August 21, 2023

Centers for Medicare & Medicaid Services
Department of Health and Human Services
7500 Security Boulevard
Baltimore, MD 21244

Re: Coverage with Evidence Development: Proposed Guidance Document June 2023

Dear Administrator Brooks-LaSure:

Thank you for the opportunity to comment on the Coverage with Evidence Development Proposed Guidance. The undersigned organizations represent a diverse group of patient advocates, caregivers, and providers who are deeply committed to advancing the well-being of patients across diverse communities and ensuring equitable access to healthcare.

Medicare's mission is to provide coverage for items and services that are deemed "reasonable and necessary" for the populations it serves. The proposed guidance states that the agency will use the National Coverage Determination (NCD) using Coverage with Evidence Development (CED) process to expand coverage and gather data when the Agency lacks sufficient information from existing clinical research to make a positive coverage determination.

We wish to highlight the first and fundamental criteria put forward by the Medicare program to consider an item or service as reasonable and necessary—namely, its safety and effectiveness.[i] These very criteria align with those used by the Food and Drug Administration (FDA) in their rigorous approval process for medical interventions. We firmly believe that any medical intervention that has undergone such comprehensive evaluation and received FDA approval being safe and effective – including being indicated (or not contraindicated) for Medicare patients merits coverage and access under the program – should in nearly all circumstances fulfill the reasonable and necessary threshold requirement. At a minimum, the Centers for Medicare and Medicaid Services (CMS) should exercise deference to the FDA regarding the assessment of expected clinical benefit and to the Congressional intent related to accelerated approval.

We appreciate the opportunity to share our perspective on CMS's proposed updated CED criteria, based on the program's historical performance and the need for transparency and clarity in criteria and endpoints. It is essential that the agency address and cure these concerns in order to ensure the CED process efficiently develops additional data and expedites, rather than impedes, access to therapeutics. We sincerely appreciate the opportunity to provide our input and look forward to collaborating with CMS in developing policies that best serve the interests of patients nationwide.

CED Clinical Studies Are Not Voluntary for Patients Who Depend on the Medicare Program for Coverage

The proposed guidance document emphasizes and reemphasizes that participation in a CED clinical study is completely voluntary for both beneficiaries and sponsors. We disagree strongly with this characterization. Beneficiaries who depend on the Medicare program for coverage are unable to decide *not* to participate in a CMS-approved clinical study for FDA-approved treatments that have an NCD requiring CED and still have access to those treatments. **We urge CMS to either remove reference to CED as "voluntary," or to add language clarifying that FDA-approved treatments under an NCD requiring CED provided outside of CMS approved studies are nationally non-covered.**

Older adults meet with their health care providers, often alongside family caregivers, to discuss the benefits and risks of treatment, according to their diagnosis and needs. It is against federal law for CMS to interfere with clinical care. Section 1801 of the Medicare law states, "Nothing in this title shall be construed to authorize any Federal officer or employee to exercise any supervision or control over the practice of medicine or the manner in which medical services are provided, or over the selection, tenure, or compensation of any officer or employee of any institution, agency, or person providing health services; or to exercise any supervision or control over the administration or operation of any such institution, agency, or person." Section 1801 was included in the law to offset the criticism made by opponents of the proposal that Federal legislation would give Federal officials the opportunity and the right to interfere in the diagnosis and treatment of the individual. [ii]

A beneficiary's decision to not participate in a CED clinical study does not necessarily reflect unwillingness, as there are often access barriers outside a patient's control. These agency-directed restrictions may include, but are not limited to, care setting or provider eligibility criteria or limits on CED clinical study enrollment.

Post-market randomized control trial requirements (RCTs) may be unpalatable to beneficiaries and present ethical issues, as RCT study design in CED may require some Medicare beneficiaries to receive a placebo for a device, diagnostic, or prescription drug already found to be "safe and effective" by the FDA. Beneficiaries may be required to pay coinsurance for a placebo in order to maintain a blinded study. Some populations may experience mistrust based on historical experience or have legal concerns that create hesitancy to have personal health data collected in a clinical study. By creating barriers to patient access, denying that there are barriers, and placing the onus for shortcomings on sponsors and patients, CMS interferes with and restricts the medical autonomy of Medicare beneficiaries.

