Role of Registries in Medicare Coverage of New Alzheimer Disease Drugs

An amyloid-directed monoclonal antibody, lecanemab-irmb (Leqembri), was approved by the US Food and Drug Administration (FDA) on July 6, 2023, to treat Alzheimer disease with mild cognitive impairment or mild dementia. In this Viewpoint, we assess how the design of the Centers for Medicare & Medicaid Services (CMS) registry could impact the ability of Medicare to evaluate whether monoclonal antibodies are reasonable and necessary in the Medicare population and help physicians understand when the drug is most beneficial to their patients.

Although the lecanemab clinical trial showed some slowing of disease, there is concern that it did not adequately assess long-term benefits and harms and that the trial participants were not representative of the Medicare population because patients with some comorbidities were excluded and Black participants and women were underrepresented. The risk of serious adverse events led the FDA to add a black box warning to lecanemab’s label. There was also concern that limited access to academic medical centers providing necessary associated services could impact effectiveness.

The CMS provides coverage for products deemed “reasonable and necessary” in the Medicare population, whereas FDA approval relies on a different standard of efficacy and safety. The CMS decided prior to the FDA approval of lecanemab that coverage for fully FDA-approved amyloid-directed monoclonal antibodies would be provided through coverage with evidence development, which is conditional coverage for interventions that are likely to provide benefit but do not automatically meet the CMS’s “reasonable and necessary” standard. Coverage with evidence development has mostly been used for medical devices and diagnostics in the past, with lung volume reduction surgery and medical management for emphysema studied in the National Emphysema Treatment Trial being a notable early success. To receive coverage, beneficiaries must participate in a new prospective registry hosted by the CMS or registries or trials hosted by other approved organizations. In addition to the CMS registry, a registry hosted by Beth Israel Deaconess has also been approved thus far. The CMS registry is available through an online portal (https://qualitynet.cms.gov/alzheimers-registry/submission) where physicians are asked to enter a patient’s diagnosis; amyloid, cognitive, and function test results; use of some concomitant medications; and signs of adverse events. Follow-up data need to be submitted every 6 months for up to 24 months.

Intervention-specific registries are useful when there is uncertainty about the benefits of using a drug or device in a certain population. Registries tend to include larger and more heterogeneous patient populations, yielding more generalizable results compared with clinical trials. Registries are also better suited for outcomes analyses compared with retrospective analyses of electronic health records (EHRs) because they are designed prospectively with prespecified outcomes. Analyzing EHR data tends to be challenging due to differences in customized EHR systems among practices, lack of standardization of records, few outcome measures, and the possibility that patients could have records in multiple EHR systems.

To facilitate enrollment, the CMS designed its registry to minimize physician burden and patient concerns. Patients are most amenable to registry participation if they are recruited by a known clinician, are not required to spend additional time, and are asked to share only medical data rather than personal data and if anonymized data are allowed to be used for research purposes. The number of questions should be minimal, and drop-down menus and yes-or-no questions should be used to reduce physician time required for data entry. In its current form, the CMS registry follows these guidelines.

There are limitations in the current approach that could lower the quality of the evidence generated. First, a control group is necessary. The CMS registry collects data only on patients taking an amyloid-directed monoclonal antibody. Researchers analyzing the outcome data will need to use Medicare beneficiaries not taking the drug as controls.

Second, uniform outcomes should be collected. There are multiple cognitive, function, and amyloid test options, and every effort should be made to standardize the outcome data collected by the CMS registry and other registries. Although providing flexibility in the data could provide additional information and increase participation, this could weaken the quality of the evidence if it is difficult to compare outcomes. Outcome data should be useful for answering the research questions of interest, and researchers should assess if a minimum standardized outcome should be required for all registries.

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Third, the registry should collect sufficient information to allow a comprehensive analysis of the benefits and harms of drugs in the diverse population of Medicare beneficiaries with comorbidities, disabilities and who are from demographic categories not adequately represented in clinical trials. One possibility is to link the registry data with either EHR or administrative claims data. Linking CMS administrative claims data is likely a simpler approach that would provide access to standardized data on patient age, sex, race, zip code, comorbidities, and a more complete list of concomitant medications. This could be done without identifying patients through encryption. This approach would efficiently leverage existing data already collected by Medicare and provide sufficient detail to understand how the effects differ by various demographic and clinical characteristics.

Fourth, despite the simple design of the registry portal, there are still concerns that physician burden could create barriers to access to monoclonal antibodies. Studies have suggested that physicians are more likely to participate in registries if data entry is low burden and if the resulting data are useful to their clinical or research activities. Practitioners participating in the CMS registry could leverage technicians to assist with data entry, a strategy used by the Centers for Disease Control and Prevention’s National Program of Cancer Registries. The CMS could provide physicians access to the recorded data to track patient progress as a strategy to encourage participation. Ultimately, however, access to healthcare services is likely to be a more important factor than physician burden in determining access.

Utilization of amyloid-directed monoclonal antibodies for Alzheimer disease requires access to infusion centers and tests including positron emission tomography scans and cerebrospinal fluid tests to determine eligibility for treatment and record baseline status. These are scarce resources with more potential to create access barriers than the burden of registry data entry. Inequities of access could also create bias in the registry sample, jeopardizing the goal of assessing the effects of these drugs in the broader Medicare population. There will also likely be a surge in demand for the required tests and infusion centers and clinics, leading to potentially unpredictable market responses that could further exacerbate inequities. The CMS should monitor the rollout of coverage through the registry to ensure equitable access, track unintended consequences, and determine ways to adjust for bias.

Fifth, prior coverage with evidence development did not always publish the data. This should be a priority to make treating physicians aware of the real-world benefits and harms of these drugs.

The CMS registry provides advantages over other methods of collecting health outcomes data while expanding access to lecanemab. To maximize the value of the CMS registry, we recommend additional steps to ensure high-quality evidence generation and enrollment of a large and diverse patient population. If steps are taken to ensure adequate data collection and facilitate widespread enrollment, the CMS registry along with other registries have the potential to generate representative real-world data on amyloid-directed monoclonal antibodies, ultimately allowing the CMS to assess whether these drugs are reasonable and necessary for a wide range of Medicare beneficiaries with Alzheimer disease.