August 21, 2023

The Honorable Chiquita Brooks-LaSure
Administrator
Centers for Medicare and Medicaid Services
U.S. Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

Re: National Coverage Analysis Evidence Review Proposed Guidance

Dear Administrator Brooks-LaSure:

On behalf of the patients, family caregivers, and providers our organizations represent, we appreciate the opportunity to offer comments to the Centers for Medicare & Medicaid Services (CMS) regarding its "National Coverage Analysis Evidence Review" proposed guidance released June 22, 2023. The scope of this guidance is limited to CMS' approach to National Coverage Analysis (NCA) evidence review, which is an important topic that we comment on below. However, our organizations strongly urge the agency to amend this guidance by adding process-related updates, including an explanation of how FDA-approved items and services will (or will not) be covered during the NCA process. Overall, the NCA/National Coverage Determination (NCD) process is opaque and challenging for beneficiaries and the general public to engage in. Additionally, Medicare beneficiary coverage and access to FDA-approved items and services during the NCA/NCD process is either unavailable or unclear. Our organizations provide several recommendations throughout our comments below for CMS to consider adding to this guidance in order to provide transparency and clarity to its NCA/NCD process.

Statement of Interest

Organizations listed here may present their own responses to CMS and will actively advocate for those positions. These comments are not intended to impact adversely the ability of individual organizations, alone or in combination, to pursue separate comments with respect to the proposed guidance on National Coverage Analysis Evidence Review.

NCDs and NCAs Should be Listed in the Federal Register

While the vast majority of Medicare coverage is provided on a local level, in certain cases, CMS decides to develop a National Coverage Determination (NCD) for an item or service to be applied on a national basis for all Medicare beneficiaries. CMS has a formal process for requesting an NCD, which is outlined on both the CMS website and in the Federal Register.[i] The Federal Register (FR) provides a means for the government to announce to the public changes to government requirements, policies, and guidance.

Unfortunately, CMS does not post notice in the FR when the agency starts a new NCD process or reconsiders an existing NCD. Instead, the Agency posts a tracking sheet on its website and issues a National Coverage Analysis (NCA)—for which the public comment 30-day period starts the same day. Advocacy organizations and other external parties must either be aware that an NCD process is imminent and know how to navigate the CMS website (which is not consumer-friendly), or they must subscribe to

the correct CMS email alerts. If not, they miss the opportunity to comment. This current process does not encourage equitable participation by stakeholders, but rather limits engagement to "those in the know." **Therefore, our organizations urge CMS to commit in this guidance to public notice and comment of all future national coverage analyses (NCAs) in the Federal Register, similar to the U.S. Food and Drug Administration.** We also ask that CMS establish longer comment periods of at least 45 days to permit a larger group of stakeholders sufficient time to comment during the NCA process.

CMS Should Explain the Reasoning Behind its Evidence Review and Evidence Questions in Each NCA

There is currently no transparency about the rationale for how each NCA process is assessed. In the "Methodological Principles" section of this guidance notes that "The methodological principles described below represent a broad framework of the issues we consider when reviewing clinical evidence. However, it should be noted that each NCD has its unique methodological aspects." The NCA serves as the agency's justification for establishment of national Medicare coverage policy—which can include an NCD, an NCD requiring coverage with evidence development (CED), or non-coverage—that has significant implications for beneficiary access.

Additionally, it is difficult to comment on NCA methodological principles, study review, and strength of evidence when CMS' ultimate evidence targets for what constitutes "reasonable and necessary" are unclear. The list of vague, general methodological principles and evidence criteria in the NCA draft guidance affords CMS the ability to arbitrarily establish differing standards of evidence from medical development research, and then pose broad evidence questions based on those inconsistent standards, that also have no defined parameters for the answers. The proposed NCA guidance is missing important guidelines on what level of evidence is expected by the agency, including the level expected by type of coverage (i.e. NCD, NCD with conditions, CED, non-coverage) under the NCD program. Standards without clear definition are not sufficient nor transparent, and open up the agency to criticisms of potential bias or improper consideration of cost in deciding which items and services are subject to a NCA and coverage restrictions through the NCD process.