The proposed guidance also notes that a motivating factor for the use of CED is that many products that are early in their lifecycle have shown limited clinical evidence. CMS specifically implicates the Food and Drug Administration's (FDA) Accelerated Approval Program (AAP) for not producing sufficient health outcomes data for the agency to determine that a therapeutic is reasonable and necessary. However, this position runs directly counter to the creation and intent of the pathway. Accelerated approval, and other expedited approval pathways, were created to allow for earlier approval of drugs that treat serious conditions and fill an unmet medical need. By issuing CED for those therapeutics, CMS ignores unmet medical need and

works counter to the intent and nature of the pathway. The AAP allows for the initial approval of a drug that treats serious and life-threatening diseases based on a demonstration of effect on a surrogate endpoint—or an intermediate clinical endpoint—that is reasonably likely to predict a clinical benefit. Accelerated approval products are approved through the same statutory provision as non-accelerated approval drugs. [iii]

Conversely, CED is not mentioned in statute, and was originally developed by CMS in a 2006 guidance.[iv] The specific statutory basis cited in the proposed guidance makes no specific mention of a CED program or any CMS led evidence collection. Congress has not ratified CMS' CED powers, or authorized CMS to conduct research studies into the effectiveness of medications or medical devices. In fact, Robert Charrow, former HHS General Counsel, previously issued an HHS Office of General Counsel Advisory Opinion explaining that CMS' interpretation of its statutory authority to use CED as the basis for coverage of items and services is "unlawful […]" because CMS's "broad reading of the term [support] is fundamentally inconsistent with" the legal definition of public health service support.[v][vi] For these reasons, we are concerned that this guidance provides pretext for Medicare to use CED to dismantle the Congressionally-mandated purpose of the accelerated approval pathway.

Overly Broad Criteria and Vague Endpoints

A major concern of the patient advocacy community is that the updated CED clinical study criteria outlined in this proposed guidance are overly broad with vague endpoints. Unfortunately, these shortcomings are not new and have repeatedly been flagged as key shortcomings of the current CED process. A seminal April 2022 article on CED published in the American Journal of Managed Care noted:

> "Currently, data collection mechanisms for the CED program are designed and implemented without a specific and transparent timeline for coverage reconsideration by CMS. This is exemplified by the wide range of program duration ... thus, potential sponsors of CED registries or trials may be reluctant to fund these initiatives due to anxiety about the program's duration, what constitutes "success," and the possibility of "failure" that may eliminate any form of CMS coverage or even call FDA clearance or approval into question … a timeline for reevaluation could offer the predictability necessary for collaborators to confidently invest resources in data collection infrastructure. Moreover, from the perspective of CMS and Medicare beneficiaries, a stalled program means either a potentially beneficial therapy is being withheld or a potentially harmful therapy is being furnished to beneficiaries. Measures of ongoing success could be in the form of clinical trial or registry milestones such as protocol design, enrollment initiation, data analysis, and the like. Regardless of the specifics, measures of progress and an assessment timeline should be identified a priori with a plan to address delays on a regular basis."[vii]

Several of our organizations publicly reiterated these concerns over the last year, including in a letter last September in response to the Agency for Healthcare Research and Quality (AHRQ)

Draft Analysis of Requirements for CED[viii] and during the February 2023 Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) on Analysis of Coverage with CED criteria.[ix] In these forums, patients and advocates raised the need for CMS to provide clear standards to help ensure that clinical trials are designed so as to meet CMS's reasonable and necessary criteria. Further, stakeholders shared the need for clear criteria and thresholds that will lead, if such results are attained, in the end of CED coverage restrictions for the affected products or procedures.

If CMS finalizes the proposed CED study criteria without addressing these key shortcomings, it will lead to an untenable situation in which CED will introduce even greater uncertainty than what exists under the status quo for patients, physicians, and sponsors.

Additionally, the criteria for clinical study standards under CED, as defined in section VI, are overly broad, lacking specific definitions for crucial terms and giving CMS officials open ended authority to enforce CED study criteria as they see fit, for example:

- In section 6.4: The section "Evidence sufficient to assess health outcomes" fails to define such thresholds and remains entirely open to CMS's interpretation.
- In section 6.7: "Beneficiary subpopulations affected by the item or services under evaluation." CMS highlights the need for expanded participation in trials while citing vague requirements for those subpopulations. CMS needs to provide a standard definition of what they consider to be representative in regard to clinical trial data. We encourage CMS to adopt a definition prioritizing representation that is reflective of the population in Medicare that experiences the disease. We also encourage CMS to avoid creating CED parameters that unintentionally prevent representative enrollment in CED trials.
- In section 6.10: "Evidentiary threshold for the primary health outcome(s)" is a criterion that is meaningless post-FDA approval, after which a drug or therapeutic has demonstrated clinical efficacy or in the case of AAP, reasonable likelihood of clinical benefit to be confirmed via confirmatory trial.
- In section 6.11: No terms that are descriptive of data quality are defined, including "provenance, bias, completeness, accuracy, sufficiency of duration of observation" or "sufficiency of sample size."
- In section 6.13: CMS must clarify the term "robustness of results."

This ambiguity can be found throughout the guidance, in which CMS has allowed themselves undefined latitude in determining what type and amount of evidence is acceptable.

We are deeply concerned about unclear criteria for ending CED, and urge CMS to create a predefined trigger mechanism to end CED coverage if interim data reporting from CED trials show overwhelmingly positive outcomes in order to ensure timely access to innovative therapies. This approach would align with the FDA's practice of ending clinical trials early when a therapy proves so effective that it becomes unethical to keep the control group on a placebo.[x]

Ethics and Equity Considerations in CED Trials

In the pursuit of comprehensive data collection, CMS cites the underrepresentation of relevant subpopulations in clinical trials as a rationale for continued study and data collection through CED. While we affirm the importance of inclusivity in research, tying data collection to coverage restrictions will have unintended consequences and disproportionately restrict access to diverse and underrepresented communities, particularly people of color and especially women of color.

