

## Understanding Payer Evidentiary Needs for Alzheimer's Disease Monoclonal Antibody Treatments

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### Discussion Guide

To further conversations around evidence development for and patient access to emerging treatments for Alzheimer's disease (AD), the Robert J. Margolis, MD, Center for Health Policy, under a cooperative agreement with the US Food and Drug Administration (FDA), is convening a roundtable on issues associated with use of monoclonal antibodies (mAbs) for AD. The roundtable will specifically focus on evidence and coverage challenges that are important to the payer community, including the following topics:

- Key issues that payers are facing in making coverage and payment decisions involving the AD mAb drug class;
- Payers' activities to review the evidence relevant to these decisions, and their initial assessment of the evidence as it is available;
- Top areas where further evidence is needed to address stakeholder needs, and whether studies in progress are likely to be adequate to address these topics; and
- Opportunities for expanding the evidence base on mAb treatments for AD to incorporate payer perspectives.

### Background

Important advancements in clinical research and development for AD have been made over the last decade. One promising category of resultant treatment candidates is mAbs to target beta amyloid, which many scientists believe is implicated in AD progression. Multiple products in this class are in advanced clinical testing, some of which have an impact on reducing amyloid plaques and have reported some promising clinical results. One drug (aducanumab) [recently received accelerated approval by the FDA](#), and [multiple additional drugs](#) are on track for submission of a marketing application in the near future pending results of their clinical trials. Current clinical trials have tended to focus on enrolling patients with relatively earlier stages of AD, and labeling for the recently approved drug notes that treatment should be initiated in patients with mild cognitive impairment or mild dementia stage of disease.

Treatments that meaningfully slow the progression of disease or reduce symptoms would undoubtedly be valuable to patients suffering from AD. As such, there is substantial interest in [assessing the value of mAb drugs](#) to guide coverage and payment, which in turn will influence patient access and use. Different stakeholders have differing perspectives on how AD treatments should be valued and priced. For example, while the Institute for Clinical and Economic Review (ICER) suggested a price range for aducanumab that is significantly lower than the list price set by the developer, arguing there is insufficient evidence to

support a higher price, some patient organizations claim that this assessment [fails to account](#) for the true value of the treatment, which includes potentially greater long-term benefits.

FDA's mandate for assuring that drugs meet its standard for safety and effectiveness does not include consideration of pricing. However, given the high prevalence and impact of AD, it is clear that evidence on this class of potential treatments that addresses the needs of multiple stakeholders could help inform coverage, payment, and appropriate use. Payer concerns are particularly urgent given the substantial costs involved – both for AD itself, and for the potential new treatments. In addition, payers have questions about what evidence FDA will consider sufficient for further AD approvals, since that evidence will be the foundation for future coverage decisions.

The evidence questions related to this important emerging drug class span issues related to effectiveness, appropriate patient access, care model design including appropriate diagnosis, long-term patient outcomes, and impact on AD-related costs. The Centers for Medicare & Medicaid Services (CMS) [has opened a National Coverage Determination \(NCD\) process](#) to seek input on the path forward for Medicare for the entire mAb class, and [other payers have endorsed](#) such an evidence review process. How well these payer evidence concerns can be identified and addressed will have implications for coverage, payment, and access for AD mAb treatments.

#### *Remaining questions on evidence related to AD mAbs*

First, the character of clinical benefits matters, and the heterogeneity of the disease means that both symptom severity and progression vary across stages of disease and from patient to patient. Some studies have also suggested that different racial and ethnic groups have a greater risk for developing AD than others. Therefore, evidence on treatment impact beyond the patients enrolled in clinical trials and across different types of patients is important.

Second, validation of the surrogate endpoint used for accelerated approval is also critical. In FDA's recent aducanumab accelerated approval, amyloid plaque reduction as measured through PET scans [was used as a surrogate endpoint](#) in clinical trials. The primary endpoint in the underlying studies is a reduction in decline in mean scores on the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB), a standard, validated measure of dementia progression. FDA's accelerated approval included a requirement for a Phase IV (postmarket) study to confirm clinical benefit, which current estimates suggest could take up to nine years to complete. A key question is whether surrogate endpoint validation can occur in a more expedited way, including through assessing evidence being developed in the other drug trials or through postmarket studies.