For example, in the proposed guidance CMS notes that in most situations randomized clinical trials (RCTs) represent the most credible source of evidence due to being least subject to a bias of outcomes. At the same time, CMS notes that in some cases observational studies can provide more accurate reflections of clinical practice and answer questions that a RCT is unable to answer. The agency also notes that "Coverage with Evidence Development (CED) observational studies may also meet high standards of credibility through a review of study proposals with AHRQ and CMS before study execution, complete transparency, faithful execution, and clear public reporting." It is unclear which standard is preferred. If CMS' answer is conditional, it is paramount to understand on what criteria those conditions are based upon. The current draft guidance provides no insight into how CMS specifically evaluates the evidence, which dilutes the usefulness of mentioning the criteria.

Further, CMS offers no clarity in the draft NCA guidance regarding evidence thresholds for CMS determining how it chooses an NCD versus an NCD requiring CED. Instead, the guidance generally states:

> "In making NCDs, CMS considers the totality of the evidence across multiple dimensions, including study design and conduct. The evidence for some outcomes, populations, or clinical settings may be of higher quality than evidence for others. Additionally, when CMS reviews evidence for NCD reconsiderations, CMS-approved CED studies may generally be more persuasive than other

observational studies because the study design, analysis plan, and data sources will generally be prespecified and posted on clinicaltrials.gov."

Understanding CMS' perspective on what types and quality of evidence differentiate an NCA evidence review that result in an NCD from one that results in an NCD requiring CED is critically important, since NCDs requiring CED impose further clinical study as a condition of coverage. While CMS maintains that CED study participation is "voluntary," non-coverage is the only option for beneficiaries outside of study participation. It is also important to note that beneficiary preference is not the only factor that limits study participation, as eligibility criteria and often extensive data reporting requirements limit access to providers providing the item or service.

Beneficiaries may be subject to a CED requiring an RCT, as happened with CMS' recent NCD on monoclonal antibody therapies targeting amyloid for early Alzheimer's approved through the FDA's Accelerated Approval Program. For the vast majority of highly innovative and novel drugs and devices approved by FDA, the premarket FDA clinical investigations have demonstrated superiority to a comparator. Post-market RCTs could present ethical issues because RCT study design in CED may require some Medicare beneficiaries to receive a placebo for a device, diagnostic, or prescription drug found to be "safe and effective" by the FDA. Further, beneficiaries may be required to pay coinsurance for a placebo in order to maintain a blinded study.

CMS also notes that RCTs (and presumably, the FDA approval that is based on the studies) may not be generalizable to Medicare due to insufficient enrollment of subpopulations, including by age, sex, race/ethnicity, the severity of disease, presence of co-morbidities, and disability status. We agree, but CMS does not provide a definition for what would be considered "representative" in clinical trial data, such as a percentage of trial participants equivalent to the percentage of Medicare beneficiaries living with the disease under study.

In terms of health equity, the restrictive eligibility criteria CMS has used in applying CED has historically produced counterproductive effects that disproportionately limit coverage to the very populations underrepresented in clinical trials. CED in particular has a tortured track record in advancing equity, as participating eligible hospitals are principally found in large, urban areas and connected to academic research centers. Rural and private clinics, along with smaller hospitals, are effectively shut out from participating in the CED trials. This has significant implications for underserved populations, who more often receive healthcare services from essential providers. In some cases, the criteria have resulted in beneficiaries in entire regions of the country not having access to the therapeutic covered under CED.[ii] As a result, many of CMS's CED trials have included deeply unrepresentative patient populations, which has, in some cases provided continued justification of coverage restrictions.[iii]

CMS also offers no insight into how the agency develops its NCA evidence questions, which are sometimes carried into NCDs requiring CED. The NCA questions often refer to "sufficient" (i.e., is the evidence sufficient?), but do not describe the threshold of evidence that is meant by "sufficient." This puts beneficiaries, providers, and sponsors in suspended states of unpredictability for coverage and access. The burden of rationale for the NCA questions is on CMS and should be explained by the agency in each NCA.

