



SUBMITTED ELECTRONICALLY

August 21, 2023

RE: Proposed Guidance Document: Coverage with Evidence Development

Haystack Project appreciates the opportunity to provide comments on the Centers for Medicare & Medicaid Services' (CMS') proposed guidance document articulating its current thinking on how the Agency intends to utilize the Coverage with Evidence Development (CED) mechanism within a National Coverage Analysis (NCA).

Haystack Project is a 501(c)(3) non-profit organization enabling our membership of 140+ rare and ultra-rare disease patient advocacy organizations to coordinate and focus efforts that highlight and address systemic reimbursement obstacles to patient access. Our core mission is to evolve health care payment and delivery systems with an eye toward spurring innovation and quality in care toward effective, accessible treatment options for all Americans. We strive to amplify the patient and caregiver voice in these disease states where unmet need is high and treatment delays and inadequacies can be catastrophic.

Because the evidentiary review standards set forth in the proposed guidance on Evidence Review would tend to drive CMS to initiate CED if an NCA were pursued for an ultra-rare disease treatment, we have attached our previous comments to that proposed guidance. As we outlined in those comments, a significant proportion of Haystack Project's advocacy and education efforts focus on unintended consequences our patient communities face when reimbursement paradigms designed for more common conditions are applied to rare and ultra-rare disease treatments. Haystack Project has also engaged with CMS, AHRQ and the MedCAC on coverage decision trends and refinements with potential to impact our patient communities' access to treatments. We have repeatedly expressed our concerns about the potential for increasing CEDs for FDA-approved drugs, heightened scrutiny over accelerated approval treatments, and process gaps in ensuring that CED participations receive all research subject protections that are ordinarily afforded within clinical studies.

CMS notes that CED is used "when the available evidence is insufficient to demonstrate that the items and services are reasonable and necessary." Our comments to the proposed guidance document highlight the challenges associated with developing and accessing rare disease treatments and urge CMS to consider and address the significant potential that NCAs for rare

and ultra-rare disease treatments will disproportionately relegate our patient communities to limited treatment access and clinical trial requirements extending beyond FDA approval.

Background

Scientific advances in understanding and addressing disease mechanisms has advanced at a pace that would have been unthinkable decades ago. Targeted treatments, gene therapy and regenerative medicine, and immunologic approaches to rare, serious, and life-threatening conditions have offered renewed hope to individuals affected by a rare disease. However, exceedingly small populations, long diagnostic journeys, and a limited natural history knowledge base can make the treatment development and regulatory processes particularly challenging.

- Of the approximately 7,000 rare diseases identified to date, 95% have no FDA-approved treatment option
- 80% of rare diseases are genetic in origin, and present throughout a person's life, even if symptoms are not immediately apparent
- Approximately half of identified rare diseases do not have a disease-specific advocacy network or organization supporting research and development.

Most rare disease patients have no available treatment beyond off-label use of therapies approved for other conditions. Coverage policies and mechanisms, particularly those within Medicare National Coverage Determinations, can present absolute, impenetrable, and persistent access barriers if they are implemented without considering the treatment needs of rare disease patients. Haystack Project remains concerned that CED mechanisms, including CMS' study criteria, have been ill-suited to drive coverage for treatments labeled for, or used off-label in, managing very rare diseases.

- Research and development on treatments for extremely rare diseases frequently relies on FDA's accelerated approval mechanisms, use of surrogate endpoints, single-arm studies, and clinical trials evaluating treatment impact over a relatively short period of time in a small set of study participants. Therapies targeted to rare conditions also tend to be costly. We have expressed our concern that CMS can, in theory, single out any, or even all, accelerated-approval treatments, subject them to the critical lens of an NCA, predictably find that the evidence is insufficient to justify "national coverage," and offer CED to give patients a chance at the access its self-initiated NCA process foreclosed.
- Most individuals living with a very rare condition rely on off-label treatments to reduce disease burden and/or slow disease progression. NCAs for treatments can fully obstruct off-label use in rare diseases unless CED mechanisms and study criteria expressly provide for or exempt off-label uses supported by evidence in very rare conditions.
- Individuals living with a very rare condition who fit within CMS' aged and disabled Medicare population (and their treating physicians) have a substantial need for certainty

with respect to treatment received. This severely complicates CED study requirements that condition coverage on participation in blinded, randomized clinical studies.

