populations. Given the comparator requirement, assessments would need to include non-treated populations as well. This is more feasible at advanced medical centers such as the Alzheimer's Disease Research Centers (ADRCs) that already collect comprehensive data on AD patients and perform such standardized clinical evaluations to assess disease progression (and thus have long-term pre-treatment data on their patients). Such a "prospective" comparative study, in which non-treated patients will likely need to provide consent, will be easier to implement in the near term outside of a broad CED requirement.

In addition to the emerging AD registries, the Alzheimer's Association's ALZ-NET and the NIA's proposed real-world data network initiative described above, there are several existing AD registries that could be a starting point for such RWE development for AD mAbs. These include facilities that are already working with NIH-supported initiatives like the Alzheimer's Disease Neuroimaging Initiative (ADNI), and the National Alzheimer's Coordinating Center (NACC), which coordinates data collection and fosters collaborative research among 33 ADRCs at major medical institutions across the country. The ADRCs collect longitudinal uniform data sets on patients by means of standardized clinical evaluations. These facilities are well-versed in data collection related to AD patients and could feasibly add drug effects to their existing data collection standards. However, these centers may not be sufficiently representative of the nationwide Medicare population with early AD/MCI, and relying on them alone will likely not satisfy CMS's diversity requirements. One of CMS's requirements for coverage is that CMS-approved studies must have study populations "whose diversity of patients are representative of the national population with MCI due to AD or mild AD dementia." Achieving diversity is a known and substantial challenge in clinical trials but may be more feasible in large observational studies. Nonetheless, the CED data collection costs and burdens may be prohibitive for many providers outside of major medical centers.

In light of these challenges, CMS, product developers, and stakeholders could consider how to advance a long-term strategy of "differential data collection" for different sites of care based on their clinical and data reporting capabilities, making sure that critical evidence questions

can be addressed. In such a tiered data collection model, a "least-burdensome" data collection requirement that is fit-for-purpose and with a core set of data elements that could be collected by a broader range of providers (e.g., basic safety monitoring using claims data, augmented over time) could support a broadly feasible CED to assess questions with straightforward data needs (e.g., characteristics and trends of treated patient populations, frequency of serious adverse events in subgroups). This could be complemented by an enhanced data model that includes complex and richer data, with the development of outcome measures that are feasible and reliable in routine practice, implemented by more advanced centers with substantial capabilities, assisted by RWE and data science companies, and potentially including a broader range of beneficiaries. There are a number of existing and planned clinical studies that could be further developed to meet the needs of the more advanced registry models. A collaborative effort starting before approval could address the extent to which these clinical research programs could address certain key CED issues that are unlikely to be resolved at the time of approval and that are not feasible to address in routine clinical practice, either currently or in the near term with some feasible additional support. Along with clinically reasonable prescriber requirements, and a path to revising these based on further RWE development either as part of a broad and simpler CED requirement and/or through supplemental studies, this approach may enable the CED goals to be achieved faster and without burdensome disruptions in patient access.

CMS has not used such a differential data collection approach through CED before. The agency could argue that it is implicitly authorized to implement this model to ensure that the data protocols that it establishes under the CED are consistent with the objectives of the CED. It could authorize broader coverage through CED of additional population groups for providers who collect additional data to address the evidence gaps for these groups (e.g., including populations such as those restricted under VA coverage). Alternatively, as noted above, the combination of restrictions on some groups and settings for coverage plus initiatives to advance evidence development to enable these restrictions to be eased could encourage more extensive data collection through specific sites and studies even outside of a CED requirement. As we describe next, Medicare payment reforms to advance longitudinal, coordinated care for AD patients would support such an enhanced infrastructure over time.

Medicare Payment Reforms for AD Care Improvement That Support Better AD Care and Help Advance Evidence Development Over Time

CMS required in the final coverage decision that CMS-approved studies use "optimal medical management," defining the term per a 2020 Lancet report that identified modifiable risk factors for dementia prevention, intervention and care. As discussed earlier, CMS also highlighted safety-related considerations for the treating care centers. The requirement for "optimal medical management" is not the standard of care for AD today. Current AD care is fragmented and reactive; care coordination is left largely to the patients and their families, and dementia caregivers (typically family members of persons with dementia) are charged with managing behavior changes and medications, and planning and implementing care transitions.[18] While some AD "memory clinics" and whole-person care models have demonstrated improved function, caregiver quality of life, and the ability to avoid costly complications, such models are not the standard of care.

In addition to providing more comprehensive support for caregivers and better integration of evidence-based therapeutic steps that can slow functional decline and improve outcomes for both patients and caregivers, wider adoption of longitudinal AD care models will advance adequate provider and site capabilities that are needed for mAb administration–such as the ability to detect and treat ARIA and other potential mAb-related complications. In turn, these capabilities will make it easier for providers to participate in developing better evidence and a learning health system.

