Submitted Electronically

November 7, 2022

Tara Hall
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Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

RE: December 7, 2022 MEDCAC Virtual Meeting on the General Requirements for Clinical Studies Submitted for CMS Coverage Under Coverage with Evidence Development

Dear Ms. Hall:

The 20 undersigned organizations are pleased to provide comments to the Medicare Evidence Development and Coverage Advisory Committee ("MEDCAC") Panel that will meet on December 7, 2022, to discuss the Centers for Medicare & Medicaid Services ("CMS") general requirements for clinical studies under Coverage with Evidence Development ("CED"). Collectively, the Task Force represents coalitions and advocacy organizations focused on chronic disease, aging, and minority and women's health. As such, we have unique insight to the CED process and the impact CEDs have on patient access to medically necessary treatment and care.

We offer our views on the requirements for clinical studies intended to satisfy CED requirements, focusing specifically on the HHS Agency for Healthcare Research and Quality's ("AHRQ") "Analysis of Requirements for Coverage with Evidence Development (CED)" dated September 7, 2022 that recommended CMS update the CED study design requirements with a particular focus toward the efficient completion of CED studies.[1] The Task Force submitted its comments driven by scientific, legal, and public policy rationales during the AHRQ public comment period and incorporates them here. For the reasons explained in detail below, we request this MEDCAC Panel and CMS revise and improve the CED criteria by requiring that CED-approved studies be clear in their scope, be finite in duration, and be reported on ClinicalTrials.Gov.

We recognize the purpose of the MEDCAC meeting is to vote on updated recommendations for CED clinical study criteria. However, more broadly, our organizations believe the CED mechanism is beyond CMS's authority, has often impeded rather than facilitated data collection on populations relevant to the Medicare program, is inherently flawed, and the process has been, and will likely continue to be, used in a capricious and discriminatory manner. Ultimately, CMS should discontinue the use of CED altogether and either: (1) issue final National Coverage Determinations ("NCDs") that do not utilize the CED process; and (2) issue NCDs that cover all drugs and biologics approved by the U.S. Food and Drug Administration (subject to appropriate conditions such as safety recalls).

[1] Agency for Healthcare Res. & Quality, *Analysis of Requirements for Coverage with Evidence Development (CED) – Topic Refinement* (Sept. 2022), https://effectivehealthcare.ahrq.gov/products/coverage-evidence-development/draft-comment.

I. The CED Process is Beyond the Powers Granted to CMS Under the Social Security Act

Congress has never authorized a "Coverage with Evidence" pathway for NCDs nor vested CMS with the powers to impose a CED. While CMS claims that the CED authority stemmed from section 1320b-12 of the Public Health Service Act, [2] that statute does not authorize CMS to adopt CEDs but only addresses AHRQ studies – a finding which the HHS General Counsel in 2020 (in a now-rescinded opinion) found did not support the process.[3] While we will not belabor the point here, we do wish to preserve the argument that the entire CED process is not legally valid, and should be rescinded.

II. Today's CED Process is Inherently Flawed

Even if Congress had authorized CMS to use the CED process, the CED process is inherently flawed and cannot be fixed by revising the existing CED criteria or creating new CED criteria. The result of today's CED process is a system that defeats many of CMS's goals for the Medicare program. Instead of providing Medicare beneficiary access to medically necessary care, the CED process contributes to an ongoing denial of access to treatment, especially for persons of color, persons with intellectual disabilities, persons living with multiple chronic conditions, lower-income Americans, and persons living in rural areas.

a. The CED Process Deprives Beneficiaries Access to Treatment Absent Meaningful Alternatives

The CED process indefinitely and effectively prevent hundreds of thousands of Medicare beneficiaries from accessing potentially disease-modifying therapies. Under CMS' terms, CEDs restrict coverage only to those few Medicare beneficiaries who are fortunate enough to be able to participate in approved clinical studies. These studies are small in number, limited in size, and available in only limited geographic areas. This means that, for example, only a select few beneficiaries are able to access anti-amyloid mABs for the treatment of AD even though an FDA-approved treatment is already available and other treatments may soon be approved and available to those with sufficient private resources to access treatment.

The CED process also enables CED trials to continue in perpetuity without a clear end in sight. According to an April 2022 study published in the *American Journal of Managed Care (AJMC)* on the CED process, only six out of the total 27 CED trials initiated over the past 15–20 years have been retired and have taken between 4–12 years to be retired.[4] Two of the six retired CED trials resulted in deferral to the Medicare Administrative Contractors for local coverage decisions.[5] Meanwhile, the other CED

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[2] Final NCD for mABs; Ctrs. for Medicare & Medicaid Servs., *Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease Proposed Decision Memo* ("Proposed NCD for mABs") (Jan. 2022), https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=Y&ncaid=305&fromTracking=Y&=.