- The unique challenges associated with research and development in rare diseases that are likely to drive increased scrutiny and create a perception of evidentiary uncertainty likely to trigger CED also create ethical issues complicating initiation of CED. This is particularly problematic when patients have limited treatment alternatives.

CED initiation should not be broadened beyond the relatively narrow statutory language authorizing its use.

As CMS has articulated in each CED NCD, its statutory authority for conditioning coverage on study participation is found in section 1862(a)(1)(E) of the Act, which provides that:

a) Notwithstanding any other provision of this title, no payment may be made under part A or part B for any expenses incurred for items or services—

...

(1)(E) in the case of research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section.

Under Section 1142, AHRQ may conduct and support research on outcomes, effectiveness, and appropriateness of services and procedures to identify the most effective and appropriate means to prevent, diagnose, treat, and manage diseases, disorders, and other health conditions. While the Act requires that AHRQ research priorities reflect the needs and priorities of the Medicare program, it does not substitute CMS' judgment for AHRQ's research priorities. Similarly, neither the Act nor the Department of Health and Human Services have delegated broad authority to CMS to leverage the NCD process as a substitute for AHRQ-determined research priorities permitting the Agency to condition coverage on research participation when scientific evidence fails to clear the unreasonably high bar of confidence that it is conclusive.

Haystack Project understands that CMS likely receives requests to initiate a National Coverage Decision for technologies that are not supported by a sufficiently robust body of evidence to gain national coverage. Haystack is concerned, however, that when CMS initiates an NCA directed at FDA-approved drugs, CED becomes an inflexible utilization management tool, beneficiaries become research subjects, and treatment "decisions" are subjected to randomization and even "blinding" on the precise intervention. In this context, CED does not simply enable access to promising treatments; it conditions access to safe and effective treatments on beneficiary willingness to place their care into the hands of researchers rather than the clinicians managing their condition(s) as well as factors beyond the patients' control (clinical trial availability, eligibility, and randomization).

CMS and AHRQ should prioritize ethical research, patient protections, equitable access, and meaningful informed consent.

We have previously urged AHRQ to ensure that its research priorities, and support for research, under Section 1142 prioritize access to care for patients covered by the Medicare program. We now urge CMS to avoid initiating the CED mechanism within the context of medically accepted uses of safe and effective treatments. Use of CED in these instances:

- Impermissibly substitutes CMS' analysis of clinical evidence and conclusions for decisions delegated to and made by FDA or appropriately left to shared decision making between patient and clinician
- Perpetuates and exacerbates health inequities associated with race, ethnicity, and socioeconomic status
- Raises significant ethical concerns by conditioning coverage for on-label use and medically accepted off-label use of FDA-approved treatments on participation in CMS-directed, potentially randomized clinical trials
- Introduces logistic impediments that deny patient access to treatments that are medically necessary for their condition
- Creates considerable tension between an access-enabling view of CED facilitating innovation versus a real-world mechanism that leverages Medicare's beneficiaries as research subjects to satisfy an amorphous bar of certainty on whether an intervention is reasonable and necessary

Institutional Review Board Review, Approval, and Oversight

Finally, Haystack Project is disappointed that CMS continues to assert that Institutional Review Board review, approval, and oversight over each individual CED study serves as a sufficient protection of patient rights within the context of research studies. Each NCA initiating CED, by necessity, a great deal of granularity on clinical study requirements and the research questions that those studies must resolve. Any entity, including CMS, engaged initiating, directing, reviewing and evaluating one or more clinical studies with a goal of utilizing data to evaluate the impact of an intervention on health outcomes ***is conducting research***. CMS and AHRQ review and approve study protocols, gather and review data on patient outcomes, and assess study results. Including a requirement that each CED study be reviewed by an IRB is important, but it does not sufficiently protect the Medicare beneficiary population. We expect that the ethical considerations associated with conditioning coverage on clinical trial participation may vary based on the disease state, availability of alternative treatment options, assessed safety and efficacy of the intervention, and other factors.