Some existing, limited Medicare payment incentives could help advance the goal of more coordinated longitudinal AD care with supporting data. Currently, Medicare has a patient assessment and planning payment ("Cognitive Assessment and Care Plan Services," for which all beneficiaries with cognitive impairment including AD and MCI are eligible) that physicians and other eligible practitioners can bill for providing a comprehensive clinical visit that results in a written care plan.[19] This code (CPT code 99483) requires an independent historian; a multidimensional assessment that includes cognition, function, and safety; evaluation of neuropsychiatric and behavioral symptoms; review and reconciliation of medications; and assessment of the needs of the patient's caregiver. While a step forward, the impact of this code has been limited for several reasons. Its current reimbursement rate of $283 with an applicable geographic adjustment may be insufficient to support robust care coordination, and documentation requirements mandated by its billing (such as a documented care plan) may limit and disincentivize its utilization.[20] Further, this code cannot be used to support ongoing care management services.[21]

CMS can also encourage better care management and meaningful participation in evidence development for AD patients through additional AD-related guidance on using its payments for Chronic Care Management (CCM) services,[22] which require that a comprehensive care plan is established, implemented, monitored and revised. Most CCM service codes are for patients with multiple chronic conditions, which would not necessarily apply to all beneficiaries with AD. However, there are two existing CCM codes (CPT Codes 99426 and 99427) that provide additional payment for principal care management services for a single chronic condition or another high-risk disease. Chronic care management services which can be paid for by these and other CCM CPT codes that may be particularly important for AD care are structured recording of patient health information, keeping comprehensive electronic care plans, and coordinating and sharing patient health information promptly within and outside the practice. USCDI+ standards for these key clinical data, and their inclusion in required electronic medical record capabilities, could make it easier for providers to use CCM codes and document key patient characteristics and outcomes that the care plan could address.

CMS could also provide quality improvement payments for data collection participation in a registry, such as through measures in the Merit-based Incentive Payment System (MIPS) program using the existing quality metrics related to dementia in the Quality Payment Program (QPP), and/or its Improvement Activities, encouraging providers to deliver better AD care and collect and report data on a few key measures.

While these additional steps involving fee-for-service billing codes could help, experts have noted that existing codes for chronic care management do not align with evidence-based dementia care models and that the reimbursement associated with them does not sufficiently reflect the time and effort invested.[23] Moreover, CMS has set the strategic goal of enabling all beneficiaries to have access to longitudinal, coordinated care by 2030, and would support better AD-related evidence development, through such mechanisms as advanced accountable medical homes, accountable care organizations, and accountable health plans. So far, however, CMS has not introduced performance measures related to AD or related to maintaining independence in its major person-focused payment and care reform models. CMS is considering an alternative payment model to support longitudinal care coordination and effective monitoring and treatment for AD patients;[24] if adopted, a version of this payment model could be extended to beneficiaries with earlier-stage disease, where appropriate diagnosis and person-centered care management will be increasingly important, with continuing advancements in early diagnosis and both pharmacologic and non-pharmacologic treatments, and associated questions about their appropriate use.

Looking Ahead: Enabling Efficient Evidence Development with Appropriate Access and Safe Use

This report provides a foundation for three options for a path forward for postmarket evidence development for AD mAbs that meet their clinical endpoints and receive traditional FDA approval, but that may have important remaining evidence gaps. This is a particularly important and challenging issue. On the one hand, AD is one of the highest-burden and most feared conditions prevalent among Medicare beneficiaries, and it is likely that different kinds of beneficiaries will respond differently to mAb treatments given the heterogeneity of the condition. Generating additional evidence on these treatments may provide valuable evidence to improve patient shared decision-making, and assessment and monitoring of patients treated with the mAbs, leading to better outcomes. On the other hand, any evidence-generation strategy should weigh the cost and burden of additional data collection against the value of the data with the impact that these requirements are expected to have on access.

Our review finds substantial gaps in the evidence-generation infrastructure that would be required in order to fully answer the three CED questions in the CMS NCD. These gaps not only add urgency for CMS and other stakeholders to take immediate steps to build upon and expand this infrastructure, but also to consider alternative ways in which critical evidence development can be facilitated outside of a broad and extensive set of CED requirements. These steps should include further stakeholder engagement, before traditional approval of any mAb if possible, to develop a clearer understanding and pathway for questions that can be reliably answered through large-scale, mostly claims-based evidence development; to clarify and improve the adequacy of existing and planned RWE systems for addressing questions that require more sophisticated clinical data "and analysis; and to implement steps like standard EHR capabilities and AD payment reforms to mitigate burdens associated with comprehensive data collection.

In the absence of better-developed CED capabilities, Medicare and other payers have imposed provider, site of care, and patient subgroup restrictions until further evidence and experience enable coverage to expand. The policy options presented here aim to provide feasible paths to evidence development given the realities of AD evidence development capabilities. CMS and stakeholders can build on these options as they work to balance additional evidence-generation expectations and reasonable restrictions to assure the appropriate use of new therapies. With a much broader range of diagnostics and therapeutics in development for AD, these questions are likely to become even more pressing in the future.

Disclosure

Mark B. McClellan, MD, PhD, is an independent director on the boards of Johnson & Johnson, Cigna, Alignment Healthcare, and PrognomIQ; co-chairs the Guiding Committee for the Health Care Payment Learning and Action Network; and receives fees for serving as an advisor for Arsenal Capital Partners, Blackstone Life Sciences, and MITRE.

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