[3] Robert Charrow, *Advisory Opinion 21-03 on Medicare Coverage with Evidence Development*, U.S. DEP'T OF HEALTH & HUMAN SERVS. at 2 (Jan. 14, 2021) (rescinded) (emphasis added).

[4] *See* Emily P. Zeitler et al., *Coverage With Evidence Development: Where Are We Now?*, 28 AM. J. MANAGED CARE 382, 382–89 (Aug. 2022). Dr. Zeitler's conclusions are not new. Other studies have similarly concluded that "CED schemes . . . are often costly, complex, and challenging." Carlo Federici et al., *Coverage with evidence development schemes for medical devices in Europe: characteristics and challenges*, 22 EUR. J. HEALTH ECON. 1253, 1253–73 (Nov. 2021).

[5] Zeitler.

trials remain ongoing and one CED trial never even commenced.[6] The inherent lack of rhyme or reason as to how or when CMS decided to retire 6 of the 27 CEDs was noted and suggests that there are bigger problems with the process than refinement of clinical study requirements: "In summary, on review of the 6 therapies with CED requirements removed, there were no clear programmatic characteristics suggesting greater or less likelihood of progressing to an NCD without CED requirements versus revocation of the NCD."

At the same time, the CED process appears to offer limited value to help CMS determine whether a drug is reasonable and necessary for purposes of coverage. The AJMC study found material inconsistency across the CED program, noting "significant variation in [CED] use over the past 15 years . . . but there was tremendous variability in execution of the program across therapies and services."[7] The flaws in carrying out CED trials do not yield reliable or consistent information to permit CMS to determine whether an FDA-approved drug should be covered by Medicare.

b. <u>The CED Process Does Not Further CMS' Goal of Promoting Health Equity</u>

Notwithstanding CMS' numerous statements emphasizing health equity, the CED process disproportionally harms diverse and already underrepresented communities of color (particularly women of color) and low-income Americans, that do not have meaningful access to clinical trial sites or physicians participating in registries. The CED process also raises doubts on whether CMS can meet CED trial recruitment goals and whether CMS can undertake an adequate number of trials and in a timely fashion. Several organizations submitting these comments are actively engaged in grassroots efforts to improve the representativeness of clinical trials, including direct recruitment of participants. While some sponsors have expressed enrollment goals aligned with or in excess of CMS' stated goals, the reality is more daunting.

CMS has also ignored reality and perpetuated guidelines that create an unharmonized set of diversity requirements and constraints that make it impossible to obtain diverse enrollment. For example, the disproportionate impact of Alzheimer's and other dementias falls upon older Black and Hispanic Americans, as compared to older white Americans,[8] yet the current CED for monoclonal antibodies for the treatment of Alzheimer's ("mAB") does not propose clinical trials that would address this known disparity. Similarly, chronic health conditions associated with higher dementia risk, such as cardiovascular disease and diabetes, disproportionately affect Black and Hispanic populations.[9] Social and environmental disparities, including lower levels and quality of education, higher rates of poverty, and greater exposure to adversity and discrimination, increase the risk for these chronic conditions and risk for dementia in Black and Hispanic populations.[10]

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[6] *Id.*
[7] *Id.*
[8] Alexander Chin et al., *Diversity and Disparity in Dementia: The Impact of Ethnoracial Differences in Alzheimer's Disease*, 25(3) ALZHEIMER'S DISEASE & ASSOCIATED DISORDERS 187, 187–88 (July–Sept. 2011).
[9] Lisa Lines & Joshua Wiener, *Racial and Ethnic Disparities in Alzheimer's Disease: A Literature Review*, U.S. DEP'T OF HEALTH & HUMAN SERVS. OFF. OF THE ASSISTANT SEC'Y FOR PLANNING & EVALUATION (Feb. 2014), https://aspe.hhs.gov/reports/racial-ethnic-disparities-alzheimers-disease-literature-review-0.
[10] Jennifer Weuve et al., *Cognitive Aging in Black and White Americans: Cognition, Cognitive Decline, and Incidence of Alzheimer Disease Dementia*, 29(1) EPIDEMIOLOGY 151, 154 (Jan. 2018).