As a final point, CMS' nod to evidence of outcomes important to patients and caregivers is incomplete and, in some cases, counter to what Medicare beneficiaries believe to be important. For example, for many patients and families facing life-threatening diseases where no treatment options currently exist, or where patients have run out of treatment options, recognition of surrogate endpoints reasonably likely to predict clinical benefit are both meaningful and vital. CMS' dismissive stance toward surrogate endpoints, and the FDA's Congressionally authorized Accelerated Approval Pathway, is deeply concerning for the patient advocacy community as well as federal lawmakers who authorized the program.[iv] In juxtaposition, CMS's use of CED under NCD is often interpreted as having questionable grounding in the NCD statute.

It is for the reasons described above that our organizations urge CMS to require a clear explanation of the reasoning behind how the agency (uniquely) assesses the strength and rigor of evidence in each NCA, including how NCA evidence questions are derived and what type and amount of evidence will be sufficient to answer them. The NCA guidance should include a section on how the agency will accomplish this end.

CMS Should Provide Coverage Guidance in Each NCA

Medicare beneficiaries and clinicians should not have to wait months for coverage and access to FDA-approved products. The current NCA process lasts 9-12 months, and implementation can take months to years after that—patients are often left waiting without coverage in the interim.[v] CMS currently provides no guidance in its NCA's on the status of Medicare coverage (including non-coverage), either nationally or to its Medicare Administrative Contractors (MACs), and this needs to change. **Our organizations urge CMS to clearly state coverage guidance in each NCA and not leave Medicare providers and beneficiaries hanging.**

Conclusion

Thank you for considering our views. If you have questions, please contact Sue Peschin, President and CEO of the Alliance for Aging Research, at speschin@agingresearch.org or the Alliance's Vice President of Public Policy and Government Relations, Michael Ward, at mward@agingresearch.org.

Sincerely,

Alliance for Aging Research
Alliance for Health Innovation
Alzheimer's Los Angeles
Alzheimer's New Jersey
Alzheimer's San Diego
Arthritis Foundation
Association of Black Cardiologists
Asthma and Allergy Foundation of America
Caregiver Action Network
Chronic Care Policy Alliance

EveryLife Foundation for Rare Diseases
Family Caregiver Alliance
Global Alzheimer's Platform Foundation
Global Coalition on Aging Alliance for Health Innovation
Healthy Men Inc.
HealthyWomen
Infusion Providers Alliance
LuMind
LUNGevity
Lupus and Allied Diseases Association, Inc.
Melanoma Research Alliance
National Consumers League
National Minority Quality Forum
National Task Group on Intellectual Disabilities and Dementia Practices
Nevada Chronic Care Collaborative
NTM Info & Research
Parent Project Muscular Dystrophy
Partnership to Fight Chronic Disease
Society for Women's Health Research
The Gerontological Society of America
The Global CEO Initiative on Alzheimer's Disease
The Mended Hearts, Inc.
UsAgainstAlzheimer's
Voices of Alzheimer's

[i] https://www.cms.gov/medicare/coverage/determinationprocess/downloads/fr08072013.pdf.

[ii] Vemulapalli, Sreekanth, et. al. *Mitral Valve Surgical Volume and Transcatheter Mitral Valve Repair Outcomes: Impact of a Proposed Volume Requirement on Geographic Access*. Journal of the American Heart Association. Vol. 9, No. 11. 27 May 2020. https://www.ahajournals.org/doi/10.1161/JAHA.119.016140

[iii] Alliance for Aging Research. Façade of Evidence. Pages 18-25. February 2023. https://www.agingresearch.org/wp-content/uploads/2023/02/Facade-of-Evidence-CED-2-13-2023.pdf

[iv] https://energycommerce.house.gov/events/health-subcommittee-legislative-hearing-1.

[v] These delays can occur as a result of the implementation of additional coverage requirements, such as the development of a RCT or data registry to support a NCD with CED.