Third, while CDR-SB is a well-validated endpoint, questions also remain about how improvement in this measure – and how use of a potential mAb therapy – translates into impact on quality of life and AD-related costs. How certain is the evidence on how CDR-SB progression translates into additional months of independent living or other key aspects of quality of life? There are also questions about the

appropriate duration of treatment and dosing: should treatment be continued indefinitely, should treatment duration be individualized, is a fixed period adequate, or should duration be based on resolution of plaques? In addition, are there any safety issues associated with use of the mAb therapies for durations longer than studied?

Payers must also consider the overall cost implications of new AD treatments. Drugs that can relieve symptoms or slow the progression of the disease have the potential to reduce the significant long-term costs of care for AD patients, including the high burden of AD for both paid and unpaid caregivers. These cost impacts also depend on how much the mAb therapies delay the loss of independence – and how much they impact the duration of time when AD patients require caregiving assistance. Alongside the potential long-term AD cost impacts are the direct costs associated with mAb treatment itself. These include not only the cost of the drug, but also the costs of ensuring accurate patient diagnosis, drug infusion, ongoing monitoring, and management of treatment complications including symptoms related to amyloid-related imaging abnormalities (ARIA).

The size of the potential target patient population may be substantial, and payers are already beginning to closely scrutinize coverage of these therapies, especially if there are questions about the magnitude and the durability of these future drugs' effect relative to their price. Some of these important issues could be addressed through additional evidence development related to the determination of the appropriate population for treatment, the extent of incremental improvement and cost-savings over time for particular types of patients, and other topics.

There are also questions about the appropriate care model for mAb treatments, which has implications for access and for translating the potential benefits of these treatments into impact on outcomes as efficiently as possible. Will drug treatment require monitoring by specialized memory clinics, which have only limited availability today? Will blood tests currently in development reduce the cost and burden of determining eligibility and monitoring progression? What is the best approach for monitoring and managing potential ARIA complications?

These evidence questions are summarized below in Table 1. Similar questions exist for many new classes of treatments, especially those for areas of unmet medical need where accelerated approval processes are most important. But the size of the potential target patient population means that questions about the magnitude and durability of drug benefits, and the impacts on associated costs, require particularly close scrutiny from payers.

These questions could potentially be addressed through studies underway now, Phase IV study requirements, and additional postmarket evidence development. However, an important issue cutting across many of these topics relates to the practical and ethical challenges of conducting randomized trials after treatments have been approved. Observational studies, for example using patient registries and electronic data collected in the usual course of care, are easier to conduct. But as [FDA's framework on real-world evidence](#) highlights, data and methods must be fit for purpose to detect incremental effects of

treatment on outcomes that are progressing over time. The data must be sufficiently complete and accurate for adequately defined target populations, and ideally include key clinical and social factors that may influence both treatment and outcomes. Methods must enable comparison of well-matched populations that are more or less likely to be treated, with well-defined initiation points. We return to these evidence development issues below.

**Table 1: Evidence Questions Related to AD mAb Treatments**

Question	Summary
Magnitude of clinical benefit and impact across AD stages and patients	Evidence on mAb treatments’ impact beyond the patients enrolled in clinical trials, and impact in different types of patients, is important to guide coverage and payment.
Validation of surrogate endpoint used in trials	FDA is using amyloid plaque reduction as a surrogate endpoint in clinical trials. The primary endpoint of interest is a reduction in decline in mean scores on the CDR-SB. FDA’s accelerated approval of aducanumab included a requirement for a Phase IV (postmarket) study to confirm clinical benefit. Timely and well-designed confirmation is needed.
Cognitive measure’s impact on quality of life and AD-related costs	Additional evidence could inform whether and how the cognitive performance metrics translate into additional, downstream quality of life, independence, and cost-reducing outcomes, e.g., does CDR-SB progression translate into additional months of independent living or other key aspects of quality of life? What is the treatments’ potential to reduce the significant long-term costs of care for AD patients? These potential long-term AD cost impacts should be examined alongside the direct costs associated with the mAb treatment, including the cost of the drug, patient screening, drug infusion, ongoing monitoring, and management of treatment complications including symptoms related to ARIA.
Treatment’s duration, dosing, and potential safety issues	There are remaining questions about the appropriate duration of treatment and dosing: should treatment be continued indefinitely, or is a fixed period adequate, or should duration be based on resolution of plaques? In addition, are there any long-term safety issues associated with chronic use of the mAb therapies, and what is the best way to monitor and manage them?
Appropriate care models	Questions regarding the appropriate care model for mAb treatments have implications for patient access and for realizing the potential benefits of these treatments. These questions include whether the drug will require monitoring by specialized memory clinics, which have only limited availability today, and whether blood tests currently in development will reduce the cost and burden of determining treatment eligibility and monitoring progression.