Other examples beyond the recent mAB CED abound -- the CMS Amyloid PET Alzheimer's Prevention Through Exercise ("APEx") CED trial enrolled 117 participants, 112 of who were white and 5 of who were black. The Cognitive Training and Practice Effects in Mild Cognitive Impairment CED trial enrolled 197 participants, 51 of who withdrew, 111 of who were white, and only 2 of who were Asian. The Cochlear Implantation CED trial, Cochlear Implantation in Adults With Asymmetric Hearing Loss Clinical Trial, studied 40 participants: 33 white, 4 not reported, 2 Asian, and 1 Black. And the TAVR CED, which remains ongoing, Safety and Efficacy Study of Lotus Valve for Transcatheter Aortic Valve Replacement (REPRISE III) had 1425 participants: 1172 White, 45 Black, 43 Not Reported, 30 Hispanic, 9 Asian, 9 American Indian, 8 Other, and 3 Native Hawaiian/Pac. Islander. These conclusions also apply with equal force to NIH-conducted trials, which are typically allowed as CED trials. These results are not surprising given the effect of CED parameters that have the effect of limiting participation among communities of color. For example, in the NCD reconsideration for TAVR, CMS continued site requirements including an annual minimum volume of heart value surgeries – which is unrelated to the minimally-invasive TAVR procedure. These requirements have the effect of limiting the providers that can provide the procedure to only facilities that have large cardiovascular programs, such as academic medical centers. These providers are typically found in areas that disproportionately serve white populations. **Citing lack of evidence on minority populations as part of the rationale to continue coverage restrictions, when CMS perpetuates policies that restricts access (and data collection) for those same populations, is illustrative of the often circular and harmful policies utilized in CED decisions.**

III. The CED Criteria Should Be Updated to Ensure that CED-Approved Studies Be Retired in a Timely Manner and Are Reported on ClinicalTrials.Gov

MEDCAC should recommend the following improvements to the CED criteria.

a. CED Study Criteria Should Include More Explicit Requirements for When and How CMS Should Retire an NCD Under CED

The MEDCAC Panel should recommend that CEDs be finite in duration of no greater than two to three years. As discussed above, CMS is not reevaluating the adverse implications of CED coverage policies because some CED studies are never started, others have no end dates, and even when concluded and additional data are available, the CED process remains open.

Zeitler and colleagues identified in the AJMC article the lack of a "clear therapy-specific rubric for successful retirement of CED data collection requirements" as a crucial barrier, stating that such a rubric "should be established a priori to enhance the authority of CMS to reconsider CEDs if criteria are not met; such a rubric would offer transparency and predictability to patients, providers, and other data collection stakeholders while better aligning access to therapies and services with the available evidence in a timely manner."[11]

Specified CED trial end dates would be consistent with CMS' own ideas. In its 2014 guidance on CED under the section "Ending CED," for example, CMS states that the purpose of the CED studies is to "produce evidence that will lead to revisions in Medicare coverage policies," and cites two examples of completed CED processes—NCDs for oncologic uses of *fluorodeoxyglucose* positron emission

[11] Zeitler.

tomography, and ventricular assist devices. CMS implies, but does not make explicit, that there should be **a clear beginning and end to the CED process.** The "Ending CED" section further states that "Studies with a specific design, such as randomized clinical trials, have established start and end dates. When enrollment and follow up are complete, the data are to be analyzed and published in the peer reviewed medical literature."[12] **However, that is not the reality, and nearly 20 CEDs initiated years ago remain pending with no end date in sight.**

Even when investigators analyze CED study data and publish in "peer reviewed medical literature," ***the current CED criteria do not outline CMS requirements to retire a CED***. For example, since 2010, access to stem cell transplant for myelodysplastic syndromes ("MDS") (cancerous bone marrow diseases in older adults) has continued to be limited under CED,[13] despite having a successful CED study published in 2020.[14] The *JAMA Oncology* study concluded, "Availability of insurance coverage affects access to HCT [allogeneic hematopoietic stem cell transplantation, or HCT]. Outcomes in patients older than 65 years are only marginally different from those in younger patients. Based on current data, we would recommend coverage of HCT for MDS by CMS."[15] Stem cell transplant is the only curative therapy available for myelodysplastic syndromes, which impact an estimated 10,000 older adults every year in the U.S.,[16] but data from 2019 Center for International Blood and Marrow Transplant Research reveal less than 1,000 HCT transplants performed in 2019.[17] The result is that patients, and particularly minorities, in need of access to stem cell transplant are being denied the only available treatment because twelve years after the start of the CED process, and two years after its completion with a positive recommendation, the CED remains open.