The Federal Policy for the Protection of Human Subjects (the "Common Rule"), has been codified with respect to the U.S. Department of Health and Human Resources (HHS) at subpart A of 45 CFR part 46. It requires that U.S. institutions engaged in cooperative research must rely on a single institutional review board (IRB) to review and approve the portion of the research conducted at domestic sites. See [45 CFR 46.114\(b\)](#). In order to be exempt from this rule, research must meet one of the criteria found at [45 CFR 46.104\(d\)](#). Of the eight categories of exempt research, the only exemption that could possibly apply to CED research is 46.104(d)(5) which exempts from the Common Rule:

Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.

It is highly unlikely that the clinical studies required under a CED NCD meet the standard for exemption from the Common Rule. In fact, HHS published a [flow chart](#) to illustrate applicability of exemption 45 CFR 46.104(d)(5) for Public Benefit or Service Programs. The chart emphasizes that the key factor is whether the research is designed to evaluate procedures, changes or alternatives to procedures, or methods or levels of payment. Although CED studies ultimately determine whether or not payment will be made, the clear intent of the exemption is to allow government agencies to broadly examine the effectiveness of their policies and programs – not to conduct randomized, controlled clinical trials examining the impact that a particular, and potentially FDA-approved, intervention has on Medicare beneficiary health outcomes.

Moreover, even if CMS were to fully consider this issue and conclude that there is no requirement that it **must** seek ethical review of its CED framework as applied to particular interventions and research questions, we strongly believe that as steward of the Medicare program it **should** do so. We urge CMS to obtain a clear and specific assessment of the ethical and patient protection concerns associated with each CED NCD and submit the CED study questions and requirements for IRB review and approval prior to finalizing any NCD requiring CED. In addition, the study criteria should include a requirement that investigators submit their protocols and other relevant information to the central IRB. We believe this is particularly important when the subject intervention is a medically accepted use of an FDA-approved treatment, and critical when such treatment addresses a life-limiting, progressive, and/or potentially fatal condition and access will be conditioned on study participation.

Finally, Haystack Project strongly believes that IRB and any other ethical review of CED NCDs should be made within the context of the Medicare population as a whole – individuals unable or unwilling to participate in clinical trials are denied access and, therefore, constitute an additional, albeit unintentional and non-consenting, “control” population.

Informed Consent

Haystack Project disagrees with CMS’ apparent belief that the “voluntary” nature of CED participation negates the potential for coercive influence on the decision to participate in a study. While CMS may be correct within the context of 510(k) cleared devices offered as one of many treatment options, patients unable to access coverage for the only, or a substantially superior, treatment option will feel all but compelled to enroll in a study if one is available to them. Depending on the patient’s condition and available treatment options, their choices could be limited to trial participation or paying out-of-pocket – a luxury that few Medicare beneficiaries can afford.

Haystack Project urges CMS to ensure that each CED study is subject to informed consent requirements that protect beneficiaries ***as patients***, including informing potential participants:

- That any FDA-approved treatment is NOT experimental or investigational
- Existence of alternative mechanisms available for individuals to obtain access to treatment outside participation in clinical trials of FDA-approved treatments, including commercial availability for patients wishing to pay for the treatment. While this may appear to “favor” individuals with financial means, withholding the information is contrary to meaningful informed consent
- Whether research subjects will be able to access treatment outside the clinical trial once their participation has concluded, including any longitudinal studies if the clinical trial results demonstrate improved patient outcomes
- Whether research subjects (or their treating providers) will be informed on whether they are in the active treatment or control arm of the clinical trial
- Costs, including copayment amounts, that patients will be required to pay within the clinical trial. This must include disclosure on whether subjects randomized to the control arm will be responsible for copayments associated with the FDA-approved therapy in the treatment arm
- Disclosure of research subject responsibilities, including any invasive and non-invasive tests and imaging studies, that are associated with data collection rather than connected to treatment monitoring
- Procedures available to appeal the CED NCA and/or its applicability to their medical condition
- Any mechanisms permitting access for individuals seeking treatment for a medically accepted use but unable to meet inclusion criteria of a particular study or to find a study site within a reasonable distance from their residence

CED is likely to perpetuate and exacerbate health inequities despite implementation of a requirement that “[t]he study population reflects the demographic and clinical diversity among the Medicare beneficiaries who are the intended users of the intervention.”