*Potential upcoming coverage decisions for AD treatments*

Given the evidence issues discussed above, how to make appropriate coverage and payment decisions is a critical and timely challenge for payers.

These decisions may be relevant to a set of mAb treatments over the next several years – with CMS noting in their [NCD analysis announcement](#) that their coverage determination will likely apply to the class as a whole. On June 7, 2021, the FDA approved Biogen’s aducanumab [through its accelerated approval track](#), allowing the agency to base approval on surrogate endpoints of amyloid plaque reduction. Current FDA-approved labeling for the drug—treating people with mild cognitive impairment due to AD or with mild AD dementia—is estimated at 1-2 million US patients. The sponsor is also required to conduct a confirmatory post-market placebo controlled, double-blind randomized phase 4 trial, to validate the clinical benefit of slowing the progression of AD.

Eli Lilly also has a mAb product currently in Phase 3 clinical testing for early-stage AD, with an estimated completion date of early 2023, using impact on trends in the Integrated Alzheimer’s Disease Rating Scale as a primary endpoint with collection of data on amyloid plaque remission and other endpoints. Based on promising Phase 1 and 2 results, Lilly [has recently stated](#) that it expects to apply for accelerated approval later in the year. Lilly’s trials employ a treat-to-target design to maximize the number of patients achieving amyloid plaque negative levels, which may support a fixed-duration dosing approach.

Eisai’s [Phase 2 study of its mAb product](#), lecanemab, in early-stage AD showed dose-dependent reductions in amyloid, some fluid biomarkers and in clinical decline using the ADCOMS, CDR-SB, and ADAS-cog measures at 18 months. Its [Phase 3 study \(Clarity AD\)](#), using CDR-SB as a primary endpoint, is expected to complete in September-2022.

Roche/Genentech’s [gantenerumab program](#) includes two 27-month trials (GRADUATE) with approximately 2,000 individuals with early AD; the primary outcome measure is the CDR-SB. In these studies, gantenerumab is administered subcutaneously at higher doses versus previous trials and readout is expected in the second half of 2022. In open label studies, gantenerumab showed significant reduction in amyloid plaques, as measured by PET scans, with 80% achieving amyloid levels below the positivity threshold at 36 months. ARIA-E rates were 27.9% with symptomatic ARIA seen in 6.5% of patients.

In their coverage and payment decisions on these products, payers are likely to focus on the state of evidence regarding the relationship between the treatment’s surrogate endpoints as shown in the clinical trials to actual cognitive outcome endpoints. Further, given the costs associated with these treatments, payers are likely to want to see that the cognitive outcome impacts other meaningful outcomes that are associated with the reduction of short and long-term costs of care, a better quality of life, and decreased caregiver burden.

Payers will also consider the associated technologies needed for patient diagnosis and management. In general, providers with appropriate training (e.g., memory clinics) can bill for evaluation and management

of patients at risk for AD progression. But PET scans, which have been used to identify plaque status and progression in mAb clinical studies, are generally not covered in AD clinical care – Medicare provides limited coverage of such scans only in the context of approved clinical trials evaluating AD progression and the factors influencing it. An alternative mode of diagnostic monitoring, cerebrospinal fluid (CSF) sampling, is covered for diagnostic purposes but is invasive. While blood tests for beta-amyloid in development to validate their use in tracking plaque formation, none have yet been approved by FDA for this purpose and thus they are generally not covered. Finally, appropriate coverage for potential ARIA-related complications is also unclear.

Lastly, the payments by payers will generally occur in the short term, during the period of AD therapy. By contrast, benefits from effective therapies for AD may be realized through health improvements, health care savings, and reduced caregiving needs that occur years in the future. Especially if these downstream benefits are relatively uncertain, payers may be reluctant to incur substantial up-front expenditures. Further, patients often change payers, and many AD costs occur outside of insured health services (e.g., long-term services and supports), so that the accrued benefits and cost-savings may not be realized by the payer that initially reimbursed the treatments. Justifications for coverage and reimbursement based on future cost-savings may not be a strong argument for payers in this case, as they will not directly realize these savings.

