VIEWPOINT

Ownership and Interoperability Challenges of Alzheimer Monoclonal Antibody Registries

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On July 6, 2023, Medicare began covering lecanemab-irmb (Leqembi [Eisai/Biogen]) for the treatment of Alzheimer disease with mild cognitive impairment or mild dementia and confirmed amyloid-β pathology. Citing uncertainty about long-term benefits and harms of amyloid-directed monoclonal antibodies in the Medicare population, including heightened risk of severe brain swelling or bleeding among patients homozygous for apolipoprotein E ε4, the Centers for Medicare and Medicaid Services (CMS) is using coverage with evidence development (CED) to cover lecanemab. CED is a way of covering interventions that are promising but do not have sufficient evidence to be deemed reasonable and necessary for Medicare beneficiaries.[1]

To collect real-world data on lecanemab's effectiveness and safety, the CED requires that beneficiaries participate in an approved study or registry to receive coverage for lecanemab. CMS is using a distributed registry approach, which means that in addition to a registry hosted by CMS, additional external registries can be hosted by institutions such as hospitals or patient organizations.[1] The external registries will collect data independently but will be expected to address research questions relevant to the CED on long-term benefits and harms in the Medicare population, adhere to specified scientific integrity standards, and make the results publicly available regardless of the outcome.[1] This approach may help increase the number of patients enrolled and granted coverage, but CMS faces potential challenges to effectively access and use the data from these registries to achieve its CED objectives. This Viewpoint addresses 3 key challenges: how the variability in data sets collected by the registries could hinder pooled data analysis, how redundancy in the data could occur if patients are enrolled in multiple registries, and how conflicts of interest could arise among pharmaceutical industry-funded registries, leading to biased data reporting.

First, clear guidance is lacking as to what specific variables should be collected by external registries. Additionally, registries are not required to share the raw data with CMS to be stored in a central hub for public access and analysis. To address these challenges, standardization requirements are needed for the external registries to collect an identical set of meaningful variables measuring real-world effectiveness and safety. This would maximize sample size and utility of the collected data by enabling pooled analyses of registry data.

The proposed registry structure contrasts with the Surveillance, Epidemiology, and End Results (SEER) and the National Program on Cancer Registries, which collect standardized variables and house data in a central hub. The data are available to physicians and researchers to inform practice and research[2] and has led to significant findings revolutionizing cancer treatment.[3] SEER data have been used to address questions about real-world benefits and harms of new drugs similar to those now relevant to Alzheimer treatments. Specifically, research using SEER-Medicare data showed that real-world outcomes among Medicare beneficiaries using new oncology drugs differed from clinical trial outcomes.[4]

Lack of data standardization could limit the possibility of sharing and analyzing data across Alzheimer registries. Unlike SEER, CMS does not have legislative authority to compel collection of data on patients with Alzheimer disease. However, CMS must approve the external registries before they can serve as avenues for drug coverage. Therefore, one option is to require that all registries collect a minimum common data set and share it with CMS for analysis.[5]

Another option yielding a higher level of interoperability would be to use a federated registry approach. In a federated registry system, the data sets generated by multiple registries use a common data model with standard definitions, formats, and relationships for each variable to enable pooled analysis, but data are not housed in a central hub.[6] This model has been successfully used by the Severe Heterogeneous Asthma Research Collaboration, Patient-Centered (SHARP) registry, which connects data from multiple European asthma registries to enable analyses of drug comparative effectiveness, monitoring of disease progression, and identification of subgroups of patients benefitting the most from certain treatments. SHARP mapped a diverse set of clinical registries to a common data model, making it a fully interoperable federated registry without housing the data into a central hub, as in the SEER model.[6] Compared with the minimum common data set approach, implementing a federated system would entail greater up-front effort to align on a common data model. However, it would greatly simplify data analysis by allowing the same analytic code to operate on all data sets, eliminating the need for registry managers to manually process and share data with CMS, reducing potential patient privacy concerns associated with housing data in a central hub, and allowing CMS to analyze data sooner rather than waiting for registry managers to report results at protocol-specified intervals, thus expediting analyses to inform coverage and clinical practice.

A second challenge with using multiple registries is that patients may be enrolled in more than one registry if they receive care from multiple practitioners. Registries could agree to use Medicare Beneficiary Identifiers (MBIs) to prevent duplication; however, not all patients enrolled in external registries will necessarily have

an MBI. There are also concerns that creating a shared MBI across registries might compromise patient privacy. To address such concerns, methodologies such as the privacy-preserving record linkage can be leveraged to securely link multiple entries in different registries for a single patient without sharing identifying information.[7]

A final challenge is that conflicts of interest could arise based on the ownership or funding sources of external registries. Registries owned or funded by pharmaceutical companies or industry groups with a financial interest in the real-world effectiveness and safety of amyloid-directed monoclonal antibodies could face pressure to avoid publishing results or sharing data if the evidence generated suggests that the drugs may not be beneficial or have important safety concerns. Some registries may also reimburse practitioners for the time spent entering data into the registry, whereas others may not—potentially motivating clinicians to use one registry over another. To mitigate these risks, external registries should be required to disclose their funding sources. Requiring external registries to share the data with CMS or allow CMS to access and analyze the data through a federated system would also increase transparency and objectivity. Alternatively, an independent third party could combine the information, report deidentified data back to CMS, and manage dissemination of deidentified data to the public.

Leveraging registries to understand real-world effectiveness of monoclonal antibodies to treat Alzheimer disease will likely be of interest to physicians, patients, and the public. The goal of the registries should be to provide patients with Alzheimer disease and practitioners with the same benefits of robust registry data as patients with cancer, such as a better understanding of real-world drug effectiveness and safety.[4] To conduct pooled analyses, CMS should either require collection of a minimum common data set with deidentified reporting and processing or use a common data model across registries to create a decentralized federated system. In either case, secure record linkage will be critical to avoiding duplication, protecting patient privacy, and would enable connection of registry data to claims databases containing patient demographic information. The anonymized results could be made publicly available, like SEER data. Lessons learned from this real-world evidence generation program for Alzheimer drugs will become increasingly relevant as new technologies with limited evidence on subgroups of Medicare patients become more frequently introduced in the US market.

ARTICLE INFORMATION

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