There is a troubling history of CMS allowing the policy objectives underlying equity standards as justification to limit coverage through CED. Unfortunately, these limitations have fallen disproportionately upon communities of color and rural areas. As a result, the use of CED has only exacerbated the inability of underrepresented communities to obtain timely access to the therapies that they need to treat their serious medical conditions.[xi] Moreover, by restricting coverage based on data collection requirements, CMS may inadvertently hinder the very data collection efforts it seeks to promote.

CMS must approach data collection and study design in a manner that respects patients' autonomy and prioritizes equitable access to approved treatments. Without a fundamental shift in approach to CED, access will be restricted for the very populations the agency aims to understand and serve.

Conclusion

CMS has failed to address the valid concerns raised by external stakeholders and members of the MEDCAC in the proposed CED guidance. This is unacceptable and CMS should reissue the guidance to address the concerns raised by our organizations.

We advocate in the strongest terms for broader access and data collection methods that facilitate inclusivity rather than imposing strict controls and cumbersome data registries. CMS must decouple the data collection process from coverage requirements to ensure that patients from all backgrounds have equitable access to innovative therapies and to foster a comprehensive research landscape. For additional questions about this letter, please reach out to Michael Ward, Vice President of Public Policy and Government Relations at the Alliance for Aging Research at mward@agingresearch.org and Adina Lasser, Public Policy Manager at the Alliance for Aging Research, at alasser@agingresarch.org.

Sincerely,

Alliance for Aging Research
Alliance for Health Innovation
Alliance for Patient Access
Alzheimer's Los Angeles
Alzheimer's New Jersey

Alzheimer's San Diego
Arthritis Foundation
Association of Black Cardiologists
Autoimmune Association
Caregiver Action Network
Chronic Care Policy Alliance
EveryLife Foundation for Rare Diseases
Family Caregiver Alliance
Global Coalition on Aging Alliance for Health Innovation
Healthy Men Inc.
HealthyWomen
Infusion Access Foundation
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 Global CEO Initiative on Alzheimer's Disease
The Mended Hearts, Inc.
UsAgainstAlzheimer's
Voices of Alzheimer's

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[i] Centers for Medicare & Medicaid Services. (n.d.). Internet-only manuals (IOMs). CMS. https://www.cms.gov/regulations-and-guidance/guidance/manuals/internet-only-manuals-ioms-items/cms019033.

[ii] Smith, J. A., & Johnson, B. R. (1985). Reflections on the enactment of Medicare and Medicaid. Health Care Financ Rev. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4195078/

[iii] 21 U.S. Code § 356

[iv] Centers for Medicare & Medicaid Services. (2014, November 20). Guidance for the Public, Industry, and CMS Staff: Coverage with Evidence Development ("CED Guidance"). CMS. https://www.cms.gov/medicare-coveragedatabase/view/medicare-coveragedocument.aspx?MCDId=27

[v] Charrow, R. (2021, January 14). Advisory Opinion 21-03 on Medicare Coverage with Evidence Development, U.S. Dep't of Health & Human Servs., 2. (Rescinded). While this advisory opinion has since been withdrawn, Charrow's legal interpretation remains valid.

[vi] Government Publishing Office. (2023). 42 CFR 93.221. https://www.ecfr.gov/current/title-42/chapter-I/subchapter-H/part-93/subpart-B/section-93.221

[vii] Zeitler, E. P., & Gilstrap, L. G. (2022). Coverage With Evidence Development: Where Are We Now? The American Journal of Managed Care, 28(8), 382-389. https://doi.org/10.37765/ajmc.2022.88870

[viii] Alliance for Aging Research. Comments on Draft Analysis of Requirements for Coverage with Evidence Development (CED). 28 Sep 2022. https://www.agingresearch.org/wp-content/uploads/2022/09/AAR-Draft-AHRQ-CED-Comments-FINAL-9.23-FINAL.pdf

[ix] Centers for Medicare & Medicaid Services. (n.d.). MedCAC meetings. CMS. https://www.cms.gov/medicare-coverage-database/view/medcac-meeting.aspx?medcacid=79&year=all&sortBy=meetingdate&bc=15

[x] Food and Drug Administration. (2006). Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees. https://www.fda.gov/media/75398/download. Sections 4.4.1.1 and 7.2.1

[xi] Peschin, S., Farber, D., & Trinh, J. Façade of Evidence: How Medicare's Coverage with Evidence Development Rations Care and Exacerbates Inequity. (13 Feb 2023). https://www.agingresearch.org/wp-content/uploads/2023/02/Facade-of-Evidence-CED-2-13-2023.pdf