#### *Next steps for the CMS*

With the high prevalence of AD in persons over 65, [80 percent of mAb drug coverage could occur through Medicare](#). CMS's coverage decisions will have direct implications both for patients in traditional Medicare and in Medicare Advantage (MA) plans. Because of Medicare's importance for this market, CMS decisions will also influence decisions by commercial payers and potentially state Medicaid plans. The important role of CMS as a primary payer for this population is reflected in the agency's rapid action to open the NCD for aducanumab and the broader mAb treatment class after public calls from both [private payers](#) and the [Alzheimer's Association](#). CMS has stated that they intend to seek extensive stakeholder input for this process including public meetings on AD mAbs in late July 2021, and that a draft NCD should be ready for public review and comment within 6 months (estimated date January 12, 2022) with a final rule soon thereafter (estimated date April 12, 2022).

Physician-infused drugs like mAb therapies for AD are covered via provider "buy and bill" under Medicare's Part B benefit, with reimbursement initially based on the product's Wholesale Acquisition Cost (WAC) then subsequently based on its Average Sales Price (ASP), net of rebates, with a 4.3 percent add-on payment. In general, Medicare has covered Part B drugs based on the FDA-approved label as well as off-label uses (e.g., from cancer drug compendia). However, while the CMS "reasonable and necessary" standard for coverage takes into account whether a treatment is safe and effective, CMS determinations also include other considerations such as whether the treatment is not investigational and evidence suggests that it is appropriate for Medicare beneficiaries.

Typically following the FDA approval of a drug, the drug's initial coverage by Medicare is subject to the review of individual Medicare Administrative Contractors (MACs), who assess whether the conditions for meeting Medicare's "reasonable and necessary" coverage standards are met. The regulatory process for such Local Coverage Determinations (LCDs) allows for MACs to take some time (on the order of months) to review evidence and consult with experts and stakeholders before making a determination. In the absence of a completed CMS NCD, the MACs and MA plans would be responsible for reviewing Medicare Part B drug claims to ensure that Medicare pays for drugs that meet the criteria for coverage. MACs have the discretion to establish LCDs that place conditions on covering use of the drug, or determine coverage claim-by-claim, in both cases potentially resulting in divergent coverage policies across the country that might create differences in the treatment's availability based on geographic locations. In contrast, NCDs are binding across all MACs and MA plans and would therefore standardize the treatment's coverage for the entire Medicare population

In addition, the process of assigning billing codes for individual drug products takes some months, likely by the end of 2021 in the case of aducanumab (making it effective in early 2022), complicating payment for the drug during that time. The uncertainty surrounding the treatment's coverage and payment has implications for providers who seek to administer the drug to their patients. Under Part B's "buy and bill" drug payment system, the provider must first acquire the drug before submitting a claim for Medicare reimbursement. Because Part B payments can only be made if they are consistent with the coverage criteria, providers will have concerns about the risk of having their claims denied in the absence of clear Medicare guidance through an NCD or MAC LCDs.

A typical NCD process takes about 9-12 months, with CMS indicating that they intend to arrive at a final determination in 9 months in the case of AD mAbs. In conjunction with public meetings and opportunities for public comment, this process also generally involves convening the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) to provide a transparent expert forum to review relevant evidence and consider options. Further, once CMS issues a preliminary NCD after considering all stakeholder input, CMS will provide a formal comment period (likely 30 days) on the preliminary NCD then consider such comments in issuing a final NCD (likely 2 months later).

In making its NCD decision, CMS could do any of the following:

- **Deny coverage of the treatment**—this would be unprecedented in Medicare's history of Part B drug coverage.
- **Limit coverage to certain populations**—for example, routine coverage could be limited to only some labeled populations, or to patients treated by providers with specific relevant capabilities or characteristics. While most examples of CMS not covering the full FDA label have involved medical devices, CMS also restricted coverage of an important class of drugs for a large population of Medicare beneficiaries in 2007 when it made an [NCD for erythropoiesis-stimulating agents \(ESAs\)](#), limiting their coverage to only a subset of labeled populations due to safety concerns.

- **Make the coverage determination contingent on the collection of additional data with the goal of developing more evidence** about the drug’s safety, effectiveness, and appropriate use in Medicare beneficiaries (and potentially other patients). The high-level July 12 announcement from CMS suggested that that the agency is considering further evidence development as part of its NCD.

This last mechanism, called [Coverage with Evidence Development \(CED\)](#), provides for Medicare coverage only in the context of the conduct of CMS-approved clinical trials, registries, studies, and/or other processes for collecting key supplemental data aimed at developing more evidence about the drug to inform a final downstream coverage decision. That decision would incorporate the results of the additional evidence development activities, at which point the CED requirements in the initial NCD would end.