The AJMC study also revealed other methodologic flaws in the CED process. "One barrier to evidence development is the requirement for substantial logistical and financial investments, and it is not always clear what entity (or entities) should share this burden." AHRQ, however, in its final report, "Analysis of Requirements for Coverage with Evidence Development (CED)" never identifies, much less addresses, any of these issues, and particularly the critical issue about lack of definitive timeframes leading to treatments being "stuck" in the CED process in perpetuity. Instead, the report appears to adopt at face value the belief from its sister agency that "CMS is confident that the CED NCD process is sound."[18] We believe this is a fundamental mistake.

b. <u>CED Criteria Should Require the Disclosure of the Core Elements of the CED Protocol on ClinicalTrials.Gov</u>

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[12] Ctrs. for Medicare & Medicaid Servs., *Guidance for the Public, Industry, and CMS Staff: Coverage with Evidence Development* (Nov. 2014), https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=27.

[13] Ctrs. for Medicare & Medicaid Servs., *Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for Myelodysplastic Syndrome Decision Memo* (Aug. 2010), https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=238.

[14] Ehab Atallah et al., *Comparison of Patient Age Groups in Transplantation for Myelodysplastic Syndrome: The Medicare Coverage With Evidence Development Study*, 6 JAMA ONCOLOGY 486, 486–93 (Apr. 2020).

[15] *Id.*

[16] Am. Soc'y of Clinical Oncology, *Myelodysplastic Syndromes - MDS: Treatment Options* (Dec. 2017), https://www.cancer.net/cancer-types/myelodysplastic-syndromes-mds/treatment-options.

[17] Health Res. & Servs. Admin., *Transplant Activity Report*, https://bloodstemcell.hrsa.gov/data/donation-and-transplantation-statistics/transplant-activity-report#summary (updated Apr. 2022).

[18] *Analysis of Requirements for Coverage with Evidence Development (CED) – Topic Refinement*, at 3.

MEDCAC should advise CMS to designate the federal website ClinicalTrials.gov as the primary public website for disclosing the core elements of the CED protocol (including data sources, key outcomes, and key elements of design).[19] Because each clinical study that is registered is assigned a unique permanent identifier (the NCT number), the CMS website can simply provide an electronic link to the unique NCT identifier electronically that will send a viewer directly to the ClinicalTrials.gov entry. Only a small subset of CED trials are "applicable device clinical trials" or "applicable drug clinical trials" pursuant to 42 C.F.R § 11.10 that legally must be publicly disclosed on this federal website. However, the ClinicalTrials.gov platform is not limited to "applicable clinical trials" and is readily accessible for voluntary entry and public disclosure of multiple types of prospective clinical investigations, including registries and observational studies, that do not legally require posting. As of October 29, 2022, there are 432,129 clinical trials registered on Clinical Trials.gov.[20] Of these, nearly one fourth are observational clinical studies (22%).[21]

The posting of CED studies on ClinicalTrials.gov as the primary site has major public policy and practical advantages for patients, clinicians, clinical sites, and federal regulators:

- Most important, it is the primary source of information for patients, patient advocacy groups, clinicians, clinical sites, and IRBs to identify specific premarket and post-market clinical studies open for enrollment for specific conditions;
- All CED decisions involve drugs, biologics, or medical devices regulated by FDA, which is the focus of ClinicalTrials.gov;
- Under the management of the National Library of Medicine, this database and its website are mature and has been under continuous expansion and improvement by experts in website design specific to clinical investigations; and
- It is readily accessible for data entry and update, easily searchable, subject to sophisticated internal quality control, includes a permanent publicly accessible history of changes to entries, and provides clear and concise "assists" for new users.

We urge MEDCAC to recommend that all CED trials be listed on clinicaltrial.gov.

c. <u>CED Criteria Should Not Include AHRQ's Proposed CED Study Design Until They Are Further Refined</u>

This MEDCAC Panel should <u>not</u> adopt AHRQ's proposed CED trial criteria enumerated in the final report "Analysis of Requirements for Coverage with Evidence Development (CED)" until they are further refined.

First, MEDCAC will need clarification on the meaning of "sponsor" in AHRQ's Item A (Team), which requires, "The study [be] conducted by investigators with the resources and skills to complete it successfully."[22] AHRQ's use of the term "sponsor" does not distinguish between: (i) the parties that will carry out the CED study; and (ii) the parties that are responsible for the overall conduct, funding, and

[19] By comparison, AHRQ proposed that the primary posting (*e.g.*, public disclosure) of the CED protocol will be the CMS website whereas posting to ClinicalTrials.gov or elsewhere will be at the discretion of the investigator. *Analysis of Requirements for Coverage with Evidence Development (CED) – Topic Refinement*, tbl. 5.
[20] ClinicalTrials.Gov, *Trends, Charts, and Maps*, https://www.clinicaltrials.gov/ct2/resources/trends (updated Oct. 27, 2022).
[21] *Id.*
[22] *Analysis of Requirements for Coverage with Evidence Development (CED) – Topic Refinement*, tbl. 5.