Haystack Project understands that research sponsors and investigators face challenges in enrolling racially and ethnically diverse populations in clinical trials, and that lack of participant diversity increases uncertainties on the subpopulation-specific benefits and risks of emerging treatments. Systemic racism has impacted Black, Latinx, and other people of color with respect to income potential, reliable access to quality health care, representation in clinical trial populations, prevalence of significant comorbidities, and poor health outcomes. There are no easy solutions to “fix” these economic and healthcare inequities.

Currently, Black patients make up just 5% of clinical trial populations. People of color are more likely to have significant comorbidities that preclude clinical trial enrollment and can face substantial economic challenges associated with transportation to clinical trial sites. Just as importantly, however, people of color have a longstanding and legitimate basis for medical mistrust, particularly with respect to any appearance or perception that participation in research is forced. As we noted in Haystack Project’s comments to AHRQ and MedCAC, any government-initiated paradigm conditioning coverage for safe and effective treatments on participation in randomized, controlled studies is likely to further, rather than reduce, medical mistrust. More importantly, however, it negates the critical element of informed consent that researchers have historically denied to Black patient populations; lack of independent ethical review and central IRBs lend a measure of credibility to perceptions and fears that the government is using health care coverage to experiment on patients.

We are similarly concerned about the impact that CED requirements have on low-income individuals. Patients with adequate financial resources have always been able to access treatments that individuals relying on insurance coverage are unable to afford. Rare disease patients and their families are, however, often forced to decide whether they can afford a non-covered but potentially promising on- or off-label treatment regimen, and too often face the crushing reality that evolving standards of care are financially out of reach. Higher participation in Medicare Advantage plans among people of color will further complicate CED study enrollment.

Finally, we remain concerned that despite our expressed concerns, there has been little, if any, discussion on the implications associated with CED studies that (1) contain burdensome study requirements and are (2) for interventions within the financial reach of some, but not all Medicare beneficiaries. We have repeatedly articulated our concern that some CED requirements, applied to some interventions, could create the appearance of a two-tiered system of access where economically advantaged patients achieve early access to care based on physician/patient decision making. Patients without financial resources, in contrast, would be

perceived as serving as research subjects for whom treatment is determined through randomization.

Additional recommendations to protect patients participating in CED studies

Haystack Project urges CMS to adopt additional CED process safeguards and clinical study requirements to protect Medicare beneficiaries participating in CED studies, including:

- Requiring that CMS implement a monitoring function over all studies to ensure that randomization of research subjects ceases when likely clinical benefit is shown (through a CMS-initiated CED study or other evidence).
- CMS creation of an alternative coverage pathway for Medicare beneficiaries who are unable (due to distance from a study site or enrollment restrictions) to participate in a CMS-approved clinical trial but seek coverage for a medically-accepted use of the intervention.
- Ensuring that CED requirements do not disrupt treatment access for Medicare beneficiaries who are receiving (or have received) the intervention (through previous clinical trial participation, coverage by another payer, or other means) and have, according to their treating provider, experienced clinically meaningful benefits. Given that clinical studies generally limit enrollment to treatment-naïve individuals to preserve scientific integrity, patients would have to initiate direct appeals of the NCD to continue their treatment.

Conclusion

Haystack Project appreciates the opportunity to communicate its concerns and recommendations on the Proposed Guidance for Coverage with Evidence Development. Patients with rare conditions rely on the hope that research and development efforts will bring treatment innovations that reduce their disease burden and/or slow its progression. We urge CMS to prioritize beneficiary access and to implement patient protections that meet or exceed those extended to individuals participating in scientific research studies that are outside CMS' CED mechanism.

Please contact Haystack Project's policy consultant, Kay Scanlan, at 410-504-2324 with any questions.

Sincerely,

Alpha-1 Foundation
Association for Creatine Deficiencies
Biomarker Collaborative

Casey's Cure Foundation
Choroideremia Research Foundation
CLL Society
CSNK2A1 Foundation
cureCADASIL
Cutaneous Lymphoma Foundation
Dup15q Alliance
Exon 20 Group
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GO2 for Lung Cancer
HealthTree Foundation
Histiocytosis Association
International Cancer Advocacy Network
International Fibrodysplasia Ossificans Progressiva (FOP) Association
International Foundation for CDKL5 Research
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