CMS could apply different CED criteria for segments of the AD population, based on expert assessments of the state of the evidence and on planned clinical studies. For example, for early-stage AD patients like those studied in the trials that supported aducanumab’s accelerated approval, CMS could opt to provide coverage that reflects the inclusion criteria in the trials used for approval, plus additional CED requirements that reflect the questions surrounding the current evidence on its clinical benefit. This could build on the FDA’s requirement that its approval under the accelerated track be “contingent upon verification of clinical benefit in confirmatory trial(s)” through specific steps to encourage participation and key data collection.

A key challenge in designing CED requirements is assuring that the benefits in terms of evidence development to support more effective use in the Medicare population exceeds the costs and burdens, and thus access implications, of the contemplated additional data collection or study participation. For example, if a well-designed Phase 4 randomized trial is contemplated for FDA approval, a CED mechanism building on it could potentially make it easier to cover more patients and recruit more sites, accelerating the speed and applicability of the study’s results. However, limiting coverage *only* to participants in a well-designed randomized trial would significantly reduce access. For beneficiaries not enrolled in trials, a CED requirement to participate in a limited registry (without randomization to treatment or not) could address some additional issues, such as the optimal use of PET scanning (and other emerging diagnostic tools like blood tests), questions about the course and management of ARIA complications, and other safety monitoring.

Some experts [have suggested](#) that a large observational registry could also augment evidence on questions of mAb effectiveness. However, given the heterogeneity of the AD population (e.g., patients with mild cognitive impairment and early-stage AD have diverse medical, genetic, socioeconomic, racial and ethnic profiles, all of which may influence both their access to treatment and the course of their AD) and the potentially incremental expected benefits for the initial mAb treatments, such observational effectiveness studies would need careful attention to data collection and methods design to yield convincing results on effectiveness questions like validating a surrogate marker or confirming other

outcome benefits. Because of these difficulties, other experts have suggested real-world randomization approaches like regional trials, where some regions would have broader access to mAb treatments, potentially enabling comparisons between populations in the “more treated” regions and the “less treated” regions, like Medicare has done for piloting some payment reforms and innovative benefits. However, a well-developed infrastructure for supporting such trials does not exist, and limiting access by region or provider may lead to both ethical and political concerns.

These approaches benefit from the timely availability of a suitable platform and infrastructure for conducting pragmatic trials or other studies. Implementing these approaches takes resources beyond those available to CMS. For example, such an infrastructure might be supported by the National Institutes of Health (NIH), the Patient-Centered Outcomes Research Institute (PCORI), or a private-sector collaboration. It would ideally use electronic data systems to collect much of the required data, such as information from claims, electronic health records, and laboratory and pharmacy data, limiting the cost and burden for participation. The technical and coordination issues involved mean that implementation is not straightforward or rapid.

All of these considerations highlight the challenges of developing high-quality real-world evidence (RWE), especially when an approved treatment is covered outside of clinical trials. Other accelerated approval products have faced difficulty in completing postmarket studies, in part because patients and their caregivers may have strong preferences for receiving treatment or not, rather than participating in randomization.

While the FDA label for aducanumab was recently narrowed to include only early-stage populations, CMS could extend limited off-label coverage to patients with moderate- and late-stage AD who participate in CED using well-designed randomized controlled trials. Less evidence on benefits and risks of mAb treatment is available in these populations, since they have generally not been included in the clinical trials to date. An NCD that limited coverage to randomized trials for such patients would not create the same extent of practical challenges as for the earlier-stage, on-label populations, and could accelerate the development of more definitive evidence on benefits and risks in such populations, limiting the occurrence of less-informed off-label use that may otherwise emerge. On the other hand, Medicare already provides coverage for routine care in the context of clinical trials, and CMS may have concerns about paying for mAb drugs themselves in this context.

Any such evidence development initiatives should consider the potential for class effects across the mAb products. For example, trials underway now may provide more evidence faster on validating plaque removal as a surrogate marker than a new Phase 4 study that is still being designed. There are also potential class effects across mAbs in terms of effective care models to support appropriate access and limit overall treatment and monitoring costs; models that work for one drug may also work for others, as evidence across the class of drugs continues to improve. Collaboration across CMS, FDA, manufacturers of mAbs for AD, and the providers who prescribe these therapies could help assure that any further evidence development takes a strategic view of evidence being developed across the therapeutic area.