oversight of the CED study. Ziegler precisely noted that a significant flaw in the current CED process includes a clear understanding of who the sponsor is.[23]

Second, MEDCAC should not accept AHRQ's "pass or fail" construct in Item E (Context), which specifies that "CMS and investigators agree upon the evidentiary threshold for the study as needed to demonstrate clinically meaningful difference in key outcome(s) with adequate precision."[24] Using veiled and ambiguous language, this requirement directly infers that all CED studies are expected to have a primary efficacy or safety endpoint with a prespecified statistical threshold for "success" (*i.e.,* statistical superiority or non-inferiority to a comparator service or product). This proposed CED "pass or fail" construct is inappropriate for post-market CED of FDA-approved drugs and medical devices to demonstrate that use of an FDA-approved product is "reasonable and necessary" for Medicare beneficiaries pursuant to 42 C.F.R. § 405.201.

The "reasonable and necessary standard," for which CED studies are intended to provide evidence to demonstrate, does not require the whimsical selection of an arbitrary statistical threshold nor an arbitrary selected level of "targeted precision," which is the prespecified boundary (confidence interval) of acceptable random error of the measured outcome result. In contrast with the FDA approval process for prescription drugs whereby "adequate and well-controlled" trials are a statutory requirement,[25] the use of post-market CED to support the multiple prongs of the "reasonable and necessary" standard for Medicare coverage usually involves consideration of multiple clinical outcomes, evolving evaluation over time as the service or product of interest is dispersed in its post-market use to multiple clinical sites, providers, and patients that are more diverse than those in studies to support FDA product approval, and the application of informed and subjective clinical judgment by CMS and its physician and patient advisors.

Third, this MEDCAC Panel should also refuse to replace RCTs with AHRQ's more confusing set of criteria in Table 5 (Items G, H, I, J, K and L, for example) that seemingly are contradictory and unrealistic in the real world.[26] AHRQ's final recommendations fail to clearly state that the use of an RCT should be rare and relied on only in unusual circumstances. The implied use in a CED decision of an RCT with blinding of participants also raises serious ethical questions. 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. An RCT study design in CED would, by definition, require some Medicare beneficiaries to receive a placebo for a device, diagnostic, or prescription drug found to be "safe and effective" by FDA.

Finally, we wish to express our reservations about the abbreviated timeframe provided for soliciting comment on the AHRQ CED report, the lack of proactive efforts to raise awareness of the report and to solicit feedback from relevant stakeholders, and the lack of time provided to AHRQ to incorporate feedback from public comment and perform additional research as necessary in advance of this MEDCAC meeting. It is vital that agencies be provided adequate time to solicit and meaningfully incorporate and respond to feedback from the public. Due to the timing of the release of the draft

[23] Zeitler.
[24] *Analysis of Requirements for Coverage with Evidence Development (CED) – Topic Refinement*, tbl. 5.
[25] *See* 21 U.S.C. § 355; 21 C.F.R. § 314.26.
[26] *Analysis of Requirements for Coverage with Evidence Development (CED) – Topic Refinement*, tbl. 5.

report and the inability of CMS to delay this MEDCAC meeting, we are concerned that sufficient time for these essential functions has not been permitted.

IV. Conclusion

Our organizations believe CMS should cease the use of CED and issue final NCDs that extend Medicare coverage for FDA-approved drugs for Medicare beneficiaries nationwide without CED. In the alternative, this MEDCAC Panel should advise CMS to improve the CED criteria to address the inherent flaws in the CED process.

We appreciate the opportunity to provide its thoughts and working alongside MEDCAC and CMS to improve the health and well-being of Medicare beneficiaries, particularly our nation's older adults and persons with disabilities.

Please contact Susan Peschin, President and CEO of Alliance for Aging Research, at speschin@agingresearch.org for additional information.

Sincerely,

Alliance for Aging Research
American Society of Consultant Pharmacists
Association of Black Cardiologists
BrightFocus Foundation
Cancer Support Community
Caregiver Action Network
EveryLife Foundation for Rare Diseases
Global Alzheimer's Platform Foundation
Global Coalition on Aging Alliance for Health Innovation
HealthyWomen
Infusion Providers Alliance
Men's Health Network
National Alliance for Caregiving
National Medical Association
National Minority Quality Forum
Partnership to Fight Chronic Disease
RetireSafe
The Balm in Gilead
The Mended Hearts, Inc.
UsAgainstAlzheimer's
Voices of Alzheimer's