Finally, while Medicare has not previously piloted an alternative payment model for a Part B drug, Part B drug payment reform pilots were considered by both previous administrations, and the Trump administration reportedly [explored but did not implement](#) an outcome-based payment arrangement for CAR-T products. Innovative payment models being developed by other payers may thus have relevance to Medicare, as we describe below.

#### *Next steps for other payers*

Private payer actions will be influenced by further CMS actions, including the process and findings of the Medicare NCD analysis. Some plans have suggested they will likely use the eligibility criteria from the clinical trials for aducanumab, reflecting current FDA labeling. This would limit coverage for now to the particular types of early-stage patients who participated in those studies, with results from the other clinical studies underway used to further adjust coverage. Information generated by the pivotal trials for other treatments in the AD mAb class, as well as other postmarket studies, could also help inform payers' coverage decisions by providing evidence in the following areas: (a) the surrogate endpoints show a strong relationship to a slowing of measures of cognitive decline; (b) the cognitive performance measures translate into additional, downstream quality of life, independence, and reductions in costs of AD-related complications; and (c) more efficient care models for diagnosing appropriate candidates, determining how long treatment needs to continue, and monitoring and limiting the consequences of side effects. Plans are unlikely to provide coverage for patients with more advanced disease until the completion of clinical trials and approvals in those populations. However, they might also provide narrow coverage in such populations, for example in the context of well-designed randomized clinical trials to address important payer-relevant questions. Such coverage decisions may also be influenced by the CMS NCD.

Related to concerns about coverage, payers are also focused on appropriate payment amounts informed by evidence-based assessments of treatment value, as noted above in the discussion of the ICER evaluation and comments from stakeholder groups. Biogen and Eisai are reportedly [discussing "value-based" contracts with tracking some outcome metrics with Cigna](#), and are working to finalize a multi-year access agreement with the US Department of Veterans Affairs. Some Medicaid groups have called for a larger Medicaid rebate for accelerated approval products until the products' clinical benefits have been confirmed. In other product areas (e.g., [hepatitis C and PCSK9 treatments](#)), payer leverage to implement value-based payments increased as more competing products entered the space.

#### *Discussion questions:*

- What are potentially achievable outcomes that payers will look for in AD mAb treatments? Based on currently available information about the drug class, as well as your own organizations' early review of this information, what are the highest priority questions where more evidence would be needed to inform coverage decisions? Specific questions to consider include:
  - For which populations might these treatments offer the greatest impact or value?

- What are the most effective ways to improve understanding of the relationship between the treatment's surrogate endpoints and cognitive outcome endpoints? The relationship between the cognitive outcomes to other measures of value, such as quality of life, independence and reduced supportive care costs and caregiver burden?
- What are the expectations associated with differing durations of treatment?
- What are the most effective and efficient care models for mAb treatment, including diagnosis, monitoring, and management of treatment complications?
- What coverage and payment decisions might be appropriate for these treatments?
  - How will payers treat populations included in clinical trials versus less-studied populations when making coverage determinations? Would coverage differ by population group?
  - What additional evidence described previously would affect payers' willingness to cover these drugs?
- What are payers' pricing and payment expectations with regard to the AD mAb drug class? What is the expected pricing dynamic when there are several similar drugs in this space?
  - How might past experiences in the context of pricing and competition help inform this discussion, for example, the approval of multiple PCSK9 drugs for lowering cholesterol and the competition that impacted hepatitis C treatment prices?
- Will the pivotal trials underway now or the planned Phase 4 (postmarket) studies provide substantial insights into the key evidence questions?
- What are near-term ways to augment these studies to fill key evidence gaps?
- Can these key evidence questions be addressed through observational real-world studies (e.g., registries), or are randomized studies needed?
- What potentially feasible further postmarket studies are most important to consider now – for both early-stage and later-stage patients?
- Are there any learnings to leverage from our collective experience with registries, practical platform trials, and other postmarket evidence initiatives?
- What should CMS consider in terms of an evidence development (e.g., CED) approach for these therapies? How might these studies be designed and executed given the existing coverage issues and challenges associated with creating a randomized controlled trial for the treatment?
- How can stakeholders work together to address these questions in both premarket and postmarket studies?
- Would additional public-private collaboration help address these questions?
- What potential payment models could address the health care spending and evidence concerns associated with these therapies?

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